

Safe distal margin resection in patients with low rectal cancer undergoing neoadjuvant chemoradiation

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ABSTRACT

Background: Colorectal carcinoma is the third most common cause of death in Iran. This study was performed in order to determine the appropriate distal clearance margin (DCM) for resection of rectal cancer in patients who undergo neoadjuvant chemoradiotherapy for sphincter preserving procedure.

Materials and Methods: This was a cross-sectional study conducted in Shahid Faghihi Hospital of Shiraz University of Medical Sciences from 2006 to 2011. We included all patients with low rectal cancer who underwent neoadjuvant chemoradiotherapy. The medical charts of patients and disease characteristics were recorded. The local recurrence, recurrence-free survival and mortality rates were compared between those with DCM ≥ 2 cm and DCM < 2 cm.

Results: Overall, 82 patients with a mean age of 56.7 ± 16.4 years were included. The DCM was found to be ≥ 2 cm in 45 (54.9%) patients and < 2 cm in 37 (45.1%). The two study groups were comparable in terms of age ($p=0.573$), sex ($p=0.505$), histopathological tumor grade ($p=0.165$), and distance of tumor to anal verge ($p=0.125$). Patients with DCM ≥ 2 cm had a lower local recurrence rate (35.6% vs. 97.3%; $p<0.001$), a higher recurrence-free survival rate (88.9% vs. 67.6%; $p=0.032$) and a lower mortality rate (11.1% vs. 32.4%; $p=0.027$). **Conclusion:** Although some studies have showed that DCM < 2 cm leads to similar results compared to DCM ≥ 2 cm, our findings revealed that obtaining a distal clearance margin of 2cm for resection of rectal cancer in patients who have undergone neo-adjuvant chemoradiotherapy is associated with a lower local recurrence rate, higher recurrence-free survival rate and lower mortality rate.

Keywords: Rectal cancer, low anterior resection (LAR), chemoradiotherapy (CRM), distal clearance margin (DCM), local recurrence.

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INTRODUCTION

Colorectal carcinoma (CRC) is currently one of the most common malignancies of the gastrointestinal (GI) tract. Reports from Iran show that annually 51,000 new cases of CRC are diagnosed and 35,000 individuals die due to the disease^(1, 2). In the United States, 150,000 new cases are diagnosed annually with a mortality number of 52,000 per year, making the CRC the second cause of mortality in the United States⁽³⁾.

The cancers of the intraperitoneal part of the rectum are similar to CRC regarding the presentation, management, prognosis and recurrence pattern⁽⁴⁾. Contrarily, the cancers of the extraperitoneal parts of the rectum are located within the bony cage of the pelvis, and the management and clinical presentation is different from that of the intraperitoneal rectal cancers⁽⁵⁾.

There are several goals in the management of rectal cancer including local control of the

cancer, increasing the long-term survival of the patient, preservation of the bladder, sexual function and, most importantly, the anal sphincter complex. Maintaining the quality of the patients' life is also an important issue that should be addressed through management of rectal carcinoma⁽⁶⁾.

Obtaining safe margins in rectal tumors is always challenging. Inadequate safe margins are associated with local recurrence, and local recurrence is associated with extensive pelvic organ involvement⁽⁷⁾. Recurrence is associated with poor patient prognosis and may require pelvic exenteration. Neoadjuvant chemoradiotherapy brings the possibility of minimal rectal resection with acceptable recurrence and distal metastasis rates^(6, 7). Therefore, currently the neoadjuvant chemoradiotherapy along with rectal resection is considered as the standard management of poorly differentiated rectal cancer^(4, 5).

For resection of the rectal carcinoma, the optimal extent of distal clearance margin (DCM) is one of the important values. Although the issue has been extensively studied and investigated⁽⁸⁻¹³⁾, controversy still exists. Most of the experts believe that a 2-cm DCM is acceptable for resection of rectal cancer^(8, 9), while others have reported that DCM less than 2-cm could be appropriate if the margins are negative⁽¹⁰⁻¹⁴⁾. Most of the authors agree that when the margins of the resection are clear, the recurrence rate and distal metastasis is independent of the DCM^(13, 14). As this subject has still remained a matter of discussion, we performed this study in order to determine the appropriate DCM for resection of poorly differentiated rectal carcinoma in patients who undergo neoadjuvant chemoradiotherapy.

MATERIALS AND METHODS

Study population

This was a retrospective cross-sectional study which was performed in Shahid Faghihi hospital, a tertiary healthcare center affiliated with Shiraz University of Medical Sciences, during a 5-year period from 2006 to 2011. We included all the

patients who were diagnosed to have low rectal cancer, received neoadjuvant chemoradiotherapy, and underwent low anterior resection. The study protocol was approved by the institutional review board (IRB) of Shiraz University of Medical Sciences and the approval of the Ethics Committee was obtained before the commencement of the study. As this was a retrospective study being performed by reviewing the medical charts of the patients, no informed written consents were required.

Rectal cancer was diagnosed by direct visualization and histopathological confirmation. We included only those patients who underwent low anterior resection and received neoadjuvant chemoradiotherapy in our center during the study period. All the patients had biopsy-proven adenocarcinoma and the tumor was located within 12 cm of the anal verge as measured before surgery by colonoscopy in all of the patients. The preoperative stage was identified by means of several modalities including colonoscopy, CT-scan and endorectal ultrasonography. Those patients with stage T3-4 and/or N1-2 were further referred for neoadjuvant chemoradiotherapy and were included in our study. Concurrent neoadjuvant chemoradiation consisted of conventional external beam radiation therapy using megavoltage photons from a linear accelerator. The energies of the used photon were 6 MV in three-field technique (one direct posterior field and two lateral fields) and 18 MV in the two-field technique (anteroposterior and posteroanterior parallel opposing fields). All the patients were treated in the prone position with a full bladder to reduce small bowel toxicity. A median dose of 45 Gy (range, 45-50.4 Gy) was delivered via a daily fraction of 1.8-2 Gy, with five fractions per week. Concurrent chemotherapy consisted of oral capecitabine at a dose of 825 mg/m² twice daily during the whole period of pelvic radiotherapy with weekend breaks. Two weeks after the completion of radiation, 2 cycles of chemotherapy (CAPEOX regimen) was administered and subsequently, all the patients were referred for surgery with a median of a 4- to 8-week interval after the last session of radiation therapy.

Those patients with multiple tumors at operation, distant metastasis, emergency operations, local recurrent tumors, abdominoperitoneal resection, incomplete resections, locally invasive tumors and previous history of fecal incontinence were further excluded from the study. Those with less than 24 months of follow-up were also excluded from the study.

Study design and assays

A total number of 82 patients diagnosed to have low rectal cancer who underwent chemoradiotherapy and low anterior resection in ShahidFaghihi hospital during 2006 and 2011 were included in the study. The data were extracted from the medical documents and charts of the patients by means of a standard data collecting form being designed in accordance with the medical documents and the required information. The medical charts were reviewed by a surgery resident and the data were further entered into an online digital database for analysis and interpretation.

All the patients received preoperative concurrent chemoradiation. Postoperative chemoradiotherapy was also provided for those with a high stage of the disease.

The excised tumor and the surrounding tissue were sent for histopathological study in the pathology department and laboratory of ShahidFaghihi hospital. The reports were reviewed retrospectively for the tumor distal margin length, tumor differentiation, TNM (tumor-node-metastasis) stage and distance from the anal verge were evaluated. All the distal clearance margins were measured before tissue fixation in formalin and embedment in paraffin by the attending pathologist. In the case of a complete response of the rectal tumor to chemoradiotherapy (absence of microscopic or gross infiltration of tumor in the specimen), the distal clearance margin was reported as the distance between the caudal edge of the remaining scar and the cut margin of the rectum. The distal clearance margin was further classified as ≥ 2 cm or < 2 cm and the outcomes measured were compared between these two groups.

All the patients had been followed for at least 24 months and the local recurrence of the rectal tumor or the occurrence of the distal metastasis were evaluated every 3 months within the first postoperative year and every 6 months within the following postoperative years. The carcinoembryonic antigen (CEA) was checked each 3 months within the first year and if it was elevated total colonoscopy, abdominopelvic and chest CT scans were performed. We reviewed all the medical documents and charts in order to determine the follow-up information. If the required data was not available, we contacted the patient via phone number and visited him or her for follow-up and determined the outcome.

Statistical analysis

SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA) was used for data analysis. Independent t-test was used to compare the parametric data between those with ≥ 2 cm distal clearance margin and those with < 2 cm. Chi-square test was used to compare proportions between these two groups. Data were reported as mean $\pm$ SD or proportions as appropriate. A p-value less than 0.05 was considered significant.

RESULTS

A total of 82 patients with rectal cancer were included in the study. There were 46 (56.1%) men and 36 (43.9%) women among the patients. The mean age of the patients was 56.7 ± 16.4 years ranging from 26 to 86 years. The baseline characteristics as well as outcome of these 82 patients with rectal cancer are summarized in table 1.

Overall, 45 (54.9%) patients were found to have a distal clearance margin of ≥ 2 cm, while in 37 (45.1%) patients it was < 2 cm. There was no patient with involved margin by tumor < 5 mm. We found that the local recurrence rate was significantly higher in those with DCM < 2 cm when compared to those with DCM ≥ 2 cm (97.3% vs. 35.6%; $p < 0.001$). The recurrence-free survival was also significantly higher in those with DCM ≥ 2 cm when compared to those with DCM < 2 cm (88.9% vs. 67.6%; $p = 0.032$). The

mortality rate was significantly higher in those with DCM <2cm when compared to those with DCM ≥2cm (32.4% vs. 11.1%; $p=0.027$). The comparisons of baseline characteristics as well as study outcomes are demonstrated in table 2.

Table 1. The baseline characteristics and outcomes of 82 patients with rectal cancer included in the current study.

	Value
Age (years)	56.7 ± 16.4
Sex	
Men (%)	46 (56.1%)
Women (%)	36 (43.9%)
Pathology	
Poorly differentiated (%)	32 (39.0%)
Moderately differentiated (%)	14 (17.1%)
Well differentiated (%)	36 (43.9%)
Distance to anal verge (cm)	5.68 ± 2.97
Local recurrence (%)	52 (63.4%)
Recurrence-free survival (%)	65 (79.3%)
Mortality (%)	17 (20.7%)

Table 2. Comparison of the baseline characteristics and outcomes of patients with rectal cancer with DCM ≥2 cm and those with DCM <2 cm.

	DCM ≥2 cm (n=45)	DCM <2 cm (n=37)	p-value
Age (years)	57.6 ± 14.2	55.5 ± 18.9	0.573
Sex			
Men (%)	27 (60.0%)	19 (51.4%)	0.505
Women (%)	18 (40.0%)	18 (48.6%)	
Pathology			
Poorly differentiated (%)	8 (17.8%)	4 (10.8%)	0.165
Moderately differentiated (%)	23 (51.1%)	20 (54.1%)	
Well differentiated (%)	14 (31.1%)	13 (35.1%)	
Distance to anal verge (cm)	7.50 ± 5.29	5.29 ± 2.11	0.125
Local recurrence (%)	16 (35.6%)	36 (97.3%)	<0.001
Recurrence-free survival (%)	40 (88.9%)	25 (67.6%)	0.032
Mortality (%)	5 (11.1%)	12 (32.4%)	0.027

DISCUSSION

We found that those who had a DCM of ≥2 cm had a lower local recurrence rate, higher recurrence-free survival rate and lower mortality rate when compared to those with DCM <2cm. Our results are contrary to previous reports that reported <2cm DCM is not associated with worse outcomes in patients with rectal cancer ^(9-11, 15), while they are consistent with some other reports ^(5, 16).

The introduction of the stapling technique accompanied by neoadjuvant radiotherapy and chemoradiotherapy the survival increased, recurrence decreased, and successfulness of sphincter preserving surgeries increased ⁽¹⁷⁾. Thus the importance of the extent of the distal margin of the resection has increased in order to minimize the risk of recurrence and distant metastasis. It has been demonstrated that microscopic involvement of resection edge is associated with at least 5 cm of grossly involved tissue ⁽¹⁸⁾. This was previously referred to as the 5-cm rule in low anterior resection of rectal cancer. This rule was further changed into a 2-cm rule in 1980s. 2-cm margin is considered adequate while tumors with extension of more than 1-2 cm are metastatic and advanced. In these cases, the distal clearance margin has limited concordance with the outcome of the patient⁽¹⁹⁾.

Recent reports have also indicated that neoadjuvant chemoradiotherapy can decrease the distal rectal margin for large tumors to 1-cm ^(9,11, 20).

Unfortunately, the importance and extent of the DCM in patients with advanced rectal cancers receiving neoadjuvant chemoradiotherapy before low anterior resection has not been fully addressed before. Theoretically, neoadjuvant chemoradiotherapy shrinks the tumor and eradicates all the focuses of distal and proximal infiltration of the tumor. This makes the surgical procedure safer. It is hypothesized that a distal clearance margin of >1 cm would not affect the outcome of the patients to a great extent. The lower distal clearance margin leads to easier preservation of the anal sphincter and its function. Thus most surgeons would prefer to

decrease the DCM in order to increase the post-operation quality of life of the patient⁽⁹⁻¹¹⁾. However, these patients usually have an advanced stage of the rectal tumor and thus the DCM could not be decreased easily due to the increased risk of local recurrence and distant metastasis^(5, 6, 8, 9).

Currently, total resection of the mesorectum is the standard method for resection of rectal tumors⁽²¹⁻²⁵⁾ which is associated with a low local recurrence rate^(23, 24). The local recurrence rate has been reported to be 3–5% using neoadjuvant chemoradiotherapy and low anterior resection accompanied by total mesorectum excision⁽²⁶⁾. Thus, many authors believe that using these management protocols would allow the surgeon to preserve the anal sphincter complex and the surrounding tissue leading to increased patients' quality of life and satisfaction. According to these observations and favorable results, the DCM was reduced to 1 cm or even less than 1 cm. They demonstrated that decreasing the DCM to 1 cm in patients with low rectal cancer receiving appropriate chemoradiotherapy would not compromise the outcome of the patients^(5, 6, 8-12). It should be kept in mind that all of these studies indicated that the DCM alone does not correlate with local recurrence, disease-free survival and mortality rates^(5, 6). On the contrary, we demonstrated that those patients with DCM <2cm had a higher local recurrence rate, lower recurrence-free survival rate and higher mortality rate. As several other factors such as stage of the tumor, distance to anal verge and age affect the outcome of the patients, we fully matched all these variables between the two study groups in order to avoid any bias. However, the overall recurrence rate was high in our study which could be because of the high number of poorly or moderately differentiated patients as well as microscopic involvement of the rectum with DCM <2 cm. Andreola and co-workers⁽²⁷⁾ reported a 3.4% versus a 5% relapse rate for patients having ≤1 or >1-cm DCM in a group of cases in order to avoid any bias correlated with major prognostic factors such as the spread of the disease into the regional nodal basin. Lučovník and Omejc⁽²⁸⁾ also showed that the local recurrence rates were

comparable between those with DCM ≤1 or >1-cm. They concluded that a distal margin of 1 cm or less may be acceptable in most patients; therefore, a sphincter saving procedure can also be considered in very low lying tumors.

There were some limitations in our study; the number of included patients was limited and the comparisons were performed between the limited numbers of the patients. However, we included all the patients that had the inclusion criteria which were meticulously defined. This enabled us to match those with DCM ≥2 and < 2-cm precisely and thus the matching bias could not affect the results. Future prospective studies with larger study populations are recommended to shed further light on this issue.

In conclusion, obtaining a distal clearance margin of 2cm for resection of rectal cancer in those who have undergone chemoradiotherapy is associated with a lower local recurrence, higher recurrence-free survival, and lower mortality rates. Distal clearance margin remains an independent predictor of the outcome in those rectal patients who undergo preoperative chemoradiotherapy.

Conflict of interest: Declared None

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