Assessment of the relation between the distal resection margin and incidence of local recurrence after low anterior resection in cases of low rectal cancer

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Introduction
One of the world's major causes of death and morbidity is colorectal cancer. It is the world's third most frequent cancer and the fourth biggest cause of cancer-related deaths, with an estimated 1 400 000 new cases and 700 000 fatalities per year. The distal resection margin is crucial in rectal cancer surgery. Surgeons in the colorectal field are frequently different between keeping an oncologically safe margin and attempting sphincter-preservation surgery. The goal of this study was to determine the oncological safety of a modest distal resection margin.

Patients and methods
This is a study that looks backward in time. We gathered patient data from Ain Shams University hospitals' colorectal and oncology departments. Patients who had a low anterior resection between January 2015 and January 2019 were included in this study.

Results
We found that distance of distal free margin, number of positive lymph node, and number of dissected lymph node were not significantly associated with recurrence, but response to neoadjuvant chemotherapy was associated with lower recurrence rate. Distal free margin was achieved in 98% of our patients, but we had one patient with infiltrated margin who had completed abdominoperineal resection. There was a discrepancy in the distance of the distal free margin and the existence of prior chemotherapy or radiotherapy among studies of low anterior resection of rectal cancer.

Conclusion
In our research, we discovered that while a free distal margin is required in rectal cancer resection, there is no link between the distance of the free distal margin and local recurrence. We also discovered that lymphovascular invasion and responsiveness to neoadjuvant chemoradiation have a substantial impact on rectal cancer local recurrence rates.

Keywords:
distal resection margin, local recurrence, low anterior resection, low rectal cancer

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Introduction

One of the world's major causes of death and morbidity is colorectal cancer [1]. It is the third most frequent cancer in the world and the fourth biggest cause of cancer-related deaths, with an estimated 1 400 000 new cases and 700 000 fatalities per year [2]. The incidence of colorectal cancer has risen dramatically in recent decades, with the number of newly diagnosed cases rising from 783 000 in 1990 to 1 361 000 in 2012 [3].

Rectal cancer develops gradually; the specific cause is unknown, but risk factors include age (over 50), family history, smoking, eating a high-fat diet, or a history of polyps or inflammatory bowel disease [4].

Rectal cancer is characterized by anemia, tiredness, shortness of breath, vertigo, and/or tachycardia. Other signs and symptoms include intestinal obstruction, feces with a small diameter, and weight loss [5].

Among the investigations performed to make a diagnosis are fecal occult blood testing, digital rectal examination, computed tomography (CT)/MRI studies, endoscopy, sigmoidoscopy, standard blood tests, and detection of carcinoembryonic antigen and CA19.9 [6].

In persons who are well enough to tolerate it, neoadjuvant radiotherapy with or without

chemotherapy, followed by surgery, is currently used to treat rectal tumors that are diagnosed preoperatively as at least T3 and/or at least N1 (stage II or III). With the main, both neoadjuvant long-course chemoradiation and short-course radiation treatment are administered. The goal is to lower the chances of a local recurrence. Neoadjuvant therapy can also reduce tumor size, produce pathological full response, and allow for sphincter-preservation surgery [7].

The three basic forms of sphincter-preserving procedures are a standard low anterior resection, low anterior resection or coloanal anastomosis with the development of a J-pouch colonic reservoir, and a low anterior resection with coloanal anastomosis. All low anterior resections necessitate resection and anastomosis between a serosalized colon and the extraperitoneal nonserosalized rectum. An intrapelvic anastomosis within the sacral hollow is used in the conventional low anterior resection; the distance of the residual distal rectum segment varies. A coloanal anastomosis, on the other hand, is an extrapelvic anastomosis that occurs at the anal canal's apex or at the dentate line, with no lingering of the distal rectum. The surgery restores the rectum's reservoir function and improves bowel function when combined with a coloanal resection or a low anterior resection [8].

The appropriateness of the distal margin in patients with rectal cancer is determined by the risk of intramural tumor dissemination as well as the distal mesorectal lymphatic spread. Up to 5 cm distant to the inferior aspect of the tumor, tumor cell deposits have been found within mesorectal lymph nodes, the concept of tumor-specific mesorectal excision was born out of the requirement to adhere to the principles of total mesorectal excision. The importance of patient and tumor selection for this technique, however, cannot be overstated. The exact criteria for this decision have yet to be determined. As a result, more research is needed to determine the criteria for selecting patients for a sphincter-preservation method with close distal margins [9].

The prevention of recurrence is the most important goal in rectal cancer treatment. If the quality of life after rectal cancer surgery is to be improved and bowel control maintained, the anus sphincter should be kept. For rectal cancers within 5 cm of the anus, microinvasion of the tumor's lower half may be possible, an abdominoperineal resection (APR) is suggested. Even when the distal resection margin (DRM) was less than 1 cm, many studies found a decreased rate of local recurrence. In addition, some studies have found that a shorter DRM does not increase the rate of recurrence. Furthermore, given the efficacy of preoperative neoadjuvant chemotherapy and radiotherapy in rectal cancer, a shorter DRM should no longer be a major stumbling block. As a result, the 2010 NCCN recommendations for locally advanced rectal cancer stage T3 with positive nodes recommended this treatment. Recent studies indicated that a small DRM, when combined with chemoradiotherapy, has beneficial oncological effects [10].

Development in colorectal surgeries and appearance of new modalities in colorectal surgery allow performing low anterior resection rather than APR, which gives better quality of life. However, low anterior resection should not breech oncological principles of radical resection of low rectal cancer [11].

Aim

This study aims to see if there is a link between a free DRM after low anterior resection and the risk of local recurrence in low rectal cancer patients.

Patients and methods

Study design

This is a study that looks backward in time. Written informed consent was obtained from the patients. The study was approved by the ethical committee. The information was gathered from Ain Shams University hospitals' colorectal and oncology departments.

Patients who underwent low anterior resection for cancer rectum at the colorectal unit of Ain Shams University hospitals between January 2015 and January 2019 were included in the study.

Inclusion criteria:

(1) Patients who underwent low ant resection for rectal cancer.
(2) Curative resection proved by histopathology.
(3) No distant metastasis.
(4) Received neoadjuvant chemoradiation.
(5) Patients completed at least 2 years of follow-up postoperatively.

Exclusion criteria:

(1) Patients with recurrent low rectal cancer.
(2) Patients who had malignancy elsewhere.

Primary objective: to determine if there is a direct relationship between the distance of free DRM after low anterior resection and the incidence of local recurrence.

Secondary objectives: to determine other contributing factors that may affect local recurrence after low anterior resection like the pathological type and grade and depth of invasion.

Data collection

Examination of the medical records and imaging studies of the patients diagnosed with low rectal cancer.

The data were collected about patients who underwent low anterior resection in the period between January 2015 and January 2019 from their files and data that were found in colorectal department and oncology department. These data include patients' investigations preoperatively and postoperatively, such as colonoscopy and pathology of the biopsy, CT and MRI pelviabdominal with contrast, laboratory investigations, tumor markers, and pathology of the specimen 2 years postoperatively. Followup with surgical and oncological department was done. Postoperative investigations include follow-up CTs, tumor markers, and colonoscopy up to 2 years postoperatively.

Approval of ethical committee of the Surgical Department of Ain Shams University hospitals was taken.

Pathological factors that affect local recurrence

(1) Histopathological report must state that the proximal margin is free.
(2) Distal margin is free from malignant cells and the length of free margin.
(3) Mesorectal margin is free with at least 2 mm.
(4) Lymph-node status, perineural, and lymphovascular-invasion status.
(5) Staging of the tumor with type of response to neoadjuvant chemoradiotherapy.
(6) Donut status.

Definition of curative resection

Specimen has the tumor completely resected with free proximal, free distal margin, and free circumferential margin proved by histopathology.

Results

Statistical analysis

The data were collected, edited, coded, and entered into IBM SPSS, version 23 (Statistical Package for Social Science) (Statistical analysis was done using IBM SPSS statistics for windows, Version 23.0. Armonk, NY: IBM Corp). When the data were parametric, it was provided as mean, SDs, and ranges; when the data were nonparametric, it was presented as median and interquartile range. Numbers and percentages were also used to represent qualitative characteristics.

When the predicted count in any cell was less than 5, the χ^2 test and/or Fisher exact test were used to compare the groups' qualitative data.

The independent t test was used to compare two groups' quantitative data and parametric distributions, whereas the Mann–Whitney test was used to compare nonparametric distributions.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the P value was considered significant as the following:

P value more than 0.05: nonsignificant.
P value less than 0.05: significant.
P value less than 0.01: highly significant.

In this study, we gathered data from 99 patients who had a low anterior resection between January 2015 and January 2019 from their medical records as well as data from the colorectal and oncology departments. Two years after surgery, 69 of these patients had completed their follow-up.

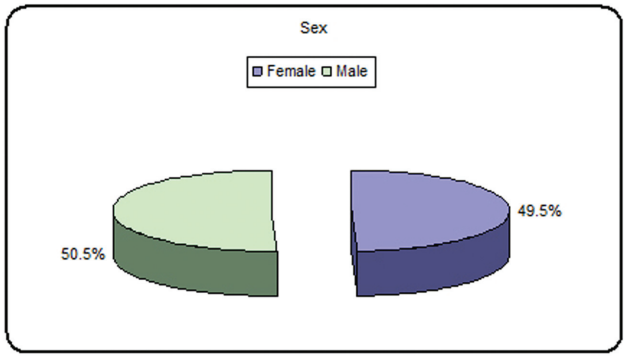
In our study patients, age ranged from 22 up to 85 years old with mean age 50 years. In total, 50 (50.5%) cases were male, while the rest (49) were females (49.5%), as shown in Table 1 and Fig. 1.

The distance between the tumor and the anal margin in our study ranged from 5 to 14 cm, with an average distance of 8.9 cm. In addition, 53 patients had tumors that were above 8 cm from the anal verge and 45 patients had tumors that were below 8 cm from the anal verge, as indicated in the graph (Table 2 and Fig. 2).

Table 1 Age and sex distribution

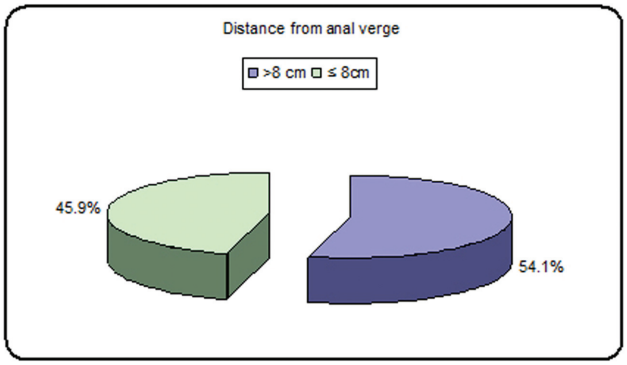
	N=99 [*n* (%)]
Age	
Mean±SD	50.91±14.23
Range	22–85
Sex	
Female	49 (49.5)
Male	50 (50.5)

Figure 1



Sex distribution.

Figure 2

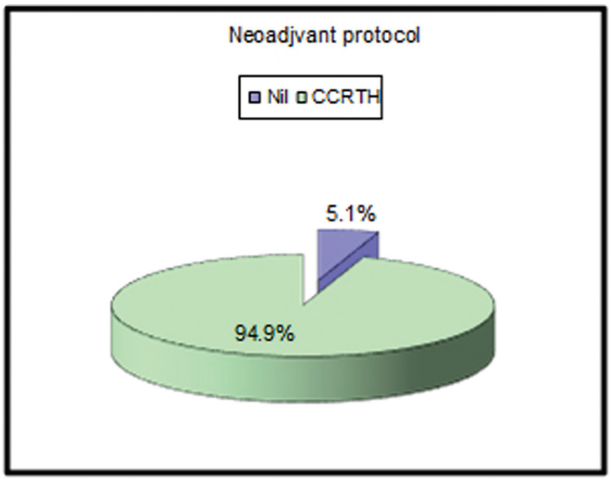


Distance from the anal verge.

Table 3 Patients received neoadjuvant therapy

Neoadjuvant protocol [*n* (%)]	Nil	5 (5.1)
	CCRTH	94 (94.9)

Figure 3

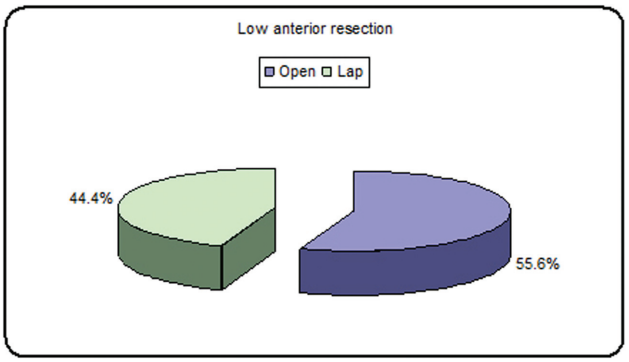


Patients received neoadjuvant therapy.

Table 2 Distance from the anal verge (cm)

	Mean±SD	8.96±2.11
	Range	5–14
Distance from anal verge (cm) [*n* (%)]	>8	53 (54.1)
	≤8	45 (45.9)

Figure 4



Type of the procedure (open or laporoscopic).

Table 4 Type of the procedure (open or laparoscopic)

Low anterior resection [*n* (%)]	Open	55 (55.6)
	Laparoscopic	44 (44.4)

Also, there were 94 patients who received neoadjuvant chemotherapy and radiotherapy and the rest (five patients) did not receive as shown in Table 3 and Fig. 3.

Also, we had 44 patients who underwent laparoscopic low anterior resection, while the other 55 patients underwent open low anterior resection as shown in Table 4 and Fig. 4.

In our study, the percentage of local recurrence was 4% in all patients, but it was 5.8% in the sample with the patients who completed 2 years of follow-up postoperatively as shown in Tables 5 and 6.

Also in our study, we found that the DRM was free in 98 patients and infiltrated in one patient as shown in Table 7 and Fig. 5.

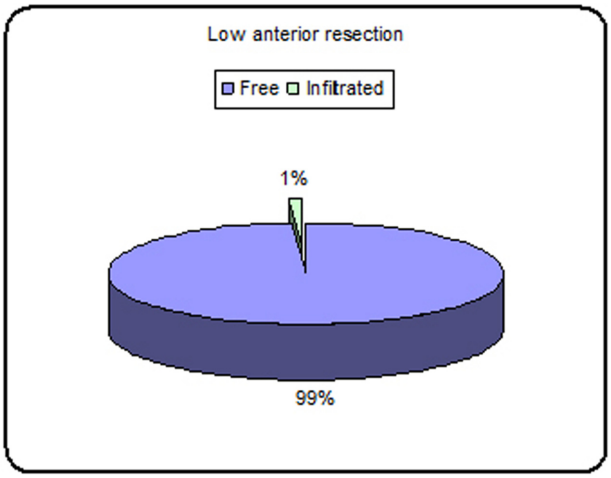
In our study, the percentage of the known distance of the distance of the DRM was 39% as shown in Table 8 and Fig. 6.

This study found a variety of histological types, with the majority of cases being grade-2 moderately differentiated adenocarcinoma (91 cases). The other categories included grade-1 well-differentiated adenocarcinoma (three instances), grade-3 adenocarcinoma (two cases), and

Table 5 Percentage of local recurrence in all patients

	N=99 [*n* (%)]
Recurrence	
No recurrence	95 (96.0)
Recurrence	4 (4.0)

Figure 5

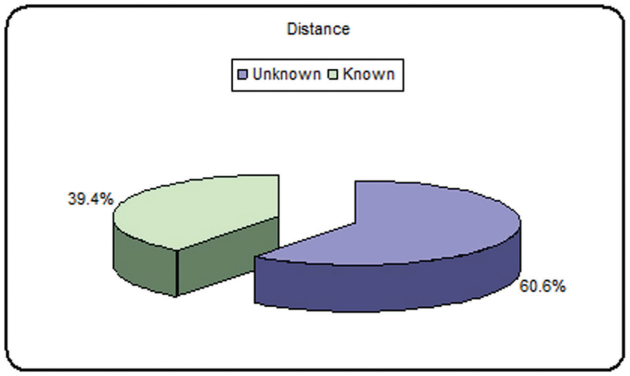


Distal resection margin (free or infiltrated).

Table 6 Percentage of local recurrence in patients who completed 2 years of follow-up

	N=69 [*n* (%)]
Recurrence in the sample with the patients who completed the follow-up	
No recurrence	65 (94.2)
Recurrence	4 (5.8)

Figure 6



The known distance of the distal resection margin.

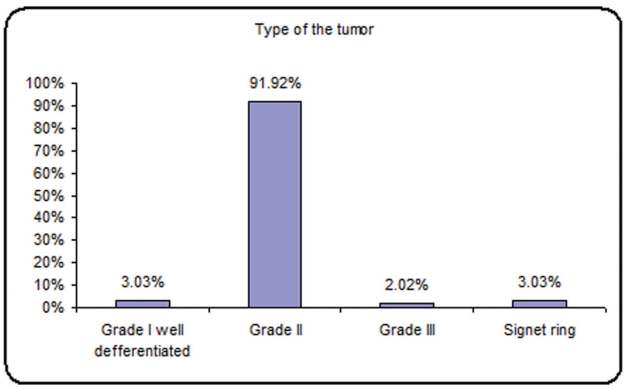
signet ring adenocarcinoma (two cases), as shown in Table 9 and Fig. 7.

One of the prognostic criteria is the lymphovascular invasion, this was detected only in three cases, which

Table 7 Percentage of distal margin

Pathology	*N*=99
Distal margin	
Free	98 (99.0)
Infiltrated	1 (1.0)

Figure 7

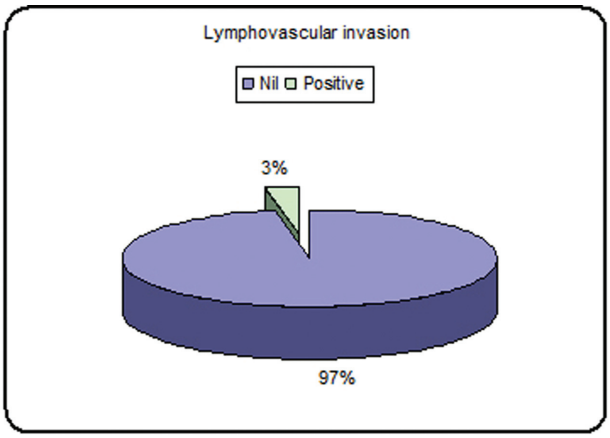


Type of the tumor.

Table 8 The known distance of the distal resection margin

Distance [*n* (%)]		
	Unknown	60 (60.6)
	Known	39 (39.4)

Figure 8



Lymphovascular invasion.

represents about 3% of the total cases as shown in Table 10 and Fig. 8.

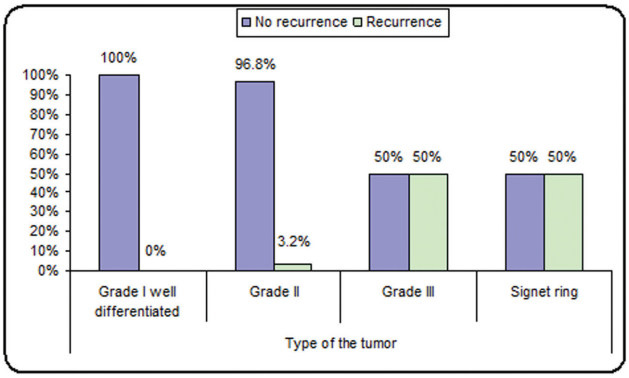
In our study, we discussed the relation between local recurrence in cases of low rectal cancer and the distance of the DRM.

Table 11 shows that there is no significant relationship between the local recurrence and the distance of the DRM in our study.

Table 9 Type of the tumor

	Grade I well differentiated	3 (3.03)
Type of the tumor [*n* (%)]	Grade II	91 (91.92)
	Grade III	2 (2.02)
	Signet ring	3 (3.03)

Figure 9

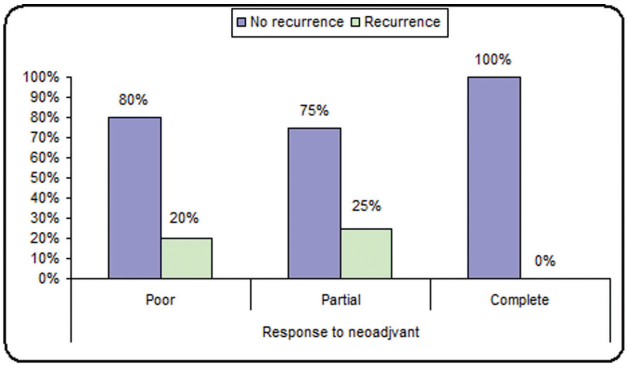


Relation between the type of the tumor and local recurrence.

Table 10 Lymphovascular invasion

Lymphovascular invasion [*n* (%)]	Nil	96 (97.0)
	Positive	3 (3.0)

Figure 10



Relation between the response to neoadjuvant therapy and local recurrence.

Also, in our study, we discussed the relation between the local recurrence in cases of low rectal cancer and other contributing factors such as the type of the tumor.

From Table 12, we found a significant relationship between the local recurrence and the type of the tumor. This relationship was not significant with low-grade tumors (grade-1 well-differentiated adenocarcinomas) and it was highly significant with high-grade tumors (grade 2, grade 3, and signet ring adenocarcinomas) as shown in Fig. 9.

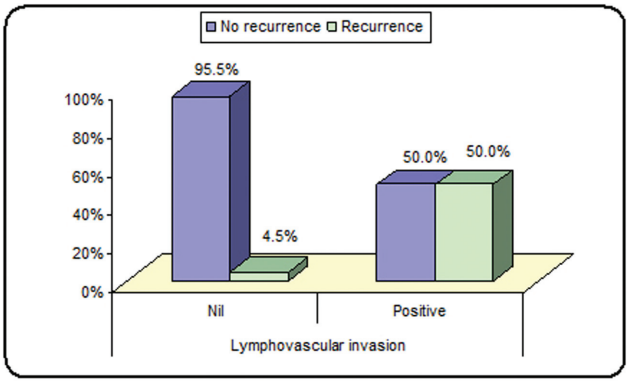
We discussed the relation between the local recurrence and response to neoadjuvant therapy.

Table 13 shows that there is a highly significant relationship between the local recurrence and the response to the neoadjuvant chemotherapy and radiotherapy also shown in Fig. 10.

The next table showed that there was higher incidence of local recurrence in patients with positive lymphovascular invasion with a highly significant relation between local recurrence and lymphovascular invasion as shown in Fig. 11 and Table 14.

In terms of adequacy of resection in our study, there is 88.9% adequate resection of lymph nodes (>12 lymph nodes) as shown in Table 15 and Fig. 12.

Figure 11



Relation between the lymphovascular invasion and local recurrence.

Table 11 Relation between the distance of the distal margin and local recurrence

	No recurrence [*n* (%)] *N*=35	Recurrence [*n* (%)] *N*=4	Test value	*P* value	Significance
Distance					
≥1	24 (92.3)	2 (7.7)	0.557	0.455	NS
<1	11 (84.6)	2 (15.4)			

Table 12 Relation between the type of the tumor and local recurrence

	No recurrence [*n* (%)] *N*=65	Recurrence [*n* (%)] *N*=4	Test value	*P* value	Significance
Type of the tumor					
Grade I well differentiated	3 (100.0)	0	0.193	0.660	NS
Grade II	60 (96.8)	2 (3.2)	7.399	0.007	HS
Grade III	1 (50.0)	1 (50.0)	7.369	0.007	HS
Signet ring	1 (50.0)	1 (50.0)	7.369	0.007	HS

Table 13 Relation between the response to neoadjuvant and local recurrence

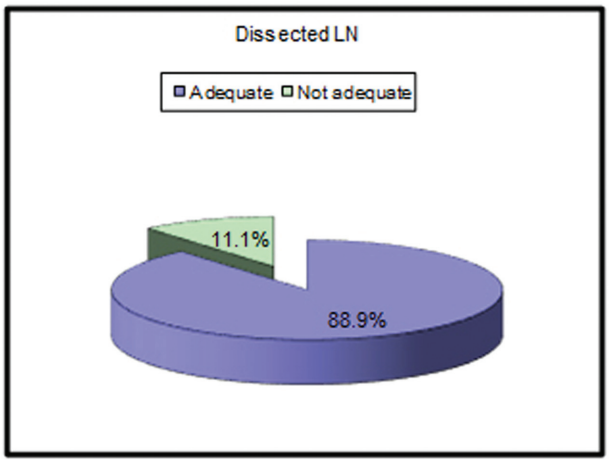
	No recurrence [*n* (%)] *N*=65	Recurrence [*n* (%)] *N*=4	Test value	*P* value	Significance
Response to neoadjuvant					
Poor	4 (80.0)	1 (20.0)			
Partial	6 (75.0)	2 (25.0)	13.226*	0.001	HS
Complete	54 (100.0)	0			

P value more than 0.05: nonsignificant. *P* value less than 0.05: significant. *P* value less than 0.01: highly significant. *χ^2 test.

Table 14 Relation between the lymphovascular invasion and local recurrence

	No recurrence [*n* (%)] *N*=65	Recurrence [*n* (%)] *N*=4	Test value	*P* value	Significance
Lymphovascular invasion					
Nil	64 (95.5)	3 (4.5)	7.369	0.007	HS
Positive	1 (50.0)	1 (50.0)			

Figure 12



Adequacy of dissected lymph nodes.

Also, in our study, we discussed the relation between adequacy of dissected lymph nodes (>12 dissected lymph nodes) and neoadjuvant therapy.

From Table 16, we found in our study that there is no significant relation between the received neoadjuvant therapy and the adequacy of dissected lymph nodes.

We also discussed in our study the relation between the local recurrence and the adequacy of dissected lymph nodes.

Table 15 Adequacy of dissected lymph nodes

Dissected LN [*n* (%)]	Adequate	88 (88.9)
	Not adequate	11 (11.1)

LN, lymph node.

From Table 17, we found in our study that there is no significant relation between local recurrence and lymph-node status and the number of dissected lymph nodes.

Discussion

With around 1 400 000 new cases and 700 000 fatalities each year, colorectal cancer is the world's third most common malignancy and the fourth leading cause of cancer-related deaths [2].

The DRM is critical in rectal cancer surgery. Surgeons in the colorectal sector are frequently torn between trying sphincter-preservation surgery and maintaining an oncologically safe margin. The purpose of this study was to see if the approved free distal margin distance for rectal cancer resection was safe oncologically.

The records of 99 individuals who had a low anterior resection between January 2015 and January 2019 were

Table 16 Relation between neoadjuvant protocol and adequacy of dissected lymph nodes

	Adequacy of dissected LN [*n* (%)] Adequate *N*=88	Not adequate *N*=11	Test value	*P* value	Significance
Neoadjuvant protocol					
Nil	4 (80.0)	1 (20.0)	0.421	0.516	NS
CCRTH	84 (89.4)	10 (10.6)			

LN, lymph node.

Table 17 Relation between lymph nodes and dissected lymph nodes regarding local recurrence

	No recurrence [*n* (%)] *N*=65	Recurrence [*n* (%)] *N*=4	Test value	*P* value	Significance
Lymph node					
Nil	51 (94.4)	3 (5.6)	0.027	0.871	NS
Positive	14 (93.3)	1 (6.7)			
Dissected LN					
Adequate	60 (93.8)	4 (6.2)	0.332	0.565	NS
Not adequate	5 (100.0)	0			

LN, lymph node.

examined in this study. We based our data on the fact that just 69 patients were able to sustain follow-up for at least 2 years after surgery.

The age of our patients ranged from 22 up to 85 years old with mean age 50 years. This mean age was less than that observed in other studies as in Manegold *et al.* [12] who worked on about 405 patients with mean age 60, less than Grosek *et al.* [13] with 63 years old of mean age of 109 patients, less than Hong *et al.* [14] with 62 years old of mean age of 218 patients, and close to Ghahramani *et al.* [15] who worked on 250 patients with mean age 54.

Sex distribution in this study showed male prevalence (50 out of 99) 50.5%, which was near the finding of Ghahramani *et al.* [15] who worked on 250 patients with 56% male predominance. Hong *et al.* [14] studied 218 patients with 59% male incidence rate but slightly less than Grosek *et al.* [13] 68% male predominance. That was also less than Manegold *et al.* [12] who revealed male predominance by 77% that may suggest the incidence of cancer rectum was higher in males, especially which we did not find a study showing female predominance totally in cancer rectum.

Histopathological examination revealed that 91 cases (about 91.9%) were grade-2 moderately differentiated adenocarcinoma compared with 43% reported by Rutkowski *et al.* [16], while it was 20% reported by Ghahramani *et al.* [15].

One of the important prognostic criteria is the lymphovascular invasion, detected in three cases in our study, which represents about 3% of the total cases. That was significantly related to local recurrence of rectal cancer and this finding was less than what was found by other investigators. Grosek *et al.* [13] reported nine patients in their study, which represented about 12.9% of the total cases. Betge *et al.* [17] also found that venous invasion was present in 23% and lymphatic invasion in 33%.

According to the National Comprehensive Cancer Network (NCCN) and the American Joint Committee on Cancer's criteria for adequacy of resection in colorectal cancer, specimens should have at least 12 lymph nodes. In our study, adequate lymph-node excision was obtained in roughly 88% of the cases. Other studies showed a less percentage of adequate resection rate, as in Senthil *et al.* [18] who achieved 74% and Gravante *et al.* [19] who presented 69% adequate resection rate, respectively. However, we discovered that the quantity of lymph nodes in the specimen, as well as the condition of lymph nodes, whether afflicted by malignancy or not, has no bearing on local recurrence. This may be due to the unique circumstances of rectal cancer treatment, in which most patients receive neoadjuvant chemoradiation prior to surgery, which frequently alters the biological outcome nature of the tumor and lymph nodes.

Also, in our study, we had 94 patients who received neoadjuvant chemotherapy and radiotherapy and the rest (five patients) did not receive neoadjuvant therapy. Also, we found that a good response to neoadjuvant

therapy associated with lower incidence of local recurrence.

Among the 99 patients included in our review, there was only one patient who had an infiltrated distal margin. This patient underwent completion of APR. Otherwise, all our patients have free proximal, distal, and circumferential margins.

The distal margin in our study was precisely measured in only 39 patients (in pathology report), while the other patients were mentioned only to have distal free margin. We had four patients with local recurrence after low anterior resection and we found no statistical relationship between the distance of free distal margin and local recurrence. We believe that this relation sounds logic because in all our patients, we achieved a pathologically free distal margin that goes with all the international guidelines for rectal cancer resection to achieve a free distal margin microscopically in all patients.

For instance, studies of Kang *et al.* [20], Han *et al.* [10], Bernstein *et al.* [21], Kiran *et al.* [22], Manegold *et al.* [12], and Rutkowski *et al.* [16] had compared groups according to distal free margin either less than 1 cm or more than 1 cm.

Kang *et al.* [20] reported that the distance between the distal free margin and local recurrence, 5-year disease-free survival, and 5-year overall survival was not connected; similarly, the connection between local recurrence and distal was not significant in our investigation.

Han *et al.* [10] reported that there was no link between the distance of the distal free margin and local recurrence or 5-year cancer-specific survival rates, according to the findings. In addition, we discovered that there was no significant association between local recurrence and distal free margin distance in our research.Manegold *et al.* [12] and Rutkowski *et al.* [16] also agreed to our findings. Compatible with our findings, Kiran *et al.* [22] compared not only 1-cm distal-free margin but also did a subgroup analysis of 0.5 distal-free margins.

However, Bernstein *et al.* [21] reported a significant association between less than 1-cm distal-free margin and local recurrence after adjustment of independent prognostic factors, while in our study, the relationship between the local recurrence and the distance of the distal-free margin was not significant.

On the other hand, studies of Ghahramani *et al.* [15], Grosek *et al.* [13], and Hong *et al.* [14] had compared groups according to distal-free margin either less than 2 cm or more than 2 cm.

Grosek *et al.* [13] and Hong *et al.* [14] reported no significant association between the distance of the distal-free margin and local recurrence. These results agree with our results that showed that there was not a significant relationship between the local recurrence and the distance of the distal-free margin.

However, Ghahramani *et al.* [15] stated that their results disagree with most studies. They reported a significant higher recurrence rate, recurrence-free survival, and mortality rates in less than 2-cm group.

Pahlman *et al.* [23] found no significant difference in local recurrence rate between 1 cm and more than 1-cm distal-free margins in a systematic assessment of seven trials (almost 600 patients). The distance of the distal-free margin is not a determinant in rectal cancer recurrence, according to data from various research. To assess variables, large multicenter propensity-scored cohorts or RCTs are required of local recurrence after low anterior resection.

Conclusion

In our research, we discovered that while a free distal margin is required in rectal cancer resection, there is no link between the distance of the free distal margin and local recurrence. We also discovered that lymphovascular invasion and responsiveness to neoadjuvant chemoradiation have a substantial impact on rectal cancer local recurrence rates.

Our research is limited to the TNM rectal cancer categorization, which has been reported in various investigations. In addition, we were unable to obtain data from 30 patients who did not complete the 2-year follow-up period. To precisely define the etiology of local recurrence after oncological resection of rectal cancer, more research with larger sample sizes and more matching factors are needed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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