Prognostic Factors Affecting Recurrence and Disease-Free Survival after Surgical Resection of Cancer Rectum

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Background: This retrospective study aimed to identify predictors of tumor recurrence and disease-free survival in patients who underwent curative surgery for rectal cancer.

Patients and methods: Authors analyzed data of 229 patients with rectal cancer who underwent curative surgery. Chi-square test and Binary logistic regression were used to identify factors predicting recurrence. Kaplan-Meier product-limit method was used to identify the relations between co-variables for time of tumor recurrence.. Cox Regression was used to multivariate analysis to detect the most significant factor predicting DFS.

Results: Factors predicting tumor recurrence were age, gender, lymphovascular invasion, the more advanced tumor stage, distal resection margin lesser than 1 cm, non-effective neoadjuvant therapy, not receiving Adjuvant therapy, greater Positive lymph node count, and greater lymph node ratio.

In Multivariate analysis, younger age, female gender, greater LNR were the main significant predictors of recurrence.

In Univariate analysis, factors significantly predicting Disease-free survival were Age, Histopathological Examination, Distal Resection Margin in cm, PLNC, Lymph node ratio, Effectiveness of Neoadjuvant therapy, Receiving Adjuvant therapy.

In Multivariate analysis, positive lymph node count and Adjuvant therapy were the main significant predictors of DFS.

Conclusion: Multivariate analysis identified younger age, female gender, and lymph node ratio (LNR) as the main significant predictors of recurrence. PLNC and Adjuvant therapy were the main significant predictors of DFS. Integrating identified predictors of rectal cancer recurrence and DFS into clinical practice might improve personalized management strategies and long-term outcomes. Identifying those factors might affect adjuvant-therapy decision-making and patient follow up planning.

Keywords: Colorectal cancer, lymph node ratio, recurrence, disease-free survival.

Introduction

Rectal cancer poses significant global health burden due to its prevalence and incidence. Colorectal cancer ranks second globally in cancer-related deaths.[1] Rectal cancer is responsible for approximately 30% of all colorectal cancers. Most cases are older individuals.[2] In Egypt, colorectal cancer is the 7th most common cancer standing for 3.47% and 3% of all male and female cancers, respectively.[3]

It is noted that rectal cancer is distinct from colon cancer in terms of risk factors and causes. The main risk factors of rectal cancer include type II diabetes, excess body fat, and high body mass index. Moreover, long-lasting rectal ulcerative colitis and Crohn's disease, and high consumption of tobacco and red meat, as well as alcohol consumption, can further increase the risk.[4]

The determination of an optimal treatment plan for rectal cancer patients is a complex process. The decision depends on the intent of the surgery, whether it is curative or palliative. Another crucial factor is the functional outcomes of the management, such as preserving genitourinary functions, the possibility of maintaining normal bowel function, and anal continence.[5]

To diagnose rectal cancer patient history, physical examination, digital rectal examination (DRE) and endoscopy with biopsy are mandatory. Concerning the metastatic workup, it is imperative to undertake a thorough renal and hepatic function test, complete blood count, computed tomography scan of the thorax and abdomen, and serum carcinoembryonic antigen. Positron emission tomography might provide further information on extension outside the pelvis, but it's considered not strong enough in all cases.[4]

It can be challenging to achieve a cure while minimizing the influence on the quality of life for distal rectal cancer cases. Furthermore, pelvic recurrence is more in rectal cancer than in colon cancer, and is related to a poor prognosis.[6]

Recurrence after curative surgery for rectal cancer is common, influenced by various co-factors. These risk factors can be attributed to the patient such as male gender and advanced age. However, the management plan may have a role in the recurrence incidence. The causes include surgical techniques with circumferential or distal margin involvement or inadequate pre and postoperative treatment use. The tumor itself is another important factor concerning the terms of advanced TNM stage, lymphatic involvement, vascular invasion, and poor differentiation.[7]

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Local recurrence occurs in 2.4–10% of rectal cancer operations. Regarding distant metastasis, it is established by the presence of tumor growth in any lymph node outside the pelvis.[7] Distant metastases have been reported in 20–50 % of cases, particularly in the lungs and liver. Fortunately, many cases can achieve cure treatment, thus efforts should target systemic disease prevention as distant metastases reduce survival. However, systematic follow-up effectiveness has not only been well documented but also tedious and expensive for the healthcare system and the patients. The American Society of Clinical Oncology (ASCO) guidelines recommend close follow-up for rectal cancer based on a conducted comparison between high-intensity and low-intensity colorectal cancer surveillance programs.[8]

Due to the progress in rectal cancer management, there has been a reduction in the local recurrence rate and an increase in the 5-year survival rate. Optimized preoperative staging, introduction of the multidisciplinary team (MDT) approach, and pre and postoperative radiotherapy and chemotherapy usage have greatly contributed to this progress.[7]

This study was conducted to identify factors predicting tumor recurrence and DFS in patients who underwent curative surgery for rectal cancer.

Patients and methods

This retrospective cohort study included 229 rectal cancer patients who were admitted to a tertiary care hospital and underwent curative surgery between 2012-2022. Sixty-nine of them received neoadjuvant therapy. The study was approved by local institutional ethical committee and was registered in https://clinicaltrials.gov/

The exclusion criteria included cases with familial adenomatous polyposis, multiple synchronous and metachronous rectal cancers

BAll cases were subjected to clinical evaluation, laboratory investigations including tumor markers, metastatic workup, and endoscopic tissue biopsy. Cancer stages were scored according to the American Joint Committee on Cancer (AJCC) Staging System, 8th edition.[9]

Demographic, histopathological, follow-up and outcome data were collected retrospectively for cases operated since 2012. The demographic information included age, gender, family history, and chief complaint at presentation. Histopathological data included tumor site, grade, LVI, LNC, PLNC.

The LNR was defined as the ratio of PLN to LNC in the histopathology specimen.

Surgical method of lymph node dissection: Total meso-rectal excision with high or middle level ligation of the inferior mesenteric artery was used. Lateral lymph node dissection was performed selectively in cases with suspicious enlarged lymph nodes.

Handling method for the specimen: The surgeon did not open the bowel segment. The specimen was oriented with sutures and then sent to the pathologist. The pathologist fixed the specimens in 10% formalin for at least 96 hours. Sampling from the tumor and radial, proximal and distal margins was performed. All LNs were identified by palpation and removed sharply by scissors and scalpel. Every single lymph node was bisected or trisected and submitted to paraffin sectioning, followed by microscopic examination. Immunohistochemistry and genetic testing were only performed for selected cases.

Follow-up: Follow up in outpatient clinic for 5 years for clinical evaluation, tumor markers follow up. Endoscopic and radiological investigations were done whenever needed.

Statistical analysis

SPSS version 26 (Statistical Package for Social Sciences, PSS Inc., Chicago, Illinois, USA) was used to analyze the collected data. Chi-square test was used in univariate analysis for factors predicting recurrence, Binary logistic regression Multivariate analysis was used to determine the main significant factors predicting recurrence.

The Kaplan-Meier product-limit method was used in univariate analysis for factors predicting DFS. Log Rank (Mantel-Cox) test was used for significance. All significant factors in univariate analysis were entered in the Cox regression Hazard model test to detect the main significant factors predicting DFS. p value < .05 was considered statistically significant.

Results

This retrospective study analyzed data from 229 rectal cancer cases who underwent curative surgery. A number of 121(52.8%) were males. Age was 18-85 (48.02±15.98) years. The most common site of the tumor was in the lower rectum in 88 (38.4%) procedure performed on 127 (55.5%) cases. cases. Low anterior resection was the most common Complications Were encountered in 60 cases. The most frequent was wound infection in 24 cases, Moderately differentiated adenocarcinoma was the most common histopathology present in 96 (41.9%) cases. LVI was present in 90 (39.3%) cases. Stage 3 rectal cancer was the most common staging in our cohort, in 135 (59%) cases. LNC was > 12 in 148 (64.6%) cases. LNC was 2-37 (13.22±6.464). PLN was 0-11) (3.94±2.658). In 39 (17%) cases, recurrence was recorded at 4-42 (13.67±9.742) months. The mortality rate was 35.4% (81 cases). Overall survival was 5-75 (25.93±14.806) months. Detailed results are presented in **Table 1.**

Table 1a: Demographic and pathological data of the studied group

Variable			Results
Age	Range		18-85
	Mean±SD		48.02±15.978
Gender (Number and percentage)	Female		108 (47.2%)
	Male		121 (52.8%)
Neoadjuvant therapy (Number and percentage)	No		160 (69.9%)
	Chemotherapy		4 (1.7%)
	Radiotherapy		4 (1.7%)
	Chemoradiation		61 (26.6%)
Lymphovascular invasion (Number and percentage)	No		139 (60.7%)
	Yes		90 (39.3%)
T Stage (Number and percentage)	T1		2 (9%)
	T2		40 (17.5%)
	T3		165 (72.1%)
	T4		22 (9.6%)
N Stage (Number and percentage)	N0		94 (41%)
	N1		67 (29.3%)
	N2		68 (29.7%)
Tumor Stage (Number and percentage	Stage 1		10 (4.4%)
	Stage 2		84 (36.7%)
	Stage 3		135 (59%)
Positive lymph node count	Range		0-11
	Mean±SD		3.94±2.658
Lymph node count	Range		2-37
	Mean±SD		13.22±6.464
Distal resection margin in cm	Range		0.5-8
	Mean±SD		2.616± 1.5562
Recurrence (Number and percentage)	No		190 (83%)
	Yes	Locoregional recurrences	26 (11.3%3)
		Distant Recurrence	13 (5.66%)
Disease-free survival in months	Range		4-42
	Mean±SD		13.67± 9.742
Survival in months	Range		5-75
	Mean±SD		25.93± 14.806

Table 1b: Demographic and pathological data of the studied group

Variable		Number of Patents (n= 229)	Percentage
Site of the tumor	Upper Rectum	85	37.1%
	Mid Rectum	56	24.5%
	Low Rectum	88	38.4%
Histopathological examination	Well differentiated adenocarcinoma	64	27.9%
	Moderately differentiated adenocarcinoma	96	41.9%
	Poorly differentiated adenocarcinoma	6	2.6%
	Undifferentiated adenocarcinoma	2	.9%
	Mucinous Carcinoma	54	23.6%
	Signet Ring Carcinoma	7	3.1%
LVI	No	139	60.7%
	Yes	90	39.3%
N Stage	N0	94	41.0%
	N1	67	29.3%
	N2	68	29.7%
	< 4	102	44.5%
	≥ 18.8%	173	75.5%

Table 1c: Demographic and pathological data of the studied group

Variable			Mean±SD
Age in years (Mean±SD)			48.02±15.978
Absolute LNC (Mean±SD)			13.22±6.464
Overall survival in months (Mean±SD)	Overall Survival in Months		25.93±14.806 (5-75)
	LNC cut-off value	≥ 12	28.21±15.432
		<12	22.22± 12.970
	PLNC cut-off value	≥ 4	21.71±11.597
		< 4	31.20± 16.634
	LNR cut-off value	Overall	32.067±20.34
		<18.8%	21.44±11.597
		≥ 18.8%	39.82± 16.634
	LVI	Present	24.80±13.337
		Absent	26.67± 15.687
Distal resection margin in cm			2.616±1.5562

Regarding factors affecting recurrence per se, the result of a univariate analysis using the chi-square and t-test analysis are shown in **Table 1**. Based on the univariate results, significant factors predicting tumor recurrence were age (p=.000), female gender (p=.036), LVI (p=.014), tumor stage ((p=.003), distal resection margin lesser than 1 cm (p=.03), non-effective neoadjuvant therapy regardless its type (p=.000), not receiving adjuvant therapy (p=.008), greater PLNC (p=.009), and greater LNR (p=.000). In binary logistic regression multivariate analysis, the main factors that significantly predicts tumor recurrence were younger age (p=.000), female gender (p=.001), greater Lymph node ratio LNR (p=.001) **(Table 2)**.

Table 2: Factors Predicting tumor recurrence after curative cancer rectum surgery

Covariates	Univariate	Multivariate analysis							
	p value	B	SE	Wald	df	p value	Exp(B)	95.0% CI for Exp(B)	
								Lower	Upper
Age	.000	-.097	.021	20.447	1	.000	.908	.870	.947
Sex	.036	-1.685	.517	10.639	1	**.001**	.185	.067	.510
Lymphovascular invasion	.014	.579	.516	1.258	1	.262	1.784	.649	4.907
Tumor stage	.003	-.933	.489	3.649	1	.056	.393	.151	1.025
Distal resection margin in cm	.03	-.080	.163	.239	1	.625	.923	.671	1.271
Neoadjuvant therapy	.0000	-.556	.601	.857	1	.355	.573	.177	1.861
Adjuvant therapy	.008	.595	.466	1.630	1	.202	1.813	.727	4.517
Lymph node ratio	.000	.048	.014	11.886	1	**.001**	1.049	1.021	1.078
Positive lymph node count	.009	.029	.108	.073	1	.787	1.030	.833	1.272

Regarding factors affecting DFS, In Univariate analysis, factors predicting DFS were Age (p=.000), Histopathological examination (p=.000), Distal Resection Margin In cm (p=.013), PLNC (p=.006), LNR (p=.004), The effectiveness of Neoadjuvant therapy (p=.003), receiving Adjuvant therapy (p=.004). In Cox regression Multivariate analysis revealed that the tested set of factors can successfully predict the time to recurrence (Statistically significant Omnibus Tests of Model Coefficients). PLNC (p=.034) and Adjuvant therapy (p= .024) were the main significant predictors of DFS **(Table 3).**

Table 3: Factors Predicting Disease-free survival after curative cancer rectum surgery

Covariates	**Univariate**	**Multivariate analysis**							
	p **value**	**B**	**SE**	**Wald**	**df**	p **value**	**Exp (B)**	**95.0% CI for Exp(B)**	
								Lower	**Upper**
Age	.000	.049	.025	3.726	1	.054	1.050	.999	1.104
Histopathological examination	.000	.094	.179	.278	1	.598	1.099	.774	1.562
Distal resection margin in cm	.013	.214	.168	1.628	1	.202	1.238	.892	1.720
Positive lymph node count	.006	.241	.113	4.513	1	**.034**	1.272	1.019	1.589
Lymph node ratio	0.004	-.009	.013	.431	1	.511	.991	.966	1.018
Neoadjuvant therapy	.003	-.187	.538	.120	1	.729	.830	.289	2.383
Adjuvant therapy	.004	-1.525	.675	5.107	1	.024	.218	.058	.817

Discussion

Recurrence following surgery for rectal cancer is a frequent event. The likelihood of recurrence, along with its timing, can be influenced by various co-factors. Factors contributing to recurrence include surgical methods that may involve circumferential or distal margin compromise, as well as insufficient neoadjuvant treatment protocols. Furthermore, tumor characteristics such as advanced TNM staging, LVI, and poor histological differentiation are critical determinants. Our study illuminated several factors significantly correlated with rectal cancer recurrence and DFS in cases undergoing rectal cancer surgery. Our study identified younger age, female gender, and lymph node ratio as independent predictors of tumor recurrence. Additionally, PLNC was identified as the paramount factor influencing DFS, underscoring its critical role in prognostic assessments for this patient population.

The current study included 229 rectal cancer cases who underwent curative, 121 (52.8%) of them were males. The cohort exhibited a mean age of 48.02 years (SD=15.98), ranging from 18 to 85 years. Based on our results, significant factors predicting tumor recurrence were younger age (p=.000) and female gender (p=.036). This result is in opposition to the findings of Du et al., who reported that older age (>60 years) was linked to decreased survival (HR=1.878, p<.001), possibly because tumors in younger patients in this cohort tend to be more aggressive. [10] Similarly, Heriot and Kumar determined that older males were at a higher risk for recurrence.[11] However, their evidence is not conclusive, and other studies dispute any influence of age or sex. [12] Additionally, Räsänen et al. did not report age as a significant factor, suggesting variability in its role across populations. [8] These discrepancies underline the need for further research to clarify the influence of age on rectal cancer outcomes. However, Du et al. found no significant association between gender and recurrence patterns or survival (p=0.113).[10]

A higher PLNC emerged as a significant predictor of recurrence in the current study (p=.009). Likewise, Du et al. reported a mean PLNC of 2.6±3.8, noting that retrieving fewer than 12 nodes was associated with specific recurrence patterns.[10] In alignment with that, Räsänen et al. recognized positive nodal status as a critical risk factor for distant metastases (HR=2.556, p<.0001).[8] Although Masaki et al. acknowledged the role of lymph node involvement, their analysis did not assess PLNC.[13] These findings emphasize the prognostic significance of nodal involvement, with the present study providing additional insights into its association with recurrence. Furthermore, a higher lymph node ratio (LNR) demonstrated a strong predictive value for recurrence in the current study (p=.000 in univariate analysis; p=.001 in multivariate analysis). While Du et al. did not specifically evaluate LNR, their observations regarding nodal involvement are consistent with its relevance as a refined prognostic indicator.[10] Similarly, Räsänen et al. emphasized the significance of nodal metastases in recurrence patterns, though they did not examine LNR directly.[8] Likewise, Masaki et al. acknowledged the prognostic importance of lymph node status but did not explicitly address LNR in their analysis.[13]

Our study reported another significant predictor of recurrence which was LVI. Supporting the prognostic importance of LVI, Räsänen et al. reported that vascular invasion significantly increased the risk of distant metastases (HR=2.722, p<.0001).[8] Similarly, Masaki et al. identified lymphatic invasion as a factor in univariate analysis but did not find it significant in multivariate analysis for specific recurrence sites.[13] It is established that the tumor stage is a cornerstone in predicting recurrence. As advanced tumor stage (T3/T4) significantly predicted recurrence in our study (p=.003). Consistent with that, Du et al. reported that the advanced primary tumor stage was associated with reduced survival (HR=1.498, p=.021).[10] Räsänen et al. also identified tumor stage as a significant factor for distant metastases (p<.0001). [8] Masaki et al. found that the depth of tumor invasion (T3/T4) significantly predicted local recurrence (p=.004).[13]

Regarding the terms of cancer treatment, achieving adequate margins remains critical for reducing recurrence risk. In our study, the distal resection margin < 1 cm was significantly associated with recurrence (p=.03). Räsänen et al. highlighted the importance of circumferential resection margins (CRM), with positive CRM significantly increasing the risk of local recurrence (HR=0.336, p=.003).[8] While Du et al. did not analyze margins below 1 cm, the mean distal margin in their cohort was 3.6±4.0 cm.[10] Masaki et al. emphasized the role of radial margin status in predicting local recurrence, with a significant correlation to specific recurrence types (OR=43.217, p<.001).[13] Moreover, our study demonstrated that non-effective neoadjuvant therapy significantly predicted recurrence (p =.000), regardless of its type. Du et al. noted that 30.6% of cases received preoperative chemoradiotherapy but did not evaluate its effectiveness.[10] Räsänen et al. observed variability in recurrence rates depending on the surgical approach, suggesting that treatment response and surgical quality collectively influence outcomes.[8] Masaki et al. focused on local recurrence patterns but did not specifically address the effectiveness of neoadjuvant therapy.[13] These findings highlight the importance of treatment response as a prognostic factor, emphasizing a gap in the literature addressed by the current study. Furthermore, not receiving adjuvant therapy was a significant factor in this study (p=.008). In contrast, Du et al. reported that only 21.7% of their cohort

received postoperative chemoradiotherapy, without assessing its impact on recurrence.[10] Räsänen et al. found that adjuvant chemotherapy was selectively administered and emphasized its role in high-risk patients.[8] Masaki et al. identified adjuvant chemotherapy as significant in univariate analysis for certain local recurrence types (p=.037).[13] This finding highlights the essential contribution of adjuvant therapy in enhancing long-term patient outcomes.

In conclusion, this study corroborates and extends the existing body of literature by identifying younger age, female gender, and lymph node ratio (LNR) as significant predictors of cancer recurrence. The disparities observed within the literature underscore the necessity for further investigation.

Conclusions

In the current study, multivariate analysis identified younger age, female gender, and lymph node ratio (LNR) as the main significant predictors of recurrence. PLNC and adjuvant therapy were the main significant predictors of DFS. Integrating identified predictors of rectal cancer recurrence and DFS into clinical practice might improve personalized management strategies and long-term outcomes. Identifying of those factors might affect adjuvant-therapy decision-making and patient follow up planning.

Ethical approval and study Registration

Ethical approval for this study was provided by the Ethical Committee of Faculty of Medicine, South Valley University, Qena, Egypt, in October 2022 IRB number SVU-MED-SUR011-4-23-4-621. The study has been registered at ClinicalTrials.gov with a Unique Identifying number or registration ID: NCT06096493 which found at: https://clinicaltrials.gov/study/NCT06096493

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Availability of data and materials

The dataset is available upon reasonable request.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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