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Factors Associated with Marginal Status among Patients with Colorectal Cancer Undergoing Colorectal Resection with Curative Intent at Muhimbili National Hospital

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Abstract

Background: Colorectal carcinoma is the third most diagnosed cancer globally and the second leading cause of death. It is the most common gastrointestinal malignancy. Its incidence increases with economic growth. Surgical resection, with or without adjuvant therapy, is the primary treatment.

Aim: To determine factors influencing surgical outcomes among patients with colorectal cancer undergoing colorectal resection for curative intent at Muhimbili National Hospital (MNH).

Methodology: A prospective cross-sectional study design was conducted from October 2022 to April 2023 and included all patients with colorectal cancer who had undergone colorectal surgery for curative intent at MNH. Demographic data, clinical presentation of the illness, treatment given before surgery, surgical procedure detail was collected using a structured questionnaire and checklist. Surgical outcomes such as resection margins status, surgical site infection, reoperation, and mortality were assessed within one-month post-operation. Data were analyzed using STATA, where measures of central tendency and frequency distributions were found and associations of variables were done by bivariate and multivariate analysis.

Results: A total of 139 patients were recruited. Of these, 75 were female (54.0%), and the mean age was 53.3±14.6. The overall rate of positive resection margins was 19.4%. Circumferential margins were positive in 13.7% of cases, distal margins in 7.2%, and proximal margins in 2.9%. Morbidity occurred in 30% of patients. This was defined as surgical site infections, peritonitis, intestinal obstruction, or acute kidney injury. The mortality rate was 10.8%. Patients who did not receive neoadjuvant therapy were 6.1 times more likely to have positive resection margins (OR 6.1). Positive microscopic nodal status was strongly associated with positive resection margins, with a 12.9-fold higher likelihood (OR 12.9) compared to negative nodal status. After adjusting for confounders, only microscopic nodal status and neoadjuvant therapy remained significantly associated with resection margin status. Patients with positive nodal status had an 11.6 times higher likelihood (OR 11.6) of positive resection margins. Those not receiving neoadjuvant therapy had a 5.6 times higher likelihood (OR 5.6).

Conclusion: Positive nodal status and omission of neoadjuvant therapy are strong predictors of positive resection margins in colorectal cancer surgery at our center. Challenges in achieving clear circumferential margins highlight the need for more precise surgical techniques and advanced perioperative care.

Keywords: *Colorectal cancer, Resection margins, Neoadjuvant therapy, Nodal status, Surgical outcomes, Postoperative complications, Curative resection, Colorectal surgery.*

Introduction

Colorectal carcinoma is the third most commonly diagnosed cancer worldwide and the second leading cause of death. It is the most prevalent gastrointestinal malignancy. In 2020, there were more than 1.9 million new colorectal cancer (CRC) cases and 935,000 deaths. The rate of CRC tends to increase with economic growth. Incidence rates are approximately 4-fold higher in developed countries compared with developing countries. However, mortality rates are higher in developing countries (1). An Increased incidence of CRC is observed in developing countries including Tanzania. This is associated with economic development, bringing lifestyle and dietary changes, such as greater intake of animal-source foods and a more sedentary lifestyle. Obesity, an independent risk factor for CRC, also increases (2). There are several therapeutic options for both rectal and colon cancers. Surgical resection and appropriate lymph node dissection remain the gold standard. In addition to surgical resection, there are other adjunct therapies which include radiation and chemotherapy (2).

The surgical technique for colorectal tumors depends on clinical stage and tumor location. Surgery can be performed by open or laparoscopic methods. Rectal cancer may be treated by local excision or radical excision (3). Post-operation complications such as anastomosis leak, ileus, infection, thrombosis, colon ischemia, intestinal obstruction, and post-site metastases are known independent risk factors for the overall survival of the patient and disease-free survival. Postoperative complications can worsen colorectal cancer survival and risk of recurrence (4,5). Several prognostic markers for colorectal resection, such as Tumour, Node, Metastasis (TNM) staging, age, co-morbidities, the number of lymph nodes examined, and neoadjuvant therapy, influence surgical outcomes. These factors have a significant impact on the healing process and hospital stay (6,7).

The rising incidence of colorectal malignancies has led to an increased demand for surgical resections. In this context, the National Hospital (MNH), faces the challenges associated with this growing caseload. However, there exists a significant gap in our understanding of the factors influencing surgical outcomes in colorectal resections, potentially undermining the quality of care for patients with colorectal malignancies and contributing to heightened treatment complications.

This study aims to bridge the knowledge gap regarding factors influencing surgical outcomes in colorectal cancer patients undergoing colorectal resection. Findings may help surgeons optimize patient selection, tailor surgical approaches, and refine techniques. These improvements may lead to better patient outcomes and higher success rates

Methods

Design and setting of the study

A prospective Cross-sectional study was conducted at MNH, a national hospital receiving referrals from different parts of the country. MNH is well-equipped with infrastructure and competent surgeons for colorectal surgeries. MNH's general surgery department admits patients in two firms with a bed capacity of 112, with well-equipped radiology and pathology departments. MNH is among hospitals with a

high volume of patients with CRC undergoing colorectal resection in Tanzania.

Target population

The study population consisted of all patients who underwent colorectal resection as a treatment modality for CRC at MNH. These patients were confirmed to have CRC through histological examination and had been subjected to surgical intervention.

Selection criteria

All CRC patients with confirmed histology who underwent colorectal resection.

Exclusion criteria

Patients with CRC who underwent a palliative operation and patients treated for a recurrent disease.

Sample size and data collection

A total of 139 participants were selected using a convenient sampling technique**.** Data were collected directly from the patients, through structured interviews using a questionnaire on demographic data, Clinical presentation of illness, course of illness, treatment given before surgery, and other relevant information. Patients were followed for one month following colorectal resection whereby surgical site infection, reoperation, and other post-operation complications were observed and documented. Follow-up was done in the ward before discharge and through the surgical clinic after discharge. Colonoscopy findings were obtained from the endoscopy reports, while histological diagnosis, resection margins, and the number of lymph nodes dissected were obtained from the histopathology report; other supportive investigations were retrieved from the Jeeva system. Intra-operative data, including complications, surgical type, and anesthetic details, were collected from intra-operative notes.

Data analysis

The data were analyzed using STATA software version 16. Numerical continuous data were presented by measure of central tendency, and categorical data were presented in frequencies and percentages. Stages of CRC at presentation to the hospital, Status of the resection margin, and post-operative complications among patients with CRC who underwent colorectal resection during the study period were described by frequency distribution tables and graphs. Factors associated with the status of the resection margin were determined by using a logistic regression model.

Ethical considerations

The study proposal was submitted to the instgitutional review board (IRB) at MUHAS as well as MNH for ethical clearance. The MUHAS Research Ethics Committee granted ethical clearance (Ref No. DA.282/298/01.C/1452, ethical clearance number MUHAS-REC-11-2022-1452), and Permission for Data collection was granted from the research and consultancy unit of MNH (Ref. No.: MNH/TRCU/Perm/2022/094). All the information gathered was kept private and used solely for research purposes. Participation in this study had no interference with the schedule for operation. Participants were told the study's aim. They were informed they could decline to participate or withdraw at any time without giving a reason and without risking their access to services.

Results

Patient Clinical-Demographic Characteristics

A total of 139 patients undergoing colorectal resection for malignancy and with curative intent were recruited. Females were 54.0%. The mean age was 53.3± 14.6. Thirty-five patients had comorbidities, and 69.2% of these had hypertension. Of 81 patients assessed for carcinoembryonic antigen (CEA), 48.2% had elevated levels. Patients who received neoadjuvant therapy were 28.1% (Table 1).

Tumor characteristics

Rectal tumors were present in 51.1% of patients. Positive lymph node status was identified in 52.8% of cases, and distant metastasis was found in 13.1%. Most tumors were T-3 (42.0%), followed by T-2 (34.6%). Patients presented to the hospital in stage III in 40.5% of cases and in stage IV in 27.0% (Table 2).

Status of resection margins

The overall positive resection margin was 27 (19.4%). The majority of the positive resection margins were circumferential resection margins of 19 (13.7%), followed by distal resection margins of (10, 7.2%) (Table 3).

Post-operative complications

42 patients (30%) developed postoperative complications. The predominant complication was surgical site infection in 28 (66.7%), followed by peritonitis in 5 (11.9%), other complications were intestinal obstruction, acute kidney injury, and pulmonary embolism in 9.5%, 9.5%, and 2.4%, respectively. The patient mortality rate was 10.8% (Table 4).

Factors associated with the status of resection margins

Patients with positive CEA had a 2.8 times higher risk of positive resection margins than those with negative CEA (p-value = 0.106). Patients who did not receive neoadjuvant therapy had a 6.1 times higher chance of having positive resection margins, with a statistically significant p-value of 0.017. Also, patients with T3 and T4 disease had a 3.2 times higher chance of positive resection margins than those with T1, and T2 disease, and finally, positive nodal status was strongly associated with positive resection margins, with a 12.9 times higher chance than nodal-negative patients. This finding was highly statistically significant, with a p-value of 0.001. Overall, these results suggest that adjuvant therapy, tumor stage, and nodal status are important factors to consider in predicting the likelihood of a positive resection margin in patients undergoing colorectal resection (Table 5.1).

After cofounders, nodal status and neoadjuvant therapy remained strongly associated with resection margins. Patients with positive nodal status had an 11.6-fold higher risk of positive resection margins than those with nodal-negative status. This finding was highly statistically significant, with a p-value of 0.004. Patients who did not receive neoadjuvant therapy had a 5.6-fold higher chance of having positive resection margins (p-value of 0.032) (Table 5.2).

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Table 1: Patients clinical-demographic characteristics

Patient Characteristic	Frequency	Percent (%)
Age		
Below 50	54	38.8
50 and above	85	61.2
Mean age 53.3 ± 14.6		
Sex		
Male	64	46
Female	75	54
Co-morbidity (n=35)		
Hypertension	22	62.9
Diabetes mellitus	5	14.3
HIV	8	22.8
Albumin level (n=70)		
Normal	40	57.1
Low	30	42.9
CEA (n=81)		
Normal 0-5ng/dl	42	51.8
Elevated >5ng/dl	39	48.2
Neo-adjuvant therapy		
Received	39	28.1
Did not receive	100	71.9
Category of operation		
Emergency	22	15.8
Elective	117	84.2

Key: SD- standard deviation, CEA-Carcinoembryonic antigen

Table 2: Tumor characteristics

Tumor characteristics	Frequency	Percent (%)
Tumor location		
Colon	71	51.1
Rectum	68	48.9
Nodal status (n=72)		
Positive	38	52.8
Negative	34	47.2
Metastatic status (n=130)		
M0	113	86.9
M1	17	13.1
Tumor T-status (n=107)		
TI	5	4.7
T2	37	34.6
T3	45	42.0
T4	20	18.7
Pathological staging(n=74)		
I	13	17.6
II	11	14.9
III	30	40.5
IV	20	27.0

Key: *M0-No Distant metastases, M1- Distant metastases, T1- Tumor invades sub-mucosa, T2- Tumor invades the muscularis propria, T3- Tumor invades pericolorectal tissue, T4- tumor invades visceral peritoneum or adjacent organ or structure.*

Table 3: Status of resection margin

Status of resection margins	Frequency	Percent (%)
Overall resection margin		
Positive	27	19.4
Negative	112	80.6
Proximal margins		
Positive	4	2.9
Negative	135	97.1
Distal margins		
Positive	10	7.2
Negative	129	92.8
Circumferential margins		
Positive	19	13.7
Negative	120	86.3

Table 4: Post operation complications

Complication (42)	Frequency	Percent (%)
Surgical site infection	28	66.7
Peritonitis	5	11.9
Intestinal obstruction	4	9.5
Acute kidney injury	4	9.5
Pulmonary embolism	1	2.4
Mortality 15 (10.8%)		

Table 5.1: Univariate logistic regression on factors associated with the status of resection margin

Variable	Cor	CI	P-value
Age			
Below 50	1	1	1
50 and above	1.3	0.554-3.254	0,513
Sex			
Male	1	1	1
Female	0.6	0.267-1.450	0.272
CEA			
Normal 0-5ng/dl	1	1	1
Elevated >5ng/dl	2.8	0.799-10.162	0.106
Albumin level			
Normal	1	1	1
Low	1.7	0.479-6.392	0.397
Neoadjuvant			
Received	1	1	1
Did not receive	6.1	1.385-27.447	0.017
Category of operation			
Emergency	1	1	1
Elective	2.2	0.817-6.26	0.116
Location of tumor			
Rectum	1	1	1
Colon	1.6	0.715-3.937	0.234

Tumor T status			
T1&T2	1	1	1
T3 &T4	3.2	1.325-8.137	0.01
Nodal status			
Negative	1	1	1
Positive	12.9	(2.707-61.955)	0.001

Key: *cOR - Crude Odds Ratio, CI - Confidence Interval, T1- Tumor invades sub-mucosa, T2 Tumor invades the muscularis propria, T3- Tumor invades pericolorectal tissue, T4- tumor invades visceral peritoneum or adjacent organ or structure.*

Table 5.2: Multivariate logistic regression on factors associated with the status of resection margin

Variable	cOR	CI	P-value	aOR	95% CI	P- value
CEA						
Normal 0-5ng/dl	1	1	1	1	1	1
Elevated >5ng/dl	2.8	0.799-10.162	0.106	1.7	0.421-7.035	0.449
Neoadjuvant						
Received	1	1	1	1	1	1
Did not receive	6.1	1.385-27.447	0.017	5.6	1.159-27.824	0.032
Tumor T status						
T1&T2	1	1	1	1	1	1
T3 &T4	3.2	1.325-8.137	0.01	1.9	0.678-5.654	0.214
Nodal status						
Negative	1	1	1	1	1	1
Positive	12.9	2.707-61.955	0.001	11.6	2.228-61.190	0.004

Key: *cOR - Crude Odds Ratio, aOR adjusted Odds Ratio CI - 95% Confidence Interval, T1- Tumor invades sub-mucosa, T2- Tumor invades the muscularis propria, T3- Tumor invades pericolorectal tissue, T4- tumor invades visceral peritoneum or adjacent organ or structure.*

Discussion

This study investigated the Factors Associated with Marginal Status among Patients with CRC undergoing colorectal resection with curative intent at MNH. The results revealed that several factors play a significant role in determining the resection margin status, including neo-adjuvant status, nodal status, and tumor stage. The study was done at MNH between October 2022 and April 2023. A total of 139 patients with CRC who had undergone colorectal resection were recruited. Males were 64 (46.0%) and females were 75 (54.0%); these results are different from the study done at Bugando Medical Centre, which showed a higher prevalence in males by 60.8%, and another study done in northern parts of Tanzania, which showed a higher prevalence in males by 62.1%. The mean age was 53.3±14.6. These findings are similar to those of the study conducted in the northern parts of Tanzania, which revealed that 58.2% occurred in people 50 years of age and older, and the mean age was 54.28 ± 16.75.(12,16)

The tumor location was in the rectum in 71 (51.1%) and colon in 68 (48.9%). Metastatic status was M0 in 115 (82.7%) and M1 in 14 (10.1%); findings similar to those reported in a

study done in Ethiopia, with unknown nodal status of 57.1%, M0 54.5%, and M1 33.9%. (17). The majority of patients presented late to the hospital, where 45 (42.0%) presented with a T3 disease and 20 (18.7%) with a T4 disease. Pathological staging was unknown in 65 (46.8%), partly due to inadequate histological assessment; the majority of these cases were due to inadequate lymph node dissection. Patients presenting in stages I, II, III, and IV were 13 (17.6%), 11 (14.9%), 30 (40.5%), and 20 (27.0%), respectively. These findings are similar to those reported in a study done in Ethiopia: T3 46.7%, T4 26.8%.(17).

With the overall positive resection margin rate of 19.4%, it is evident that achieving complete tumor removal remains a challenge in a substantial proportion of cases. Notably, the majority of positive margins were found to be circumferential resection margins (13.7%), indicating that ensuring clear margins along the outer circumference of the tumor represents a key area for improvement. Similar findings were found by M. Ashraf Balbaa and colleagues, where the most common positive resection margins were 34% for circumferential resection margins as compared to 12% for longitudinal margins. These findings call for a closer examination of surgical techniques and the potential need for more comprehensive preoperative strategies to reduce the incidence of positive resection margins in rectal tumor resections. Further research and clinical interventions may be warranted to enhance patient outcomes and minimize the risk of local recurrence.(18)

Postoperative complications are a significant concern in surgical procedures. This study revealed that 30% of patients developed postoperative complications, with the most predominant being surgical site infection at 66.7%, followed by peritonitis at 11.9%. Additional complications such as intestinal obstruction, acute kidney injury, and pulmonary embolism were also observed, though at lower rates. Notably, the mortality rate stood at 10.8%. This is similar to findings reported from Bugando, with the incidence of postoperative complications at 26.2%, with a lower rate of surgical site infection accounting for 41.9% of cases. Moreover, they noted that 5.5% of their patients required additional operations for various reasons, including perineal wound breakdown, intra-abdominal abscess or peritonitis, and anastomotic breakdown. Their recorded mortality rate was 10.5%. These findings highlight the importance of rigorous postoperative care to improve patient outcomes in surgical settings.(12).

In this study, patients who did not receive adjuvant therapy had a 6.1 higher chance of having a positive resection margins (p-value = 0.017), which was statistically significant. This suggests that a relationship between positive resection margins and operating on patients who did not receive adjuvant therapy is strong. The study also found that T status played part in influencing the resection margins after surgery. Our analysis indicates that, T3 and T4 disease had a 3.2 risks or chances of positive resection margins compared to T1 and T2 disease. (p-value = 0.001) which is statistically significant. Positive nodal status had a 12.9 chance of having a positive resection margin compared to nodal negative results, with a p-value of 0.001, which is statistically significant.

These findings corroborate the existing literature, as patients with positive nodal status are associated with a higher likelihood of positive resection margins compared to their nodal-negative counterparts.(19)

These findings align with a study conducted by Smith et al.in the United States who noted a strong correlation between positive nodal status and positive resection margins in colorectal surgery. Additionally, a comprehensive meta-analysis by Li and colleagues further supports our research by highlighting the global significance of nodal involvement in surgical outcomes. Patel et al.in the United Kingdom, emphasized the role of neoadjuvant therapy in achieving clear resection margins and improved patient outcomes. (20,21)

This study provides valuable insights into the factors that influence surgical outcomes among patients undergoing colorectal resection. The findings suggest that presentation to the hospital with an early disease stage without lymph node involvement and receiving neoadjuvant therapy reduces the chance of having positive resection margins. Further studies are needed to explore the association between resection margin and survival rate in our settings.

Conclusion

The findings of this study have brought to light the substantial influence of key factors, namely nodal status, the administration of neoadjuvant therapy, and the staging of tumors, on the status of resection margins. Achieving clear resection margins continues to be a formidable challenge in a significant percentage of cases, with particular emphasis on the concern surrounding circumferential resection margins.

Recommendations

This study underscores the importance of early CRC detection, neo-adjuvant therapy, and optimized surgical techniques in improving resection margins and patient outcomes. Adequate lymph node dissection and enhanced postoperative care are crucial in reducing complications. Future research should explore survival outcomes based on margin status within the Tanzanian healthcare setting.

Study limitations

Around half of patients 69 (49.6%) were not assessed for serum albumin levels, and 58, (41.7%), were not assessed for CEA, which are important prognostic factors for surgical outcome in colorectal resection. Inadequate histological assessment and reporting, inadequate lymph node dissection have contributed to a high proportion of unknown pathological staging, affecting assigning appropriate TNM staging.

Abbreviations

CEA: Carcinoembryonic Antigen

CRC: Colorectal Cancer

HIV: Human immunodeficiency virus

MNH: Muhimbili National Hospital

MUHAS: Muhimbili University of Health and Allied Sciences

TNM: Tumor, Nodes, and Metastases

SD: Standard deviation

Authors' Contributions

RHK, PNK, AM, MM participated in study conception, design and data interpretation. RHK & PNK acquired and analysed data, and prepared the first draft of the manuscript. All authors revised and provided inputs for and approved the final manuscript.

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