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RESEARCH ARTICLE

The Impact of Body Mass Index on the Oncological Outcomes of Locally Advanced Rectal Cancer: A Comparative Study in a Country with High Obesity Rates

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ABSTRACT

Aim: To evaluate the effect of body mass index (BMI) on the short- and long-term oncological outcomes and postoperative complications of patients with rectal cancer who underwent total mesorectal excision (TME) following neoadjuvant chemoradiotherapy (NACRT). Obesity is a known risk factor for colorectal cancer. Patients classified as obese are more likely to have increased morbidity and prolonged hospitalization; this is particularly relevant in Jordan-a country ranked high in the worldwide obesity index.

Method: A retrospective cohort of 294 patients with locally advanced rectal cancer (stage 2 T3/4 node negative or stage 3 node positive) who underwent TME after NACRT between 2006 and 2018 was divided into two groups (obese: ≥30 kg/m^2 and non-obese: <30 kg/m^2) according to BMI. Clinicopathological comparisons between the groups were performed in addition to a survival analysis, which was plotted on a Kaplan-Meier curve. The main outcomes were disease-free survival (DFS) and overall survival (OS), and the secondary outcomes were complete pathological response (pCR) and post-operative complications.

Results: There were 140 and 154 patients in the non-obese and obese groups, respectively. The mean age of the entire cohort was 54.2 years, the mean BMI was 28.4 kg (+/– 6.1), and the median time interval between NACRT and surgery was 10.3 weeks (interquartile range: 8.4, 13.4). The mean follow-up period was 42 months. Both groups had similar baseline clinicopathological characteristics. Patients with obesity were more likely to achieve a pCR (p=0.034) and have a higher percentage of positive lymph nodes in their resected specimens (p=0.05). Patients with obesity also had a higher risk of developing incisional herniation but not other complications (p=0.018). OS was comparable between the groups, while DFS was higher in patients with obesity.

Conclusion: In our local cohort of patients, obesity affected incisional hernia formation. It did not have an impact on OS; however, the patients in the obese group had higher DFS and pCR rates than those in the non-obese group.

Keywords: Obesity, BMI, neoadjuvant chemoradiotherapy, total mesorectal excision, rectal cancer, rectal surgery, survival

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common cause of cancer mortality.[1] In Jordan[2], it is the most common cancer among men and the second most common among women. Obesity has been identified as a risk factor for the development of CRC and has also been significantly associated with cardiovascular, metabolic, and respiratory morbidity.[3,5] It may lead to an increased risk of intraoperative and postoperative complications,[4] and intraoperatively, it is likely to yield a higher rate of conversion and prolonged surgical duration.[5] Jordan is ranked the 13th most obese country in the world, with a rate of 35.5% among adults.[6] With the rising number of obesity cases, the World Health Organization (WHO) declared obesity a global epidemic in 1997, with even higher projections for the next decades as the obesity rate tripled between 1975 and 2016.[7]

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The primary objective of this national study was to evaluate the effect of body mass index (BMI) on the oncological outcomes of patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy (NACRT) followed by total mesorectal excision (TME). The secondary objective was to assess the impact of BMI on postoperative morbidity and pathological response.

Materials and Methods

The study utilized a retrospective design to evaluate a cohort of patient records. Cases were selected from the King Hussein Cancer Center (KHCC) Registry-a tertiary care center. Data, including the patients' characteristics, clinical and pathological findings, and clinical outcomes, were retrospectively retrieved from prospectively maintained electronic patient records. The impact of BMI on treatment outcomes encompassing operative morbidity rate, complete pathological response (pCR), disease-free survival (DFS), and overall survival (OS) was investigated.

Patients with locally advanced rectal cancer (stage 2 T3/4 node negative or stage 3 node positive) who completed NACRT followed by curative rectal surgery between 2006 and 2018 were identified. Patients who underwent rectal surgery as part of a staged or simultaneous approach for metastatic disease were excluded. Patients with incomplete records were ineligible to participate in this study.

Our patients were assessed by a consultant surgical oncologist. Staging investigations included colonoscopy and biopsy; computed tomography of the chest, abdomen, and pelvis; and magnetic resonance imaging of the pelvis. Rectal tumors were defined as those at a distance of less than 12 cm from the anal verge.

All patients with stage 2 and 3 disease were considered for NACRT according to our institution's guidelines. The radiotherapy dose was 45-50.4 Gy over 25-28 fractions spanning five to six weeks. The chemotherapy regimen was capecitabine based on the daily continuous infusion of 5-fluorouracil (200-225 mg/m^2) over 24 hours or oral capecitabine (825 mg/m^2) twice daily for five days per week for five weeks. Patients with locally resectable non-metastatic disease underwent TME at six to eight weeks after NACRT either laparoscopically or through an open approach. All patients received and completed postoperative adjuvant chemotherapy.

Ethical Considerations

This retrospective cohort received approval from the Institutional Review Board at King Hussein Cancer Center (approval number: 17KHCC42). The King Hussein Cancer Center Institutional Review Board is guided by the principles described in the World Medical Association's Declaration of Helsinki (1964) and its amendments. Due to the retrospective nature of the study and the lack of personal or clinical details of participants that could compromise anonymity, the need for consent was waived.

Definitions

For cancer recurrence, mortality indices, and BMI, the following definitions were utilized:

Disease-Free Survival

DFS was defined as the time from surgical resection to radiological evidence of disease recurrence (including loco-regional failure or metastases) or death by any cause. Loco-regional failure was defined as anastomotic site tumor recurrence in the residual rectum or intrapelvic relapse. Any form of extra-pelvic recurrence was deemed a distant failure.

Overall Survival

OS was defined as the time interval from surgical resection to either death from any cause or the final follow-up.

Body Mass Index

BMI was calculated as the patient's weight on the first day of neoadjuvant treatment (in kilograms) divided by the patient's height squared (in meters). Patients' BMI-the most widely used indicator of obesity-was used to subdivide patients with rectal cancer into two categories: BMI <30 kg/m^2 and BMI ≥30 kg/m^2, the latter of which is defined as obese according to the WHO's classification.

Statistical Analysis

Data were analyzed using the SPSS 24 (Chicago, Illinois, USA) software package. Results were expressed as medians and interquartile ranges. Comparisons between the two groups were performed using an χ^2 test for categorical variables and a t-test for continuous variables. Survival functions were compared using the non-parametric Kaplan-Meier estimator. Significance was accepted at the 5% level.

Results

A total of 294 patients were included in the study: 154 patients with BMI ≥30 kg/m^2 and 140 with BMI <30 kg/m^2. The population comprised 171 (58.2%) males and 123 (41.8%) females. The mean age at diagnosis was 54.2 years. The majority of patients (89.1%) (n=262) presented in stage 3. Both groups were similar in terms of tumor site in the rectum (p=0.900). The patients' clinicopathological characteristics are presented in Table 1. Patients with obesity and rectal cancer were at a higher risk of having diabetes mellitus and hypertension (p<0.01). There was no significant difference in the presence of other comorbidities (Figure 1).

Table 1. Patients' clinicopathological characteristics

Name	Value	Total, 294	Non-obese, (n=140) (47.6%)	Obese, (n=154) (52.4%)	p-value
Age	≤50 y	104	49	55	0.407
	50 to 65 y	128	57	71	
	≥65 y	62	34	28	
Gender	Male	171	88	83	0.120
	Female	123	52	71	
Clinical stage	2	32	17	15	0.516
	3	262	123	139	
Tumor site (AV)	0-4 cm	58	28	30	0.900
	>4-10 cm	144	69	75	
	10-12 cm	11	4	7	
	N/A	81	39	42	
Pathological stage	0	28	6	22	0.041
	I	48	22	26	
	II	98	54	44	
	III	118	57	61	
	IV	2	1	1	
Treatment response	Complete	28	6	22	0.034
	Partial	128	65	63	
	Stable disease	131	65	66	
	Disease progression	7	4	3	
Surgery type	APR	79	31	48	0.081
	LAR +/– stoma	215	109	106	
Margin	Positive	15	9	6	0.442
	Negative	279	139	140	
Lymph node harvest (mean)			17	18	0.122
Lymph node positivity (mean)			1.4	2.4	0.05

AV: Anal verge, APR: Abdominoperineal resection, LAR: Low anterior resection

There was no difference between the groups in terms of the stage of disease at presentation. The median time interval between NACRT and surgery was 10.3 weeks [interquartile range (IQR): 8.4, 13.4]. The majority of patients (n=215, 73.1%) underwent low anterior resection with or without a stoma compared with 79 (26.9%) who underwent abdominoperineal resection. Patients in the obese group were more likely to achieve a pCR (p=0.034) and have a lower pathological stage after resection (p=0.041). The median number of lymph nodes harvested was not statistically different between the groups (non-obese: 17 vs obese: 18) (p=0.122). However, the percentage of lymph node involvement was higher in the obese group (2.4 vs 1.4, p=0.05).

The short- and long-term postoperative outcomes are summarized in Table 2, which shows that the patients with obesity had a higher rate of developing an incisional hernia (11.0% vs 4.0%, p=0.008), but not other complications, than those without obesity.

At a mean follow-up of 42 months, loco-regional and distant failure occurred in 60 patients (16 local and 44 distant recurrences) (non-obese: n=36, obese: n=24, p=0.090). The DFS curve showed a statistical difference in favor of the obese group of patients (Figure 2, Table 3). At the five-year follow-up, only 56% of patients in the non-obese group had no events related to their disease compared with 78% of those in the obese group (p=0.033). The OS at five years was

similar in both groups (non-obese: 73.9% vs obese: 80%, p=0.119) (Figure 3, Table 4).

Discussion

To the best of our knowledge, this is the first study examining the effect of obesity on rectal cancer oncological outcomes in a Middle Eastern population. As our population has a high obesity rate and a younger age at cancer diagnosis, we considered that it was important to investigate a causal relationship.

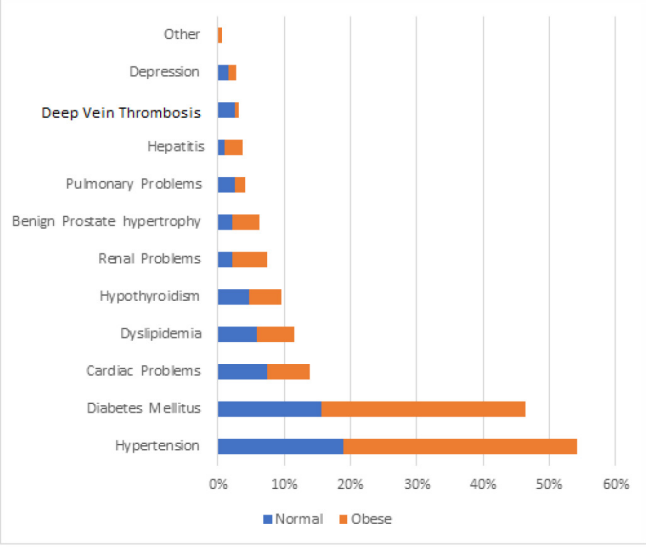

Figure 1. Comparison of co-morbidities

Obesity is well linked to increased CRC risk, which becomes more accentuated the higher the BMI.[3] It has also been shown to increase the risk of conversion to an open approach during surgery, with increased operative times and blood loss. A higher likelihood of post-operative complications has also been shown in several studies.[8,9] Additionally, obesity increases the rate of adverse events, including mortality, during chemotherapy.[10]

Despite the increased risk of developing cancer, multiple publications have failed to show negative effects on oncological outcomes. An Irish study on 414 patients with CRC showed no difference in DFS or OS between patients with and without obesity.[11] In a Japanese study on 263 patients with rectal cancer who underwent surgery, obesity (defined in the Asian population as BMI ≥25 kg/m^2) was associated with a significantly lower incidence of distant metastases (6.7% vs. 19.7%, heart rate: 0.32; 95% confidence interval: 0.11-0.94; p=0.04).[12] Another study from New York also mentioned no impact on oncological outcomes, with an obese group of patients having longer operative times.[13] This result has been further replicated in other published studies.[14-16]

Our findings suggest a positive association between obese BMI and oncological outcomes. This was previously reported by Chang et al.[17] in a systematic review of studies on rectal cancer. Our study also showed a positive correlation between obesity and pCR, a result that has also been published in a study by Lee et al.[18] from Korea.

Table 2. Post-operative events

		Total	Non-obese, (n=139) (47.6%)	Obese, (n=153) (52.4%)	p-value
SSI	Yes	42	15	27	0.095
	No	252	125	127	
Intra-op blood transfusion	Yes	2	2	0	0.137
	No	292	138	154	
Hernia	Yes	27	7	20	0.018
	No	267	133	134	
VTE	Yes	5	2	3	0.731
	No	289	138	151	
Stoma	Yes	19	8	11	0.619
	No	275	132	143	
Metastasis	Yes	44	26	18	0.098
	No	250	114	136	
Recurrence	Yes	16	10	6	0.220
	No	278	130	148	

SSI: Surgical site infection, VTE: Venous thromboembolism

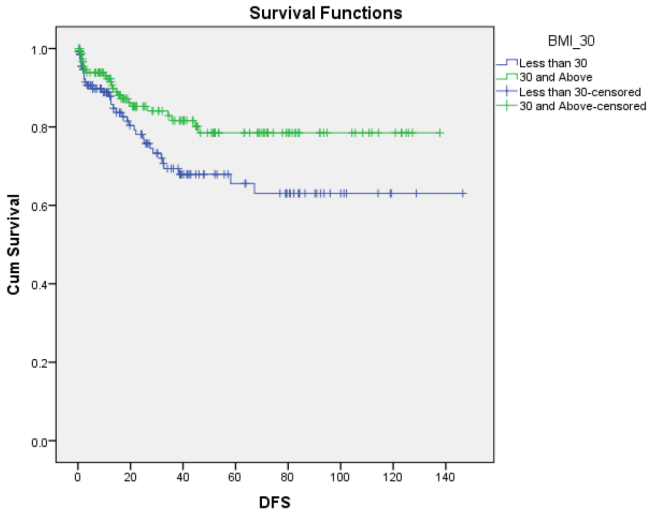

Figure 2. Disease-free survival Kaplan-Meier curve (p=0.033)
BMI: Body mass index, DFS: Disease-free survival

Table 3. Disease-free survival rate

BMI	42 months (3.5 years)	60 months (5 years)
<30	67%	56%
≥30	81%	78%

BMI: Body mass index

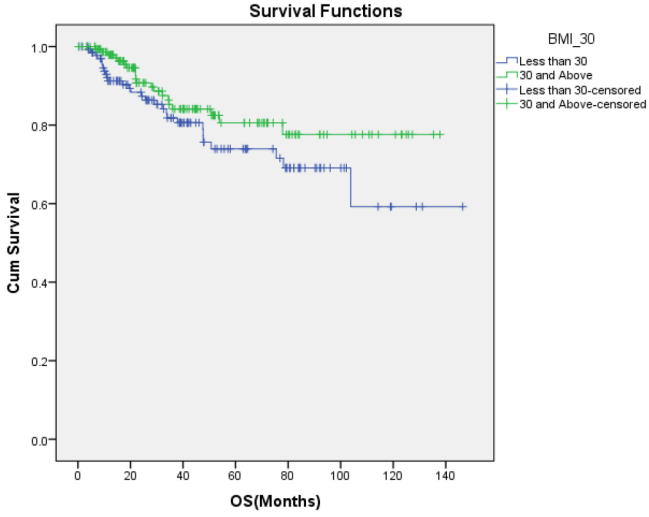

Figure 3. Overall survival Kaplan-Meier curve (p=0.119)
BMI: Body mass index, OS: Overall survival

The literature has attributed this phenomenon to the state of chronic inflammation, evident in the increased number of macrophages and cytokines as adipose tissue harbors a high number of macrophages, resulting in the subsequent increased production of inflammatory cytokines.[19] Thus, the interaction between obesity and immune response is

Table 4. Overall survival rate

BMI	42 months (3.5 years)	60 months (5 years)
<30	80%	73.9%
≥30	84%	80%

BMI: Body mass index

believed to alter a tumor's microenvironment and increase its response to radiotherapy. A protective nutritional effect in well-nourished patients with CRC translating into reduced operative complications may be implied, as patients with obesity may tolerate the weight loss associated with cancer and its treatment.[20]

The degree and pattern of obesity faced in Middle Eastern and Asian populations differ significantly from those of their Western counterparts. Ethnic differences in body composition and obesity patterns are well established in the literature.[21,22] Although our study did not consider BMI as a continuous variable when investigating the impact of obesity on oncological and post-operative complications, patients with mild obesity in Asian and Middle Eastern ethnic groups may represent a state of good nourishment or over nourishment rather than major perioperative morbidity.

Choi et al.[23] found obesity to be the only independent predictor for reduced local control. Clark et al.[24] reported visceral adiposity rather than BMI as an increased risk factor for recurrence after NACRT in rectal cancer, which was explained by limited surgical visibility in subjects with obesity. The largest European retrospective cohort (n=406 patients) evaluating the influence of visceral obesity on postoperative complications in rectal cancer surgery established a significant association between visceral obesity, intraoperative blood loss, postoperative complications, and an increased length of hospitalization.[25] Visceral fat is strongly linked to metabolic disease and insulin resistance even in patients with a normal BMI. Subcutaneous fat does not share the same risks and may be protective. Moreover, obesity induced by following a high-fat diet triggers low-grade inflammation, whereby macrophages include insulin resistance.[26]

The obesity paradox is well known in the literature, having been demonstrated in critically ill patients with chronic medical conditions and also in post-coronary procedures.[27-34] This has been also demonstrated by Mullen et al.[35], where patients with obesity had a lower risk of mortality after non-bariatric surgery.

Study Limitations

Although this study is limited by its retrospective nature, the KHCC remains the only tertiary center in Jordan

that guarantees well-documented long-term follow-ups involving a thorough clinical exam with appropriate labs and imaging modalities. We also acknowledge that we used post-diagnosis BMI, where the weight of patients was affected by their disease before presenting to our care. A pre-diagnostic BMI would have been more valid; however, it would not have been as accurate to use because of possible recall bias, as most patients asked did not have documented recent BMIs.

Conclusion

Obesity in patients with rectal cancer treated with NACRT and surgery was associated with an improved likelihood of a pCR and DFS. Our study's findings correspond with those already published in the literature and reinforce the obesity paradox in rectal cancer.

Ethics

Ethics Committee Approval: This retrospective cohort received approval from the Institutional Review Board at King Hussein Cancer Center (approval number: 17KHCC42). The King Hussein Cancer Center Institutional Review Board is guided by the principles described in the World Medical Association's Declaration of Helsinki (1964) and its amendments.

Informed Consent: Consent was waived, and the study was approved by the IRB of KHCC.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.M., A.M., B.A., Concept: M.A.M., Design: M.A.M., Data Collection or Processing: A.M., Analysis or Interpretation: M.A.M., A.M., B.A., Literature Search: M.A.M., A.M., B.A., Writing: M.A.M., A.M., B.A.

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