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Original research

The impact of metabolic syndrome on outcome and response to neoadjuvant chemoradiation in locally advanced rectal cancer patients

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HIGHLIGHTS

- The importance of metabolic syndrome risk factors on rectal cancer treatment response.
- Hypertension has a significant negative effect on tumor response and surgical complications.
- Importance of focusing on pre-treatment risk factor control prior to rectal cancer treatment.

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ABSTRACT

Background and objectives: Metabolic syndrome (MetS) is a constellation of cardiovascular risk factors shown to increase the risk of developing various malignancies, as well as diminish tumor response to conventional therapies. The effects of MetS and its individual components on therapeutic response and treatment-related outcomes were examined in patients with locally advanced rectal cancer (LARC).
Methods: Data was retrospectively collected on LARC patients treated with neoadjuvant chemoradiation (nCRT) and surgery. Medical records were reviewed for patient characteristics, staging, treatment plan, and outcomes.
Results: One hundred two patients were included in the study. Patients with HTN had a significantly decreased nCRT response and were four times more likely to experience a poor response to treatment compared to patients without HTN. Additionally, HTN was found to significantly increase the rate of surgical complications. Neither DM nor obesity exhibited any significant effect on therapeutic response or complication rates, either individually or in combination with another risk factor.
Conclusion: This study demonstrates the importance of considering underlying MetS risk factors, especially HTN, when predicting tumor response in LARC patients undergoing nCRT followed by radical surgery. The results provide support for an increased focus on pre-treatment risk factor control to optimize cancer therapy outcomes.

1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in the United States [1]. Current treatment strategies for locally advanced rectal cancer (LARC) involve neoadjuvant chemoradiation (nCRT) followed by radical resection [2–4]. However, response to treatment is variable. Only 60% of patients demonstrate any response to treatment. A complete response leaving no residual tumor is achieved in only 10–30% of patients [2]. The various factors influencing tumor response are poorly understood.

In 1988, insulin resistance was first recognized to play a role in the etiology of diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, and ultimately cardiovascular disease [5].

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Originally described as "Syndrome X", this constellation of cardiovascular risk factors constitutes what is now known as metabolic syndrome (MetS). The well-accepted definition by the National Cholesterol Education Program Adult Treatment Program III (ATP III) requires three of the following medical conditions: abdominal obesity, high fasting glucose, hypertension, hyperlipidemia, and hypertriglyceridemia [6]. Recent studies have demonstrated that MetS-related factors such as obesity, hyperinsulinemia, hypertension, and hypercholesterolemia can increase the risk of developing various malignancies, as well as diminish tumor response to conventional therapies [7]. Although the exact mechanism is unknown, metabolic syndrome has been proposed to exert its effects by promoting carcinogenesis and decreasing treatment response through insulin resistance, inflammation, and increased insulin-like growth factors [8].

A prior study examined the effect of metabolic syndrome and its components on recurrence and survival in colon cancer. Diabetes mellitus was found to have a significant adverse effect on overall survival (OS) and disease-free survival (DFS) in patients with advanced colon cancer. Additionally, the study found that the presence of HTN was independently associated with worse OS and DFS in patients with early-stage disease [9].

Based on literature searches, no prior studies have examined factors affecting OS and DFS such as nCRT response and complication rates in the setting of metabolic syndrome. To address this research gap, the current study examined the effect of MetS and its individual components on therapeutic response and treatment-related outcomes in LARC patients. It was hypothesized that LARC patients with metabolic syndrome would demonstrate decreased response to neoadjuvant chemoradiation as well as have increased treatment and surgical-related complications compared to patients without metabolic syndrome. Given the prior findings highlighting the impact of HTN on outcomes and survival in CRC, the independent role of HTN on treatment response in LARC patients was also explored.

2. Methods

An IRB-approved single institution retrospective review of patients with LARC between 1996 and 2010 was performed. Hospital and clinic notes, pathology, operative logs, radiology reports, and laboratory values were reviewed. Data collected included demographics, body mass indices (BMI), random blood glucose measurements, blood pressure, past medical history, staging studies and results, neoadjuvant therapy, surgical therapy, pathology, complications of both neoadjuvant therapy and surgery, and recurrence. Patients were defined as having DM based on past medical history or medications. A diagnosis of HTN was based on past medical history, medications, or systolic blood pressure (SBP) recorded >140. Due to the retrospective limitations of patient records, the level of DM or HTN control due to medication adherence could not be ascertained. Obesity was defined as a body mass index greater than or equal to 30 (BMI $\geq$30).

One hundred two LARC patients treated with neoadjuvant chemoradiation followed by radical resection were identified. Patients underwent initial tumor, nodal, metastasis (TNM) staging based on endoscopic ultrasound (EUS), computerized tomography (CT), and/or magnetic resonance imaging (MRI). Tumor staging following nCRT was determined by surgical pathology following resection. Tumor response was characterized as a pathologic complete response (CR) if there was no pathologic evidence of residual tumor following nCRT. A partial response (PR) was defined as tumor downstaging by 2 T stages or any N stage. Any response (AR) was defined as either a partial or complete response. No response (NR) was defined as no change in stage compared to pre-treatment EUS. The associations between aspects of metabolic syndrome and response to nCRT as well as treatment and surgical complications were examined.

Demographic characteristics were compared between MetS and non-MetS patients via t-tests or Chi-square tests, as appropriate. Logistic regression models were then used to determine whether there were any associations between metabolic syndrome factors and outcomes of interest, including surgical complications and response to nCRT. All models were adjusted by age, race, and gender. Initially, adjusted models only included one metabolic syndrome factor, and all three factors (HTN, BMI>30, DM) were examined individually. Factors that showed a significant relationship with outcome were then combined with a second factor, and the interaction between the two components was reviewed to determine how having multiple factors of metabolic syndrome impacted the outcome. All three factors were not examined together given the study size and the lack of ability to detect differences.

3. Results

3.1. Demographics

A total of one hundred two patients were included in this study. Examination of the individual MetS components revealed 51 patients had HTN, 19 patients had DM, and 26 patients had a BMI>30. Six patients had all three components of metabolic syndrome (MetS). MetS patients were defined by the presence of all three characteristics of the syndrome – hypertension, diabetes mellitus, and obesity (Table 1). Patients that did not meet all MetS criteria were considered non-MetS patients (n = 96). Mean (SD) age was 64.1 (10.3) and 58.7 (12.9) years for the MetS and non-MetS group,

Table 1
Characteristics of MetS and non-MetS patients.

Variable*	MetS (n = 6)		Non-MetS (n = 96)		P-value**
	n	%	n	%	
Age[a]	64.1	(10.3)	58.7	(12.9)	0.3
Gender					0.8
Male	4	67	69	72	
Female	2	33	27	28	
Race					<0.01
African-American	4	67	15	16	
Caucasian	2	33	80	83	
Asian	0	0	1	1	
T Stage					>0.9
T1	0	0	0	0	
T2	0	0	2	2	
T3	5	83	73	79	
T4	1	17	17	18	
N Stage					0.7
Unclear	0	0	2	2	
N0	2	33	48	52	
N1	4	67	38	41	
N2	0	0	4	4	
Surgical Procedure					>0.9
APR	4	67	45	48	
LAR	2	33	38	41	
Coloanal	0	0	1	1	
Local excision	0	0	4	4	
Multivisceral resection	0	0	3	3	
Unresectable	0	0	2	2	

* Variable-specific frequencies may not total sample size due to missing data.
** P-values for categorical variables based on Chi-square tests. P-values for continuous variables are based on t-tests.
[a] Descriptive measures for age (years) are mean and standard deviation instead of n and %, respectively.