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The Impact of Metabolic Syndrome on Outcome and Response to Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer Patients

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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

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followed by radical surgery. The results provide support for an increased focus on pre-treatment risk factor control to optimize cancer therapy outcomes.

Keywords

Metabolic syndrome; rectal cancer; neoadjuvant; chemoradiation; hypertension; diabetes; obesity

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]. 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 ≥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, respectively (p=0.3). The MetS group was 67% male and 33% female, while the non-MetS group was 72% male and 28% female (p=0.8). The groups were further analyzed by tumor characteristics. In the MetS group, no patients were T1 or T2, 83% were T3, and 17% were T4. In the non-MetS group, no patients were T1, 2% were T2, 79% were T3, and 18% were T4. There was no statistical difference between the two groups with regard to tumor characteristics (p>0.9). Furthermore, T stages were found to be distributed similarly across the individual MetS components (DM, HTN, BMI ≥30). Additionally, there was no statistical difference in nodal stage depending on MetS status (p=0.7) (Table 1). Differences in surgical approach were also examined between the two groups, and showed no statistical difference (p>0.9) (Table 1).

3.2 Tumor Response—Of the six MetS patients, one patient showed complete response (17%), and the other five patients did not show any response (83%). The three most common components of metabolic syndrome were further analyzed individually for therapeutic response. There were a total of 19 diabetic patients, of which four showed a complete response (21%), and three showed a partial response (16%) to neoadjuvant chemoradiation. Of the 51 HTN patients, only six showed a complete response (12%), and 20 showed a partial response (39%) to neoadjuvant chemoradiation. Lastly, there were 26 obese patients (BMI>30), and seven of those (27%) exhibited a complete response with an additional five patients having a partial response (19%). Overall, regardless of MetS status, 17 patients showed a complete response (17%), 30 patients had partial response (29%), and the remaining 55 patients did not show any response to neoadjuvant chemoradiation (54%) (Table 2).

Among the MetS components, only HTN had an impact on complete response rate (p=0.03). The odds of having complete response were 4.2 times higher (95% confidence interval: 1.2 to 14.3) in patients without HTN compared to those with HTN. When combining DM with HTN, the interaction was not significant (p=0.7), implying that the impact of HTN on complete response did not change when considering whether someone had DM or not. The same was true when adding BMI ≥ 30 to the model with HTN: the interaction was not significant (p=0.8), and the risk level remained similar to that when HTN was the only risk factor included. Metabolic risk factors were also studied when expanding the criteria to include any response (complete or partial) to neoadjuvant chemoradiation. None of the three risk factors were significantly related to any response (vs. no response) either individually or in any combination with one another (Table 3).

3.3 Treatment Complications—The effect of these metabolic risk factors on treatment complication rates was examined. Neoadjuvant treatment complications experienced included diarrhea, perineal pain, and rectal bleeding. A total of 38 patients had recorded treatment complications, including 20% of MetS patients. Among the components, 24% of diabetic patients, 41% of HTN patients, and 43% of patients with BMI>30 had treatment complications (Table 4). None of the three individual risk factors were significantly related

to treatment complications, although DM was marginally significant (p=0.06) on its own (Table 5).

3.4 Surgical Complications—Surgical complications, including wound infection, dehiscence, and obstruction, were also examined. A total of 37 patients had recorded surgical complications, including 33% of MetS patients. Among the components, 42% of diabetic patients, 48% of HTN patients, and 40% of patients with BMI>30 had surgical complications (Table 4). HTN was the only risk factor that led to increased rates of surgical complications. The presence of HTN was significantly related to having surgical complications (p=0.03), with the odds of having surgical complications 2.8 times higher (95% confidence interval: 1.1 to 7.3) in patients with HTN compared to those without HTN. The interaction between DM and HTN was not significant (p=0.7), implying that adding DM to HTN did not change the impact of HTN on having a complication. The same was true when adding BMI ≥ 30, with the interaction between BMI ≥ 30 and HTN being non-significant (p=0.3) (Table 5).

4. Discussion

The prevalence of metabolic syndrome is estimated at around 1 in 4 adult Americans with rates increasing by 5% over a fifteen-year period [10,11]. The risk of developing metabolic syndrome has been shown to increase with age and even more dramatically with higher BMI [10]. In addition to increased rates of cardiovascular disease, individuals with MetS are at a higher risk of developing various malignancies, including pancreatic and colorectal cancer [7,12]. Given the high rates of colorectal cancer in the U.S., as well as the growing elderly population and ongoing obesity epidemic, understanding the consequences of metabolic syndrome as it pertains to the management of CRC is becoming more relevant. Previous work demonstrated that diabetes and hypertension independently negatively impacted OS and DFS in CRC patients [9]. The aim of this study was to extend this work by examining the effect of MetS and its components on tumor response as well as surgical and treatment complication rates in MetS patients with LARC undergoing neoadjuvant chemoradiation treatment followed by surgery.

Upon examining the individual components of MetS (DM, HTN, BMI ≥30), this study demonstrated the significant effect of decreased nCRT response in LARC patients with hypertension. These patients were more likely to experience a poor response to treatment compared to patients without hypertension. Additionally, hypertension was found to significantly increase the rate of surgical complications experienced during resection of the tumor. Neither DM nor obesity exhibited any significant effect on therapeutic response or complication rates.

The clinical impact of these findings can be best appreciated in the context of existing literature on MetS (and its components) and colorectal cancer. The MetS component of HTN has previously been associated with worse OS and DFS in colorectal cancer patients undergoing conventional treatment [9]. The current study found HTN to have a significant negative effect on tumor response to nCRT and increase the risk of surgical complications. Based on literature searches, no other studies have examined the effect of hypertension on

CRC treatment response or complication rate. Taken together, this study provides new insight into the contributory factors affecting treatment outcomes and survival in hypertensive patients undergoing conventional colorectal cancer treatment. Despite the widespread prevalence and impact of hypertension on overall health, the exact mechanism by which hypertension influences cancer pathogenesis and treatment response is uncertain [13]. Some studies indicate that hypertension predisposes individuals to be more susceptible to chromosomal aberrations induced by carcinogens [14,15]. Another theory is that confounding variables such as diet, exercise, and lifestyle influence hypertension's apparent effect on cancer [16]. This theory can be extended to cancer treatment response. This study provides useful information to consider in the planning and management of treatment of LARC patients with hypertension. Future studies investigating the underlying mechanism of hypertension on LARC treatment is warranted.

Supportive of these findings, a prior study found that despite the technical difficulties of surgical resection due to increased body mass, obesity (BMI ≥30) did not affect overall patient outcomes [17]. There was no effect on tumor response to nCRT or post-operative morbidity among obese patients, as was the case with data seen here.

Diabetes, another MetS component, has been previously shown to negatively affect OS and DFS rates in colorectal patients undergoing conventional treatment [9]. A separate study further examined the role of diabetes on tumor response and found DM to be a negative predictor of response [8,18]. Interestingly, the current study did not demonstrate the negative influence of diabetes on tumor response.

Limitations of the study include the small number of MetS patients as well as the retrospective design. In 102 patients, only six patients (6%) had all three components of metabolic syndrome, a rate much lower than the estimated national average [10]. When examining the individual components of MetS, respective rates were significantly closer to national averages. The retrospective study design and limited MetS component-related data on patients may also explain why results likely underestimated the effect of DM on tumor response. The DM group was determined in a manner similar to a previous study that found diabetes to be a negative predictor of tumor response [18]. Patients were classified as being diabetic through either a history of diagnosis or medication. Due to limitations in patient records, however, the level of diabetic control was unable to be reviewed for all DM patients through hemoglobin A1C level and therefore could not account for any long-term control or subsequent variation within the DM group. This may explain why the study did not find diabetes to be significantly related to tumor response.

5. Conclusions

The results of this study demonstrate the importance of considering underlying MetS risk factors, especially hypertension, when predicting tumor response in LARC patients undergoing neoadjuvant chemoradiation followed by radical surgery. The results provide support for an increased focus on pre-treatment risk factor control or “prehab” through optimizing blood pressure control prior to the initiation of cancer therapy.

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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.

Table 1

Characteristics of MetS and non-MetS patients

	MetS (n= 6)		Non-MetS (n= 96)		
Variable*	**n**	**%**	**n**	**%**	**P-value****
Age†	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.

† Descriptive measures for age (years) are mean and standard deviation instead of n and %, respectively.

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Table 2

MetS and MetS components: Response Rates

		Complete Response (n=17)		Partial Response (n=30)		No Response (n=55)	
Variable (n)*		**N**	**%**	**N**	**%**	**N**	**%**
MetS							
	Yes (n=6)	1	17	0	0	5	83
	No (n=96)	16	17	30	31	50	52
Diabetes							
	Yes (n=19)	4	21	3	16	12	63
	No (n=82)	13	16	27	33	42	51
Hypertension							
	Yes (n=51)	6	12	20	39	25	49
	No (n=50)	11	22	10	20	29	58
BMI ≥ 30							
	Yes (n=26)	7	27	5	19	14	54
	No (n=64)	8	13	22	34	34	53

* Variable-specific frequencies may not total sample size due to missing data.

Table 3

Effect of MetS Components on Response Rates

		Complete response			Any response		
		OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
DM		1.21	(0.32, 4.52)	0.8	0.53	(0.17, 1.63)	0.3
HTN		0.24	(0.07, 0.85)	0.03	1.25	(0.52, 3.03)	0.6
BMI ≥ 30		2.32	(0.69, 7.82)	0.2	0.86	(0.33, 2.26)	0.8
HTN+ DM							
HTN				0.06			0.4
DM				0.4			>0.9
HTN*DM				0.7			0.5
	DM (no vs. yes) at no HTN	0.39	(0.04, 3.64)		0.98	(0.11, 8.97)	
	DM (no vs. yes) at HTN	0.69	(0.10, 4.84)		2.60	(0.69, 9.77)	
	HTN (no vs. yes) at no DM	4.15	(0.95, 18.17)		0.63	(0.24, 1.66)	
	HTN (no vs. yes) at DM	7.42	(0.51, 107.13)		1.67	(0.15, 18.57)	
HTN + BMI ≥ 30							
HTN				0.08			0.3
BMI ≥ 30				0.2			0.3
HTN*BMI ≥30				0.8			0.1
	BMI ≥30 (no vs. yes) at no HTN	0.30	(0.05, 1.65)		0.46	(0.10, 2.06)	
	BMI ≥30 (no vs. yes) at HTN	0.40	(0.05, 3.36)		2.44	(0.65, 9.21)	
	HTN (no vs. yes) at no BMI ≥30	4.90	(0.81, 29.76)		0.54	(0.18, 1.65)	
	HTN (no vs. yes) at BMI ≥30	6.54	(0.78, 54.98)		2.90	(0.51, 16.48)	

Table 4
MetS and MetS Components: Complications

	Treatment Complications (n=38)		Surgical Complications (n=37)	
Variable (n)*	**N**	**%**	**N**	**%**
MetS				
Yes (n=6)	1/5	20	2/6	33
No (n=96)	37/83	45	35/90	39
Diabetes				
Yes (n=19)	4/17	24	8/19	42
No (n=82)	34/71	48	29/77	38
Hypertension				
Yes (n=51)	19/46	41	23/48	48
No (n=50)	19/42	45	14/48	29
BMI≥30				
Yes (n=26)	10/23	43	10/25	40
No (n=64)	25/58	43	21/61	34

*Variable-specific frequencies may not total sample size due to missing data.

Table 5

Effect of MetS Components on Complication Rates

		Treatment complications			Surgical complications		
		OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
DM		0.29	(0.08, 1.07)	0.06	1.19	(0.40, 3.55)	0.8
HTN		0.87	(0.34, 2.22)	0.8	2.83	(1.10, 7.28)	0.03
BMI ≥30		1.05	(0.38, 2.87)	0.9	1.37	(0.51, 3.71)	0.5
HTN+DM							
HTN				0.8			0.06
DM				0.7			0.7
HTN*DM				0.5			0.7
	DM (no vs. yes) at no HTN	1.51	(0.12, 18.94)		1.51	(0.14, 16.47)	
	DM (no vs. yes) at HTN	4.50	(0.97, 20.88)		0.94	(0.25, 3.52)	
	HTN (no vs. yes) at no DM	0.85	(0.31, 2.34)		0.37	(0.13, 1.04)	
	HTN (no vs. yes) at DM	2.53	(0.15, 42.75)		0.23	(0.02, 3.05)	
HTN + BMI ≥ 30							
HTN				0.3			0.008
BMI ≥ 30				0.4			0.3
HTN*BMI ≥ 30				0.2			0.3
	HTN (no 1vs. yes) at no BMI ≥ 30	2.06	(0.42, 10.13)		0.42	(0.08, 2.25)	
	HTN (no vs. yes) at BMI ≥ 30	0.52	(0.13, 2.02)		1.31	(0.35, 4.92)	
	BMI ≥ 30 (no vs. yes) at no HTN	1.80	(0.57, 5.71)		0.18	(0.05, 0.63)	
	BMI ≥ 30 (no vs. yes) at HTN	0.45	(0.07, 2.75)		0.56	(0.09, 3.33)	