Quantitative Measures of Visceral Adiposity and Body Mass Index in Predicting Rectal Cancer Outcomes after Neoadjuvant Chemoradiation

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BACKGROUND: The association between body mass index as a measure of obesity and rectal cancer outcomes has been inconsistent. Radiologic measures of visceral adiposity using CT scans have not been well characterized among rectal cancer patients. The objective of this study was to examine quantitative radiologic measures of visceral obesity compared with body mass index in predicting patient outcomes among patients undergoing neoadjuvant chemoradiation and resection for locally advanced rectal cancers.

STUDY DESIGN: We identified 99 rectal adenocarcinoma patients treated with neoadjuvant chemoradiation and surgical resection. Visceral and subcutaneous fat areas, as well as perinephric fat thickness (PNF), were recorded and categorized as obese (body mass index $\geq$30, visceral fat area to subcutaneous fat area ratio [V/S] $\geq$0.4, or median PNF). The Kaplan-Meier method, log-rank test, and Cox proportional hazards models evaluated overall and disease-free survival differences by adiposity.

RESULTS: Viscerally obese rectal cancer patients (V/S >0.4 or PNF) were more likely to be older, male, and have pre-existing obesity-related conditions (eg, diabetes, hypertension, and/or hypercholesterolemia). Elevated V/S or PNF was associated with shorter disease-free survival ($p = 0.02$) or overall survival time ($p = 0.047$), respectively. Among patients with well to moderately differentiated tumors, visceral obesity was associated with poorer disease-free survival (V/S >0.4: adjusted hazard ratio = 5.0; 95% CI, 1.2−22.0).

CONCLUSIONS: Visceral fat area to subcutaneous fat area ratio and PNF were strongly associated with key preoperative metabolic comorbidities, and body mass index was not. Findings suggests that elevated visceral adiposity was associated with an increased risk of recurrence, which was most evident among patients with well to moderately differentiated tumors and those with incomplete response to neoadjuvant chemoradiation treatment. Quantitative measures of visceral adiposity warrant large-scale prospective evaluation. (J Am Coll Surg 2013;216: 1070−1081. © 2013 by the American College of Surgeons)

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Obesity is a major public health problem of epidemic proportions and is linked to the development of a number of malignancies, including colorectal cancer (CRC).[1-3] Nearly 66% of the US population is overweight or obese, as defined by body mass index (BMI) $\geq$25.[1] More than 90,000 cancer deaths per year are attributable to obesity or being overweight in the United States, and obesity plays a role in >20% of the approximately 150,000 CRC cases diagnosed each year.[4]

Obesity has been associated with increased risk for CRC recurrence and death.[5-10] However, there have been a number of studies that have reported no association between BMI and CRC outcomes,[11-14] and of those

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Abbreviations and Acronyms
AHR = adjusted hazard ratio
BMI = body mass index
CRC = colorectal cancer
DFS = disease-free survival
OS = overall survival
PNF = perinephric fat thickness
SFA = subcutaneous fat area
VFA = visceral fat area
V/S = visceral fat to subcutaneous fat ratio

with significant findings, there are inconsistencies about level of obesity, outcomes (eg, overall survival [OS] or disease-free survival [DFS]), and the role of sex.[6-8] Factors clustering with insulin-resistance syndrome (or metabolic syndrome) have also been associated with increased CRC mortality and recurrence.[15-17]

Additionally, when focusing on the select population of patients with rectal adenocarcinoma (rather than all CRC patients) the data become even more unclear. The most recent studies involving rectal cancer patients reported no difference in survival in patients with higher BMI after total mesorectal excision and neoadjuvant chemoradiation, and one study even reported a survival advantage in obese patients.[3,18] Others have reported obese men have a significantly higher risk of locoregional recurrence; however, no associations were observed for women or OS, regardless of sex. One explanation for these inconsistencies could be that a majority of studies use BMI as a measure of obesity, which does not provide a consistent or accurate measure of abdominal (eg, visceral) obesity. It is possible that visceral obesity can have an unrecognized detrimental impact on optimal dosing and/or delivery of chemotherapy and radiation.[6,19,20] (Although increased BMI has not been associated with increased rates of positive surgical radial margins, it is possible that visceral obesity might better reflect greater technical challenges with total mesorectal excision.)[18] In addition, from a biological standpoint, excess abdominal adipose tissue promotes a greater degree of obesity-related metabolic derangements, including insulin resistance, perturbations in adipokines, and chronic inflammation compared with subcutaneous adipose tissue.[21-24] Visceral adipose mass might be a more accurate measure of dysfunctional adipose tissue that facilitates cancer development and progression than BMI.

Quantitative radiologic measures of visceral adiposity using standard CT scans have been reported as the gold-standard method for assessing visceral adiposity.[25,26] This precise and reliable measure of abdominal fat compartments allows for the possibility of redefining obesity in terms of visceral fat rather than BMI. In a heterogeneous group of both colon and rectal cancer patients, Moon and colleagues demonstrated that individuals with high visceral adiposity had a considerably shorter DFS compared with those with low visceral adiposity, and BMI had no influence.[27] To date, there have been no investigations focused on the association between visceral adiposity and oncologic outcomes in patients specifically undergoing neoadjuvant therapy and resection for locally advanced rectal cancers. In undertaking this study, we hypothesized that quantitative CT measures of visceral adiposity would be associated with key pre- and postoperative clinicopathologic variables and significantly associated with patient outcomes, DFS and OS. We also hypothesized that visceral adiposity variables might have stronger associations with patient outcomes than BMI.

METHODS

Patient selection and chart review

A retrospective database of surgical cases performed at the Moffitt Cancer Center between 1998 and 2010 for rectal cancer was developed with IRB approval. Patients with stage II or III rectal adenocarcinoma who were treated with neoadjuvant chemoradiation followed by radical resection (low anterior or abdominoperineal resection) were identified. Data were collected on patient demographics, preoperative comorbidities, TNM stage, histopathologic features, perioperative complications, disease recurrence, and survival. Chart reviews were performed solely by experienced clinicians and data were abstracted on standardized abstraction forms. Clinical response to neoadjuvant treatment was defined as "no response" if there was no clinical change in the tumor; "partial response" if a residual palpable lesion was present but with a clinical reduction in size; and "complete response" if no tumor or very minor scar tissue was present on completion of treatment. Pathologic response was defined as a "complete response" if tumor regressed to T0N0 after neoadjuvant therapy; "partial response" if there was a reduction in tumor size and/or nodal status with residual tumor cells; and "no response" if there was no change in the tumor or progression of stage after neoadjuvant treatment. Data were entered into a secure Microsoft Access database.

Adiposity measures

Patients with a pretreatment CT scan archived at Moffitt were included in this study (n = 99). Radiologic measures of adiposity were obtained from routine diagnostic CT scans using a Siemens CT Leonardo digital workstation (Siemens Medical Solutions). Visceral and