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Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Subcutaneous adipose tissue characteristics and the risk of biochemical recurrence in men with high-risk prostate cancer

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Received 20 March 2017; received in revised form 8 May 2017; accepted 11 July 2017

Abstract

Purpose/objective(s): To assess subcutaneous adipose tissue characteristics by computed tomography (CT) as potential imaging biomarkers predictive of biochemical recurrence in men with high-risk prostate cancer receiving radiotherapy (RT).

Materials and methods: This retrospective study included men with high-risk prostate cancer (PSA $>$ 20 ng/ml, Gleason score $\geq$8, or clinical extraprostatic extension) treated between 2001 and 2012. All patients received definitive, dose-escalated external beam RT along with a course of neoadjuvant, concurrent, and adjuvant androgen deprivation therapy (ADT). Each patient also had a treatment planning CT that included the L4-L5 vertebral interface and prostate specific antigen (PSA) measurements for at least 2 years following RT. The subcutaneous adipose tissue was contoured on a single axial CT slice at the level of L4-L5. The average CT attenuation, in Hounsfield units (HU), of the structure was calculated and defined as SAT_{HU}. SAT_{AREA} was defined as the cross-sectional area of the structure (in cm^2) that was then normalized by the square of patient height. Biochemical failure (BF) was defined as a PSA rise of 2 ng/ml from the nadir. Freedom from BF (FFBF) was calculated from start time of ADT using the Kaplan-Meier method. Estimates of FFBF were stratified by SAT_{HU} and SAT_{AREA} quartiles.

Results: A total of 171 men met the inclusion criteria with a median follow-up of 5.6 years. The mean SAT_{HU} ($\pm$standard deviation) was $-$99.2 HU ($\pm$6.1 HU), and the mean SAT_{AREA} was 93.2 cm^2/m^2 ($\pm$39.4 cm^2/m^2). The 5- and 8-year rates of FFBF across all patients were 81.5% and 73.5%, respectively. Patients in the lowest quartile of SAT_{HU} experienced significantly higher FFBF compared to the other quartiles (Q4 vs. Q1, $P = 0.017$; Q4 vs. Q2, $P = 0.045$; Q4 vs. Q3, $P = 0.044$). No other differences in FFBF were observed between quartiles of SAT_{AREA} or other quartiles of SAT_{HU}.

Conclusion: Lower subcutaneous adipose tissue density was associated with a lower rate of BF following RT with ADT for men with high-risk prostate cancer. Further research is needed to elucidate the biological underpinnings of this clinical finding and the role adipose tissue plays in modulating oncologic behavior and outcomes.

Keywords: Prostate cancer; Imaging biomarker; Body composition; Adipose tissue density; Computed tomography

1. Introduction

The oncologic effects of adipose tissue are being increasingly recognized for many cancers [1–5]. The metabolic activity of adipose tissue has been shown to have significant tumorigenic effects on prostate cancer cells in vitro [6–9]; however, outcomes studies designed to assess the clinical effects of adiposity have been contradictory [10–12]. One potential explanation for the inconsistent results of prior studies is that traditional anthropometric assessment of body fat, such as body mass index (BMI) and skinfold measurement, may be poor indicators of the underlying metabolic profile related to adiposity.

Cross-sectional imaging has recently been shown to be a useful tool for quantitatively and qualitatively assessing body fat depots. Measuring the area of adipose tissue on a

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http://dx.doi.org/10.1016/j.urolonc.2017.07.012
1078-1439/

single abdominal axial image is very strongly correlated with total body adipose tissue volume [13,14] and the radiodensity of adipose tissue has also recently been described as a novel imaging biomarker that is highly correlated with various adipokines [15,16]. Preclinical evidence has, in turn, suggested that adipokines such as interleukin-6 (IL-6) and insulin-like growth factor-1 may signal prostate cancer proliferation via the androgen receptor [8,17]. The purpose of this study was to explore computed tomography (CT) assessed adipose measurements as potential imaging biomarkers associated with biochemical outcomes among men with high-risk prostate cancer treated with radiotherapy (RT). We hypothesized that men with a greater amount of body fat would experience higher rates of biochemical recurrence. Since CT is routinely performed as part of prostate cancer RT planning, these measurements could be performed without the need for additional testing.

2. Methods and materials

2.1. Inclusion criteria

We retrospectively reviewed the records of all men who received definitive external beam RT for prostate cancer in our department between 2001 and 2012. All men with National Comprehensive Cancer Network high-risk disease [18] who had a treatment planning CT inclusive of the L4-L5 vertebral interface and at least 2 years of prostate specific antigen (PSA) follow-up were included in this study. This study was approved by the institutional review board of the University of Alabama at Birmingham.

2.2. Treatments

We have previously described our RT technique for high-risk prostate cancer in detail [19]. Briefly, the vast majority of patients treated before 2005 received conventionally fractionated dose-escalated RT using a shrinking field technique. An initial 4-field box plan delivered 45 Gy to the pelvis followed by a 10 Gy boost to the prostate and seminal vesicles and then a final prostate boost, for a total prostate-directed dose of 75 to 79 Gy. Treatment planning and delivery was via 3-dimensional conformal RT except in a minority of cases where intensity modulated RT was used for the final prostate boost. A small number of patients were treated to a total prostate dose of 70.2 Gy as part of the Radiation Therapy Oncology Group 9902 study [20].

Patients treated 2005 and onwards received conventionally fractionated pelvic intensity modulated RT with a simultaneous hypofractionated boost to the prostate. The pelvic lymph nodes (obturator, presacral, internal iliac, external iliac, and distal common iliac) and distal seminal vesicles were prescribed 50.4 Gy. The prostate was prescribed 70 Gy. All dose levels were treated simultaneously in 28 fractions and the proximal seminal vesicles were prescribed 56 to 70 Gy at the discretion of the treating physician.

All patients were recommended a course of neoadjuvant, concurrent, and adjuvant androgen deprivation therapy (ADT). ADT was begun approximately 2 months before the the start of RT, and generally recommended to continue for a total of 24 months depending on patient tolerance. ADT consisted of a gonadotropin releasing hormone agonist with or without a short course of bicalutamide at the discretion of the treating physician.

2.3. Subcutaneous adipose tissue measurements

All simulation scans were obtained in the supine position using a CT scanner compliant with the American Association of Physics in Medicine Task Group No. 66 recommendations [21]. Scans generally extended from the midlumbar spine through the midfemur. Image analysis was performed using Varian Eclipse (Varian Medical Systems, Palo Alto, CA), a commercially available radiation oncology software suite.

Segmentation of subcutaneous adipose tissue (SAT) was performed on a single slice at the level of the L4-L5 vertebral interface by a single investigator (A.M.). Using the Eclipse CT ranger tool, all voxels between −195 and −45 Hounsfield units (HU) were segmented and this structure was manually adjusted to include only the area outside of the abdominal wall as illustrated in Fig. 1.

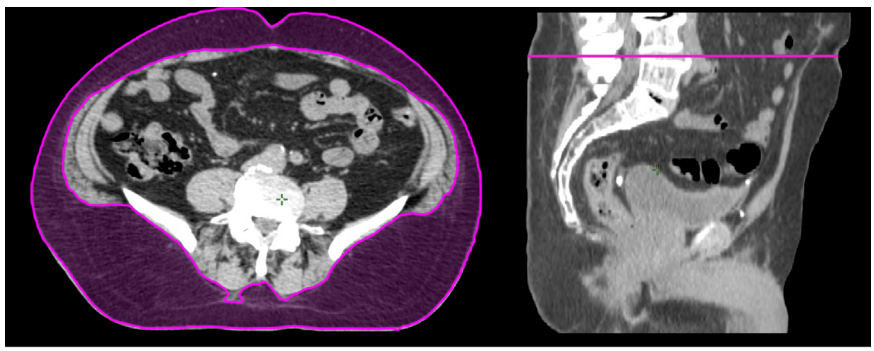

Fig. 1. Single slice delineation of subcutaneous adipose tissue for an example patient. (Color version of figure is available online.)