Presence of the metabolic syndrome is associated with shorter time to castration-resistant prostate cancer

J. Flanagan1,2, P. Kathryn Gray3, N. Hahn1, J. Hayes4, L. J. Myers5,6, C. Carney-Doebbeling1,7 & C. J. Sweeney1,4*

1Division of Hematology/Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis; 2Kansas City Cancer Center, US Oncology, Kansas City; 3Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard School of Public Health, Boston; 4Department of Medicine, Dana Farber Cancer Institute, Boston; 5Division of General Internal Medicine and Geriatrics, Department of Medicine, Indiana University School of Medicine, Indianapolis; 6Health Services Research and Development Center of Excellence on Implementing Evidence-Based Practice (CIEBP), Roudebush VA Medical Center, Indianapolis; 7Regenstrief Institute Inc, Indianapolis, USA

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Background: Metabolic syndrome (MS) is a set of risk factors that includes obesity and insulin resistance and has been implicated in the development of prostate cancer. Its impact on androgen deprivation therapy (ADT) efficacy has not been studied.

Patients and methods: Retrospective study of prostate cancer patients seen from 1998 to 2005 in a medical oncology clinic. MS, as defined by modified Adult Treatment Panel III criteria, was assessed at the time of initiation of ADT. The study end points were time to prostate-specific antigen (PSA) progression and overall survival (OS) from time of starting ADT.

Results: Eighty-two patients treated with ADT and data to assess for presence of MS were identified. Median age in men with and without MS was 70 years and 49% of the patients evaluated met criteria for MS. Median time to PSA progression for patients with MS was 16 versus 36 months without MS (P = 0.003). The median OS for patients with MS was 36.5 months after commencing ADT compared with 46.7 months for those patients without MS (P = 0.061).

Conclusions: This preliminary data suggest that MS is a risk factor for earlier development of castration-resistant prostate cancer and support the need for a prospective evaluation of this finding.

Key words: hormonal therapy, metabolic syndrome, prostate cancer, resistance

introduction

Prostate cancer is the second leading cause of cancer death in men in the United States [1]. Prostatectomy and/or radiation therapy are the preferred treatment modalities in men with locally confined disease. Androgen deprivation therapy (ADT) is used in the adjuvant setting and for the treatment of metastatic prostate cancer. Androgen deprivation is achieved either with bilateral orchiectomy or with luteinizing hormone-releasing hormone (LHRH) agonists.

The metabolic syndrome (MS) is a clinical entity influenced by genetic, hormonal, and lifestyle factors. It is characterized by a cluster of disorders which includes high blood pressure, insulin resistance, excess body weight with central obesity, and dyslipidemia [2]. The syndrome increases the likelihood of developing coronary heart disease, stroke, and diabetes [3, 4]. Over the past two decades, the number of people diagnosed with this syndrome has steadily increased and is associated with a global increase in obesity and diabetes [5]. MS has been associated, either directly or indirectly, with the risk of developing several cancers, including prostate cancer [6, 7].

Individual components of the MS such as hyperinsulinemia [8], hypertension [9], obesity with prominent abdominal fat distribution [10], and dyslipidemia [11] have each been linked in some studies to an increased risk of prostate cancer. Other studies have shown no association between these individual factors and prostate cancer risk, and there has been particular controversy over the role of diabetes and prostate cancer outcomes.

Several studies have now examined the MS as a composite risk factor for developing prostate cancer. The results from these studies have also been inconsistent. A Finnish prospective population-based study showed that middle-aged men with the MS were nearly 2-fold more likely to develop prostate cancer than those without [12]. Similarly, a prospective cohort trial in Norway demonstrated a trend for increased incidence of
prostate cancer among men with MS [13]. In contrast, a recent analysis of an American cohort study showed a 25% risk reduction for development of prostate cancer in men with Adult Treatment Panel III (ATP-III)-defined MS [14]. The cause of the conflicting data is unknown. However, it is possible that the study of the American cohort may differ from the European cohorts by inclusion of prostate-specific antigen (PSA)-detected clinically indolent cancers which may have a biology which is distinct from more advanced cancers. Gong et al.’s analysis of data from the Prostate Cancer Prevention Trial supports this hypothesis, and their results demonstrate an increase in high-grade disease in obese patients, with a simultaneous decreased risk of low-grade disease [15].

It is of note we are not aware of any previous study examining the impact of MS on the efficacy of ADT for the treatment of patients with recurrent or de novo metastatic prostate cancer. This retrospective review therefore focused on this more homogenous population with a poor prognosis. The study specifically evaluated the effect of the MS on the time to development of PSA progression (castration-resistant disease) and overall survival (OS) in patients with recurrent or metastatic disease treated with ADT.

patients and methods

study design and patients

This study was conducted as a retrospective chart review, with data extracted from the Veterans Administration electronic medical record. We identified 100 consecutive patients with adequate chart information who were treated with LHRH agonist for prostate cancer at the Roodebush Veteran’s Administration, Indianapolis, Indiana Medical Oncology clinic from 1998 to 2005 in Indianapolis, Indiana. Eighty-two patients were identified who had treatment for either biochemical (PSA) relapse after definitive local therapy and/or radiographic evidence of distant metastasis. These 82 patients were all subsequently treated with LHRH agonists. Each patient had adequate information available to evaluate for the presence of MS at the start of ADT. Eighteen of the 100 patients were either not treated with ADT or did not have adequate information available to establish the presence or absence of the MS and were not included in this analysis. Local Institutional Review Board/Human Subjects approval was obtained. There were no external funding sources (institutional resources only) and there are no conflicts of interest.

Primary outcomes were time to PSA progression and OS. The time to PSA progression on ADT (castration-resistant prostate cancer) was defined as the time from start of ADT to 50% increase in PSA from nadir or the time to 25% increase from baseline and was confirmed per PSA consensus criteria [16] or clinical progression if occurred before PSA rise. OS was calculated starting from the time of ADT initiation.

definition of MS

The presence of MS was assessed at the time of LHRH agonist initiation and was defined according to modified ATP-III criteria. A subject was classified as having MS if three of the following five criteria were present: hypertension (SBP \( \geq 140 \text{ mmHg} \) and/or \( \text{DBP} \geq 90 \text{ mmHg} \) on two outpatient visits); obesity [body mass index (BMI) \( \geq 30 \)]; hypertriglyceridemia (\( >150 \text{ mg/dl} \) on two fasting laboratories); fasting high density lipoprotein (HDL) \( <40 \text{ mg/dl} \); fasting glucose \( >110 \text{ mg/dl} \) (two outpatient morning values while not on glucocorticoids). In the ATP-III criteria, waist circumference \( >102 \text{ cm} \) is used rather than elevated BMI.

However, waist circumference was not available in this retrospective review, so a BMI \( >30 \) was used as an indicator of central obesity. This substitution has been validated in previous studies [17, 18].

statistical analysis

Association of MS status and patient characteristics was assessed using the Fisher’s exact test (for categorical variables) or Wilcoxon test (continuous variables). Kaplan–Meier estimates of time-to-event end point (PSA progression and OS) were calculated. The analyses of comparing presence or absence of MS status for the time to PSA progression and OS used log-rank test. The hazard ratios (HR) and the corresponding 95% confidence intervals (CIs) were estimated using Cox proportional hazards model, both without (unadjusted) or with (adjusted) the adjustment of baseline and prognostic factors, including age at diagnosis, race, presence of metastatic disease at diagnosis, PSA doubling time prior to ADT, PSA at diagnosis, PSA at time of ADT, time to PSA nadir on ADT, PSA nadir on ADT, primary prostatectomy, and primary radiotherapy. All significance tests for the comparisons were two sided. The analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC) and R 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria).

results

Patient characteristics are summarized in Table 1. Prostate adenocarcinoma was biopsy proven in 73 of 82 patients, while the remaining patients had a clinical diagnosis of prostate cancer based on PSA and radiographic evidence of metastasis. Gleason scores were available for 62 of the 82 patients. There was no statistically significant difference for age at diagnosis, race, Gleason score, or presence of metastatic disease at the time of diagnosis between the two groups. Similarly, the PSA at time of ADT initiation and PSA doubling time prior to ADT were not statistically different in the MS and no MS groups. The median period of follow-up was 27 months for the group overall (26 months in the group without MS and 29 months in the MS group). Twenty of the 82 patients were African-American, and there was no statistically significant difference in percentage of African-Americans in the MS group compared with the non-MS (20% versus 29%). Compared with patients without MS, patients with MS were more likely to have used metformin (\( P = 0.025 \)), though the overall number of usage was small. There was no difference in statins use. For the patients analyzed, there was no difference in the presence of metastatic disease at the time of prostate cancer diagnosis between those with and without MS.

The results from Cox proportional hazards model for time to PSA progression from time of initiation of ADT between patients with MS and those without MS are presented in Table 2. Both univariate (unadjusted) and multivariate (adjusted) HR for the time to PSA progression by MS status, as well as other events, such as fasting HDL <40, elevated triglycerides, BMI >30, hypertension, and fasting glucose >110 were assessed. In the multivariate analysis, HR were adjusted for age, race, presence of metastatic disease at diagnosis, PSA doubling time before ADT, PSA at diagnosis, PSA at time of ADT, time to PSA nadir on ADT, PSA nadir on ADT, primary prostatectomy, and primary radiotherapy. MS remained a significant predictor of PSA progression after the adjustments.
The individual components of MS, including BMI >30, hypertension, low fasting HDL, and elevated fasting glucose also showed a statistically significant effect on PSA time to PSA progression in multivariate analysis. The median time to PSA progression (Figure 1A) was 36 months for patients with MS, versus 16 months for no MS ($P = 0.0032$).

The univariate (unadjusted) and multivariate (adjusted) HR for OS are presented in Table 3, using the same covariates adjusted for in assessing time to PSA progression. In multivariate analysis, patients with MS had a 2.65-fold increased risk of death ($HR = 2.65$, 95% CI $1.02–6.87$, $P = 0.045$) compared with those who did not have MS (Table 3). Of the other variables evaluated, only MS and hypertension had statistically significant HRs for OS.

Seventeen of 36 patients (47%) without MS who did not have metastatic disease documented at initiation of ADT subsequently developed radiographically proven bone metastases during the period of follow-up. In contrast, 23 of 36 (64%) patients with MS and no documented metastatic disease at time of starting ADT developed radiographically proven bone metastases during the period of follow-up ($P = 0.235$ from Fisher’s exact test).

**discussion**

In this preliminary study, men with MS and recurrent or newly diagnosed metastatic prostate cancer demonstrated a shorter time to development of castration-resistant prostate cancer and...
shorter OS than men without MS. This was noted for both end points on univariate and multivariate analyses. To our knowledge, this is the first study to evaluate the effect of the MS as a composite end point on disease control with ADT in this patient population. The effect on OS was not mediated by obesity alone in this study. As a single component of the MS, hypertension was a statistically significant variable affecting OS. All components of the MS were associated with shorter time to progression with the exception of elevated triglycerides. Development of bone metastasis occurred in 64% of men with MS who did not present with metastatic disease versus 47% of those without MS during the analysis period. In total, this would suggest that the poor clinical outcome and shorter OS in this prostate cancer population may be associated with the presence of the MS.

Strengths of the study include the depth and specifics of chart data compared with population studies that depend on coding to define outcomes. The clinical definition of MS in the current study was sound, with complete vital signs, medications, and laboratory and radiology data available on each patient. PSA measurements and clinical assessments of the patients were done every 3 months as a standard for patients on ADT. The completeness of the available data was an asset when defining MS and prostate cancer outcomes retrospectively.

Limitations of the current study include small numbers of patients overall and a retrospective design and lack of standardized treatment at time of castration-resistant disease. Due to the missing values from some covariates, i.e. PSA doubling time before ADT (38 patients), PSA at time of ADT (19 patients), and time to PSA nadir on ADT (18 patients), there is limitation in the interpretation of their adjusted effects on the estimates of the multivariate analysis results (HR and CIs). Despite missing values before nadir being documented, patients were assessable for time to progression based on the actual nadir values. Given the fact this is a retrospective review, it was difficult to accurately determine from the medical records the cause of death. Nevertheless, our study suggests that the shorter time to castration resistance and greater frequency of bone metastases developing on therapy points to the shorter OS being due to more rapid deaths from prostate cancer.

The most widely adopted definition of MS, the ATP-III criteria, utilizes waist–hip ratio rather than BMI to define obesity. Numerous studies have demonstrated the importance of central adiposity in the pathogenesis of insulin resistance and MS, and an elevated waist–hip ratio is a better clinical indicator than elevated BMI of central obesity. In the current evaluation of chart data, waist and hip measurements were not available. Previous studies have substituted BMI $>30$ for waist size in defining MS and this was the only approach available for this retrospective study [17, 18]. Future prospective studies of the interaction of obesity, MS, and prostate cancer should utilize waist and hip circumferences as well as BMI where possible.

A review of the literature does, however, provide some biological rationale for why the MS may be associated with ADT being less effective in controlling prostate cancer. Common denominators potentially linking the MS and prostate cancer may include alterations in insulin and insulin-like growth factor (IGF)-I and IGF-binding proteins [19, 20]. Prostate cancer cell lines have shown reduced growth and increased apoptosis with decreased levels of insulin and IGF-1 [21]. Population studies have also suggested an association between the blood levels of IGF-I and its binding proteins and the risk of prostate cancer [22].

MS also modulates hormone levels including testosterone. Low testosterone has been shown to have a strong correlation with the development of MS and with frank diabetes and replacement of testosterone has been shown to improve insulin resistance, central obesity, and dyslipidemia [23, 24]. It is postulated by us that that the lower testosterone state in men with MS may lead to development of prostate cancer which is less dependent on androgens and thus becomes androgen independent more quickly. This is turn may lead to lower efficacy when treated with ADT.

Another mechanism proposed to mediate the relationship between prostate cancer and the components of MS has been the activity of adipokines. Adipokines are polypeptide hormones produced by adipocytes. Two adipokines are of interest as they relate to prostate cancer: adiponectin and leptin [25]. Leptin levels correlate with obesity and MS [26] and have been shown to promote angiogenesis, proliferation of endothelial cells, and stimulate the growth of androgen-independent prostate cancer cells in vitro [27]. In contrast, adiponectin levels are highest in thin patients and low in those with central obesity, and adiponectin levels have been reported to be inversely related to prostate cancer risk and disease stage [28]. This observation is supported by a preclinical study which demonstrated that intermittent caloric restriction was...
associated with an increase in adiponectin and a delay in time
to tumor detection in the transgenic adenocarcinoma of the
prostate (TRAMP) model [29].

Elevated interleukin-6 (IL-6) levels are also associated with
MS and elevated C-reactive protein [30]. IL-6 levels have been
shown to be increased in human prostate cancer, and elevated
circulating IL-6 levels have been associated with advanced
prostate cancer, distant metastases, and worse OS [31]. It is
therefore conceivable that growth of prostate cancer in patients
with MS and its associated ‘inflammatory state’ [32] is
supported by the associated elevated cytokines such as IL-6.

It is also worth noting that ADT induces its own metabolic
changes. Smith et al. [33] have shown that the metabolic
changes of LHRH agonist therapy differ from MS in some key
aspects. In men with prostate cancer, LHRH agonists increase
fat mass and waist circumference, decrease insulin sensitivity,
and increase serum triglycerides, akin to what is seen with MS.
However, in contrast to the MS, LHRH agonists preferentially
increase s.c. fat, increase HDL cholesterol and adiponectin
levels, and do not change the waist-to-hip ratio, blood pressure,
or C-reactive protein levels.

This retrospective study cannot examine whether
interventions to counteract complications of the MS could
affect the clinical outcomes of men on ADT. However, there is
an increasing amount of literature which suggests that strategies
which combat MS may improve prostate cancer outcomes in

**Figure 1.** (A) Time to PSA progression by presence or absence of metabolic syndrome. (B) Overall survival by presence or absence of metabolic syndrome.
patients who also have the MS. One such intervention could be metformin use. Only five of our patients with MS and none without were taking metformin and, as such, the numbers were too small to carry a meaningful analysis. Increasing attention has been paid recently to metformin, an oral antihyperglycemic agent frequently used in the management of type II diabetes mellitus and is associated with a decrease in the incidence of DM II in patients with impaired glucose tolerance [34]. The interest in metformin as a potential preventative and therapeutic agent in prostate cancer has been rising as a result of recently published preclinical and population-based studies. Epidemiologic studies have demonstrated a decreased incidence of solid tumors and decreased cancer-specific mortality in men taking metformin [35]. In patients with breast cancer, metformin has been shown to increase the rate of pathologic complete responses in women receiving neoadjuvant chemotherapy as compared with those taking other diabetic medications [36]. In prostate cancer, metformin use has been associated with a 44% reduction in relative risk of developing prostate cancer in Caucasian men in a population-based case–control study [37]. Moreover, a retrospective study found that diabetic men taking metformin were significantly less likely to develop prostate cancer than men taking insulin [38].

The mechanism underlying metformin’s protective effect is incompletely understood but may relate to its ability to counter hyperinsulinemia, and the latter’s consequent increased risk of prostate cancer [8]. Suggested metformin-associated anti-tumor mechanisms observed in prostate cancer cell lines have included inhibition of cyclin D1 and activation of AMP-activated protein kinase, thus reducing cellular proliferation and protein synthesis as well as inhibiting mammalian target of rapamycin. Metformin has also been shown to affect levels of nuclear factor-kappa B and extracellular signal-regulated kinases 1/2 [39]. Future prospective studies will be needed to address whether intervention with metformin would benefit these men.

This study highlights the need as well as provides the support for future prospective investigation to better characterize the association of MS and its individual components with adverse clinical outcomes in prostate cancer. This analysis will be done as part of the ongoing Eastern Cooperative Oncology Group lead trial (E3805) in men with metastatic prostate cancer. Additional studies will also be necessary to elucidate the pathogenesis of the adverse outcomes associated with MS seen in this study, for example by correlating components of the MS with baseline testosterone, IGF-1, IGF-binding proteins and adipokine levels at the time of prostate cancer diagnosis or initiation of ADT. If the findings in this study are confirmed, it would provide very strong rationale for future studies to evaluate the effect of lifestyle or medical interventions, for example with metformin, on disease progression as well as on the MS. As the incidence of MS increases globally, effective management of this condition has the potential to not only improve prostate cancer outcomes but also the overall health of men with advanced prostate cancer.

disclosure
The authors have declared no conflicts of interest.

references

Table 3. Unadjusted and adjusted HR for overall survival by variables

| Variables          | Comparison                  | Unadjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value*
<table>
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<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>Yes versus no</td>
<td>1.93 (0.96–3.89)</td>
<td>0.06</td>
<td>2.65 (1.02–6.87)</td>
<td>0.045</td>
</tr>
<tr>
<td>Fasting HDL &lt; 40 mg/dl</td>
<td>Yes versus no</td>
<td>1.54 (0.77–3.06)</td>
<td>0.22</td>
<td>2.38 (0.84–6.79)</td>
<td>0.104</td>
</tr>
<tr>
<td>TG &gt; 150 mg/dl</td>
<td>Yes versus no</td>
<td>1.22 (0.58–2.56)</td>
<td>0.6</td>
<td>1.7 (0.6–4.82)</td>
<td>0.321</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>Yes versus no</td>
<td>1.18 (0.59–2.33)</td>
<td>0.64</td>
<td>1.18 (0.47–2.97)</td>
<td>0.731</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes versus no</td>
<td>0.95 (0.39–2.33)</td>
<td>0.92</td>
<td>4.87 (1.06–22.27)</td>
<td>0.041</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Yes versus no</td>
<td>1.86 (0.89–3.87)</td>
<td>0.09</td>
<td>1.52 (0.57–4.07)</td>
<td>0.399</td>
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*Adjusted for age at Dx, race, presence of metastatic disease at Dx, PSA doubling time before ADT, PSA at diagnosis, PSA at time of ADT, time to PSA nadir on ADT, PSA nadir on ADT, prostatectomy treatment, primary radiotherapy treatment.

ADT, androgen deprivation therapy; CI, confidence interval; Dx, diagnosis; HR, hazards ratios; PSA, prostate-specific antigen.


