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Risk Factors for Metastatic Prostate Cancer: A Sentinel Event Case Series

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Abstract

Background—Root cause analysis is a technique used to assess systems factors related to “sentinel events” –serious adverse events within healthcare systems. This technique is commonly used to identify factors, which allowed these adverse events to occur, to target areas for improvement and to improve health care delivery systems. We sought to apply this technique to men presenting with metastatic prostate cancer.

Methods—We performed an in-depth case series analysis of 15 patients who presented with metastatic disease at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center using root cause analysis to refine a list of health system factors that lead to late stage presentation in the current era.

Results—Key factors in late diagnosis of prostate cancer included lack of insurance, lack of routine PSA testing, comorbidities, reticence of patients to follow up actionable PSA, and aggressive disease. Three patients had aggressive disease that would not have been discovered at an early stage in the disease process, despite routine screening. However, analysis of the remaining 12 patients illuminated health system factors led to missing important diagnostic information, which might have led to diagnosis of PCa at a curable stage.

Conclusions—The cases help highlight the need for systems based approaches to early diagnosis of prostate cancer. A heterogeneous group of barriers to early diagnosis were identified in our series of patients including economic, health systems and cultural factors. These findings underscore the need for individualized approaches to preventing delayed diagnosis of prostate

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cancer. While limited by our single-institution scope, this approach provides a model for research and quality improvement initiatives to identify modifiable systems factors impeding appropriate diagnoses of prostate cancer.

Keywords

Metastatic prostate cancer; Risk Factors; PSA screening; Sentinel Events; Case Series; Root-cause Analysis; Health Services Research

Introduction

Between 2004 and 2013, 4.6% of men diagnosed with prostate cancer (PCa) presented with distant metastases.¹ Only 28% of these men survive for 5 years, and each approved treatment for metastatic PCa offers only about 4 extra months of survival.² The financial cost of treating metastatic prostate cancer can be higher than localized disease,³ and therapies carry significant and detrimental side effects.⁴

Several interrelated factors have been identified as leading to late presentation: (1) lack of general access to health care,⁵ (2) underutilization of primary care,⁶ (3) lack of PSA testing,⁷ (4) PSA cost issues,⁸ (5) comorbidities,⁹ (6) misdiagnosis of symptoms,¹⁰ (7) rising/elevated PSA,⁷ (8) symptomatic PCa,¹¹ and (9) reticence of patients to follow up with specialists.¹² Five of these nine factors (1–4, 7) are related to PSA testing.^{5–9,13} Given declines in utilization of PSA screening^{14,15} following the 2012 United States Preventative Services Task Force (USPSTF) recommendations against screening, these may play a growing role in the development of metastatic cancer. We therefore designed a case series study to assess the root cause of late diagnosed prostate cancer in a series of men.

In contrast to large, population-based studies, case-series analyses can reveal under-appreciated sources of excess disease or mortality because they illuminate contextual conditions and detailed processes related to adverse events.¹⁶ This technique has been used to analyze serious adverse events such as wrong-site surgeries.¹⁷ The term “sentinel” originally referred a soldier or guard whose job is to stand and keep watch.— in modern health care, “sentinel event” is typically used to refer to serious and avoidable adverse events which can alert providers to unsafe health systems. Sentinel event analysis is used to understand the root cause of such events. The number of cases does not have to be large to provide potentially practice changing insights; most case series use 10 or fewer cases.¹⁸ Our hypothesis is that men present with metastatic PCa due, in part, to modifiable health care system-factors rather than disease factors such as aggressive disease. We conducted a “sentinel event” case series analysis seeking to identify systems issues or barriers to early detection, risk stratification and effective treatment of clinically significant PCa.

Materials and Methods

Setting and Recruitment

This study, approved by the Johns Hopkins (JHU) Institutional Review Board, was conducted by identifying patients from the JHU Cancer Registry who had first presented with metastatic PCa between January 2013 and December 2014 and were being treated by

five physicians on the Medical Oncology faculty at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at JHU. Of the 29 patients (21 white, 8 AA) who met those criteria, treating physicians referred 18 patients (13 white, 5 AA) based on their availability at planned clinic visits to meet with the interview team, as well as a determination that their patients were not too ill to support the consent and interview procedures.

At routine clinic visits, the primary treating oncologist asked eligible patients if they would be willing to be interviewed. Before the interview, researchers explained the study and obtained written consent. Two patients declined; one consented patient dropped out when a close family member passed away, leaving 12 white and 3 AA participants.

Data collection—Interviews of 30 to 60 minutes were conducted during outpatient clinic visits between January 2014 – December 2015.

Data were gathered from medical records (age, race ethnicity, Gleason score and PSA at diagnosis) and from a JHU-refined questionnaire and included:

- Medical history, including PSA testing and other screening
- Prostate and other health complaints
- Perceived quality of care
- Health insurance
- Socioeconomic and family support status

The questionnaire drew from validated instruments including the Centers for Disease Control Behavioral Risk Factor Surveillance System PCa screening 2011 questions¹⁹ and the Meharry-Vanderbilt Alliance questionnaire for the Southern Community Cohort Study.²⁰

Analysis—Our process followed the case study research methodology of Yin,²¹ beginning with a hypothetical logic model of the groups of factors leading to late presentation of mPCa. We tested each case against the model and through an iterative process, identified factors that resulted in late stage presentation. Along the way we considered rival logic models and arrived at a logic model with a smaller number of factors that explained late presentation in all cases.

The hypothetical logic model was developed through a literature review that identified nine cascading groups of factors (Table I) that implicitly or explicitly cause patients to drop off the conventional pathway that patients follow when their PCa is discovered in time to be cured or delayed through primary therapy (radiation or prostatectomy) or, when slow growing, appropriately followed and treated through active surveillance. We analyzed each patient history to identify the factors causing patients to drop off the conventional care pathway, reexamining and adjusting the list of factors to reflect the different experience of each successive patient. This led us to a model comprised of a sequence of causal factors.

Results

The final logic model (Figure 2) includes five primary causal factors leading to initial presentation with mPCa in a case series of 15 patients who first presented with PCa at SKCCC Medical Oncology Department between January 2013 and December 2014.

Study enrollment

Of the 15 participants, 73% (11/15) were white, 20% (3/15) were AA, and 7% (1/15) were white Hispanic. Sixty-seven percent (10/15) were married or engaged; 87% (13/15) had health insurance; 27% (4/15) were 70 years or older, and 27% (4/15) had a family history of PCa including 2 AA patients.

Figure 1 defines the nine groups of factors identified in existing literature as associated with late presentation. Five were excluded from the model because they were not observed in any of the cases or because other factors were dominant. For example, rising/elevated PSA without appropriate follow-up, was observed in four patients, but lack of PSA testing (1 patient), patient reticence to follow up (1 patient) and comorbidities (2 patients) were primary. The other factors that were not determinative were access not utilized, PSA cost issues, misdiagnosis of symptoms, and symptomatic PCa. Cost of PSA testing for the patient did not arise because the two patients without insurance did not have the option to have PSA testing. Insured patients did not cite this as an issue. Misdiagnosis of symptomatic PCa were not determinative by the authors: comorbidities masked PCa or caused the PCP to focus on the comorbidities. Access not utilized was not observed because all the patients who had insurance received primary care in our series.

The remaining five groups of factors can be seen in Figure 1 to have played important roles leading to late presentation of PCa in these 15 patients. Four groups of factors were included in our logic model: lack of access to the health system caused by lack of insurance (2 patients), no PSA testing (6 patients), comorbidities (4 patients) and reticence to follow up (1 patient). Aggressive disease was added as the 10th factor because of two patients, one with metastatic disease despite consistently low PSA levels and one with extremely rapidly rising PSA levels.

Figure 2 illustrates the stages of care each of the patients that preceded their late presentation. Factors associated with late presentation of mPCa are seen below dotted line. Using transition probabilities to describe, 87% (13/15) had access to primary care physician (PCP) care, 54% (7/13) of those had routine PSA testing, 57% (4/7) of those had actionable PSA discovered, and 0% (0/4) of those had adequate follow-up.

Factors leading to late presentation

Lack of insurance coverage: Two patients (13%) lacked insurance. One reported irregular employment leading to lack of health insurance to cover routine screening. The other had been unemployed for 20 years and relied on hospital emergency rooms for medical care.

Lack of routine PSA testing among men with regular primary care: Of the 13 patients with regular PCP care, 46% (6/13) did not have routine PSA testing. Three were 67 or older,

one was 41, and two were 59. Both of the men who were older than 74 had continued routine PSA testing. Five patients reported their PCPs said they followed guidelines to avoid routine testing of asymptomatic or older men. One of those PCPs reportedly referred to the guidelines to explain why he wasn't testing PSA in a 59 year old man with a family history of PCa. In the 6th case, the PCPs reasoning was unknown.

Aggressive disease with lack of actionable PSA: Three patients had aggressive disease that was not discovered despite routine PSA testing. In one, PSA never rose above 3 ng/ml and metastatic disease was discovered when the patient was admitted to the hospital for severe anemia with generalized back and leg pain. A bone marrow biopsy confirmed PCa. The second patient had no family history of PCa and when his PSA level reached 4.0 ng/ml, he was prescribed testosterone for fatigue. A year later he presented with a PSA over 1000 ng/ml, a positive bone and CT scan, and a biopsy confirming mPCa. The third patient's PSA rose from 2.1 to 9.2 ng/mL in 12 months; CT confirmed metastatic disease.

No follow up of actionable PSA: One AA patient whose PSA rose from 28 to 132 ng/ml in one year, had a family history of PCa, but ignored his PCP's recommendation to see a urologist. A physician-friend who was a member of his church told him he was already in his 70s, and there was no reason to do a biopsy because PCa "would take 20 years to grow." The friend also told him God said he should "anoint his prostate with oil." While it is possible that he already had metastatic cancer when PSA was 28, workup could potentially have identified treatable localized or locally advanced prostate cancer at that time.

Comorbidities: Three patients had actionable PSA levels but comorbidities caused them and their physicians to prioritize other medical issues. One patient's physician did not follow up rising PSA levels assuming the patient's lung cancer would lead to death before PCa. However the lung cancer was slow growing and PCa came to the forefront for treatment decisions. A second patient had localized colon cancer that required significant diagnostic evaluation and treatment. In some cases prioritizing other malignancies is reasonable, however for these two men it led to late stage prostate cancer diagnoses. A third patient had orthopedic comorbidities and thought he had been cured of prostate problems through treatment of benign prostatic hypertrophy.

Race and ethnicity—Figure 2 also shows racial categorization at each transition level. The 3 AA patients and one Hispanic (H) patient followed different paths. One AA patient had no insurance. One of the 2 AA patients with insurance was the patient who chose to ignore actionable levels of PSA exceeding 130 ng/ml for cultural reasons. The other AA patient was a 60-year old male with a family history of PCa who presented with metastatic disease despite a PSA of 1.8 ng/ml. The Hispanic patient had lung cancer; his PCP did not follow up actionable levels of PSA. The non-Hispanic white men include one who had no insurance and a second who presented with low PSA.

Discussion

This case series analyzes the root cause of late presentation among a series of men who presented with an initial diagnosis of metastatic cancer at our urban academic medical

center. We found that two principal medical decisions (not to test PSA annually and not to follow up on actionable PSA levels) contributed to late stage presentation in 80% of the cases (12/15). The three exceptions were men with aggressive disease who presented with mPCa despite low PSA levels (1.8 ng/mL) in one case and rapid increase in PSA in the two other cases. Metastatic disease despite a PSA under 2 ng/ml is very uncommon, ranging from 1–4% of cases.^{22,23}

Of the eight patients who did not have routine PSA testing, two lacked health insurance while 6 others saw PCPs who decided to forego regular testing because of a combination of PCP preference and comorbidities. In one case, the PCP decided against PSA testing for an AA patient who had a family history of PCa. This decision is consistent with the USPSTF recommendation, which does not take into account any risk factors; but AUA and EAU guidelines call for testing PSA in men with a family history of PCa or are AA,^{24,25} and the American Cancer Society recommends men “have an opportunity to make an informed decision with their health care provider about screening for PCa after they receive information about the uncertainties, risks, and potential benefits.”²⁶ Metastatic disease in the 6 men whose PSA values were not regularly tested illuminates potential risk associated with the new USPSTF recommendations. While conflicting data exists about whether PSA screening does confer a population based survival benefit, our study suggests *lack of psa* can be a feature in the causal pathway leading to late stage presentation. The population based impact of screening changes remain to be seen, but we have seen an increase in incidence of late stage presentation from 4.0% in 2011 to 7.3% in 2014 at SKCCC where we treat a PCa population with higher Gleason scores and greater likelihood of mPCa than the national PCa population.²⁷ The USPSTF recommended cessation of routine screening for men over 74 in 2008 and for all men in 2012. Based on divided opinions about the right path in clinical early detection and preventive care, the USPSTF decided in 2016 to undertake a new, systematic review of the evidence on impact of PSA-based screening on PCa morbidity and mortality and how those impacts vary by subpopulation and risk factors.²⁸ In a regional study during this time (2010–15), patients were referred at increasingly higher PSA levels and were referred to urologists less often.²⁹

Despite substantial outreach efforts in our plan to accrue 10 AA patients, we were able to accrue only 3 AA men to the study. Although 7 AA men were candidates for participation, 2 were not selected because they were unavailable for interviews, and 2 others dropped out after selection. Family emergencies, restrictive insurance precluding return visits and other personal issues explained these dropouts. Each of the 3 AA cases illustrated factors commonly associated with race disparities. One patient lacked insurance leading to no PSA screening. A second had aggressive disease despite low PSA levels. The third patient faced cultural issues in the form of church members who recommended strongly that he allow God to take care of him rather following physician advice to see a specialist in response to actionable PSA levels. Some evidence does exist that PSA screening may be appropriately increased among African American men.³⁰ However, the small number of AA men in our study limits detailed insights into this population. With respect to overall patterns of race based prostate cancer incidence, 20% is actually an over representation.

Our study reflects two limitations commonly associated with case series analysis including recall bias and potential exclusion of one or more important factors that could have led to late-stage analysis. To deal with recall bias, we used probing, open-ended questions to supplement the standard questions to test the logic diagram for each patient and identify additional elements that provided important detail. When appropriate we supplemented these data with data from medical records for all 15 patients. The second limitation of potentially important factors leading to late-stage presentation missed in our literature search or in our case series remains an unknown. The generalizability of our results is limited given our urban setting. Rural men with prostate cancer—especially those in underserved rural settings may have substantially different obstacles to prostate cancer setting. Additionally, to some extent setting of the study at a large urban medical center may limit generalizability—health systems and practices at a large academic center may differ from that in the community although in most cases the initial workup of men in our series was performed in a community setting. Despite this, our ability to analyze the unique factors in each man's path towards late diagnosis provides insight into the pathways leading to late stage diagnoses, which can complement large, population based studies and clinical trials.

Conclusions

Overall, late presentation is a result of patient, systems and cultural factors. This case series constitutes a qualitative root-cause analysis of the factors that may lead to late-stage diagnosis. These represent subjects for future academic study and as well as targets for systems and policy based interventions.

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Groups of factors associated with late presentation	Patient														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
(1) Lack of access (no insurance)															
(2) Access not utilized															
(3) No actionable PSA testing															
(4) Patient-level PSA cost															
(5) Comorbidities															
(6) Misdiagnosis of symptoms															
(7) Rising/elevated PSA															
(8) Symptomatic PCa															
(9) Reticence of patients to follow up															
(10) Aggressive disease															

Black cells indicate the primary causal factor for late stage presentation, determined jointly by Drs. Paller and Kanarek. Gray cells indicate factors also observed, but not the primary causal factor for late presentation. Bold groups of factors were included on the logic diagram (causal) and are included in Figure 2.

Figure 1.

Factors associated with late presentation present in each patient's treatment history.

Figure 2.
Flow chart of prostate cancer patients initially presenting with metastatic disease

Table I**Factors Tested for Relationship to Delayed Diagnoses**

Factor group	Relationship to Late Presentation	Findings
1. Lack of general access to health care	Patient lacks a usual source of care or has not seen a doctor for a number of years. Lack of insurance can be a contributing factor. Leads to lack of PSA screening and/or lack of follow-up to early symptoms of PCa.	✓
2. Access not utilized	Problematic when a patient's regular primary care physician leaves his or her practice and the patient has no ready access to another provider ⁶ or when the handoff between providers is faulty.	
3. No PSA testing	Patient does not know about PSA; physician does not discuss PSA testing; physician decides not to employ PSA testing due to PSA screening guidelines or other reasons, or simply that the patient was never tested.	✓
4. PSA cost issue	Inability to afford PSA testing leading to inadequate PSA screening frequency, and fragmented tracking of PSA velocity. However, the \$40–\$80 price of PSA testing may be low enough to be eliminate cost as a deterrent to PSA testing.	
5. Comorbidities	Physicians may focus on managing existing health problems and not on PCa screening. Anticipated comorbidities likely to be associated with late stage diagnosis were congestive heart failure, paralysis, weight loss (failure to thrive), anemias, and alcohol abuse, other cancers and advanced age.	✓
6. Misdiagnosis of symptoms	Delayed diagnosis may coincide with comorbidities when busy practitioners are faced with multiple problems in a single patient.	✓
7. Rising/elevated PSA	May be a high PSA; no follow-up PSA and high PSA velocity; or lack of a diagnostic workup, all leading to "late presentation."	
8. Symptomatic PCa	Patient <u>did not acknowledge symptoms</u> were serious enough to see a doctor, or attributed them to a current condition.	
9. Reluctance of patients to follow up	Lack of trust in clinicians may make this an especially important factor for patients who are African American and/or Hispanic.	✓

Table II

Patient Demographics and Disease Characteristics at Diagnosis

Patient	Race/ETH	Marital status	Health insurance	Family history of PCa	Age at diagnosis (years)	PSA at diagnosis (ng/ml)	Gleason score
1	W	Married	No	Yes	51	403	NA
2	AA	Unmarried	No	No	64	412	4+5=9
3	W	Married	Yes	No	70	286	5+4=9
4	AA	Married	Yes	Yes	78	380	4+5=9
5	W	Divorced	Yes	Adopted	41	26	4+5 = 9
6	W	Married	Yes	Yes	59	25	4+5=9
7	W	Unmarried	Yes	No	67	1550	NA
8	W	Widowed	Yes	No	69	112	4+4=8
9	W	Divorced	Yes	No	59	5	5+5=10
10	W	Married	Yes	No	73	26	NA
11	W	Married	Yes	No	69	9	5+4=9
12	W	Engaged	Yes	No	82	44	4+4=8
13	W	Married	Yes	No	74	1044	4+3=7
14	W/H	Married	Yes	No	62	15	4+5=9
15	AA	Married	Yes	Yes	60	2	5+4=9

W=white, AA=African American, H=Hispanic