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Disparities in PET imaging for prostate cancer at a tertiary academic medical center

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ABSTRACT

The purpose of this study was to evaluate differences between patients receiving ^{18}F-fluciclovine and ^{68}Ga-prostate specific membrane antigen (^{68}Ga-PSMA-11) for biochemical recurrent prostate cancer at a tertiary medical center.

Methods: All ^{18}F-fluciclovine and ^{68}Ga-PSMA-11 PET studies performed at the University of California, San Francisco 10/2015-1/2020 were reviewed. Age, race/ethnicity, primary language, BMI, insurance type, and home address were obtained through the electronic medical record. A logistic regression model was used to evaluate the predictor variables.

Results: 1,502 patients received ^{68}Ga-PSMA-11 and 254 patients received ^{18}F-fluciclovine. Black patients had increased odds of receiving imaging with ^{18}F-fluciclovine versus ^{68}Ga-PSMA-11 compared to non-Hispanic white patients (OR 3.88, 95% CI 1.90-7.91). There were no other statistically significant differences.

Conclusion: In patients receiving molecular imaging for prostate cancer at a single U.S. tertiary medical center, access to ^{68}Ga-PSMA-11 for Black patients was limited, compared to non-Hispanic white patients, by a factor of nearly four.

Key words

Health disparities, prostate cancer, PET, ^{68}Ga-PSMA-11, ^{18}F-fluciclovine

INTRODUCTION

Prostate cancer is the most common cancer in men in the United States (US) and the second most common cause of cancer death. In 2020, an estimated 191,930 new cases of prostate cancer will be diagnosed in the US and 33,330 men will die from the disease (*1*). In May 2016, the US Food and Drug Administration (FDA) approved the use of ^{18}F-fluciclovine positron emission tomography/computed tomography (PET/CT) imaging to evaluate disease burden in patients with suspected biochemical recurrent or persistent prostate cancer; this molecular imaging agent was covered for Medicare patients starting in 2017 (*2*). ^{18}F-fluciclovine is a synthetic amino acid that is not metabolized or incorporated into proteins. It targets the transmembrane amino acid transporters ACST2 and LAT1, which are overexpressed by prostate cancer cells (*3*). It improves the ability to detect metastatic disease when compared with conventional imaging (CT abdomen and pelvis or MRI pelvis and skeletal scintigraphy with ^{99m}Tc-labeled methylene-diphosphonate) and choline-PET/CT (*4,5*).

Prostate-specific membrane antigen (PSMA) is overexpressed on prostate cancer cells, and radiotracers targeting this antigen are increasingly used to evaluate extent of disease in patients with prostate cancer (*6*). The most commonly used PSMA-targeted radiotracer is ^{68}Ga-PSMA-11. Importantly, recent studies have shown that ^{68}Ga-PSMA-11 offers significantly improved detection rates compared to ^{18}F-fluciclovine (*7,8*). However, ^{68}Ga-PSMA-11 is not yet FDA-approved and has only been accessible in the US through clinical trials through a cost-recovery mechanism.

Health disparities in patients with prostate cancer by race/ethnicity are well-established (*9,10*). Incidence and mortality rates of prostate cancer are significantly higher in men of African ancestry when compared to men from other population groups in the US, the Caribbean, the

United Kingdom, and in parts of South America. Many interrelated factors have been noted as contributory, including differences in socioeconomic status and lifestyle exposures, access to healthcare, racial and ethnic discrimination, language and cultural barriers, and delayed disease diagnosis in socioeconomically deprived communities. The purpose of this study was to evaluate demographic differences between patients receiving ^{18}F-fluciclovine versus ^{68}Ga-PSMA-11 PET/CT imaging for prostate cancer at a tertiary academic medical center, in order to identify potential disparities in access to state-of-the-art care in intermediary steps of health delivery, which may contribute to disparities in prostate cancer health outcomes.

MATERIALS AND METHODS

Patient population

The study has been approved the institutional review board and the need for written informed consent was waived. All ^{18}F-fluciclovine and ^{68}Ga-PSMA-11 imaging studies performed at a single tertiary academic medical center between October 2015 and January 2020 were identified through a comprehensive search of the radiology report database. Patients undergoing ^{68}Ga-PSMA-11 PET imaging studies were enrolled in five separate prospective imaging trials performed under a cost-recovery mechanism (NCT02611882, NCT02918357, NCT02919111, NCT03353740, NCT03803475). The cost recovery mechanism is a mechanism provided by the FDA to allow for charging of patients or insurance companies for the direct cost associated with the manufacturing of a drug. The charge associated with cost recovery at our institution ranged between $900 and $1400, depending on the number of syntheses performed in a year.

Race/ethnicity (Asian American or Native Hawaiian/Other Pacific Islander, Black or African-American, Hispanic, Non-Hispanic White, or unknown), primary language (English or

Not English), body mass index, primary insurance payor (commercial, government, or unknown), and home address were obtained through the electronic medical record database. Duplicate patient records within each category of imaging study were removed. Maps depicting the distribution of patient zip codes were created for those receiving each of the two radiotracers through Google My Maps software (Mountain View, CA) (Figure 1).

Statistical analyses

Demographic characteristics were summarized for each patient cohort. Home addresses were geocoded to Census Block Groups and assigned to a tertile of neighborhood socioeconomic status (nSES) using a previously described composite measure based on statewide distribution (*11*). Demographic percentages were calculated for each group. The association of each demographic variable with use of ^{18}F-fluciclovine versus ^{68}Ga-PSMA-11 was modeled using a multivariate logistic regression analysis. All demographic variables were selected a priori on the basis of potential for related referral bias and all were included in the multivariable model. For patients missing specific demographic information, the available covariates were entered into the model. All analyses were performed using Stata (College Station, TX), and values with $p<0.05$ were considered statistically significant.

RESULTS

1,756 patients were included in the study, including 1,502 patients who received ^{68}Ga-PSMA-11 and 254 patients who received ^{18}F-fluciclovine (Table 1). Non-Hispanic white patients made up 78.8% of the entire study population (1,383/1,756) and minorities composed 21.2% (373/1,756). 66.6% of patients were from the highest tertile of nSES (998/1,498), followed by the middle

tertile (24.7%, 370/1,498), and the lowest tertile (8.7%, 130/1,498). Regarding the intersection of race/ethnicity and nSES, Black patients had the lowest percentage of patients in the highest nSES tertile (40.0%, 16/40) and the highest percentage of patients in the lowest tertile (27.5%, 11/40) (Table 2). Hispanic patients had the next lowest percentage of patients in the highest nSES tertile (51.0%, 26/51) and the next highest percentage of patients in the lowest tertile (25.5%, 13/51).

Age was similar among patients who received ^{18}F-fluciclovine (mean 69.8 ± 7.9 years) and ^{68}Ga-PSMA-11 (mean 69.6 ± 7.7 years). BMI was also similar between both groups. There were relatively few patients in the study that did not indicate English as their preferred language with non-English speakers making up 3.1% of the ^{18}F-fluciclovine group (8/254) and 1.9% of the ^{68}Ga-PSMA-11 group (28/1,502).

As seen in Table 1**,** Black patients had approximately four times the odds of receipt of ^{18}F-fluciclovine imaging compared to ^{68}Ga-PSMA-11(OR 3.88, 95% CI 1.90-7.91). There were no significant differences in other patient demographics between the two groups. A trend was noted toward increased odds of imaging with ^{18}F-fluciclovine compared to ^{68}Ga-PSMA-11 for patients identifying as Asian American or Native Hawaiian/Other Pacific Islander (OR 1.64, 95% CI 0.95-2.85, p=0.073). Patients with government insurance and increased age also showed trends toward increased odds of imaging with ^{18}F-fluciclovine, but the magnitude of the differences were relatively small.

DISCUSSION

This study found differential utilization patterns of molecular imaging modalities by race/ethnicity. While both ^{18}F-fluciclovine and ^{68}Ga-PSMA-11 have dramatically improved the ability to evaluate overall disease burden in patients with prostate cancer, ^{68}Ga-PSMA-11 has

emerged as the superior tracer with higher sensitivity (*7*). The current study demonstrates that when available through clinical trials, access to ^{68}Ga-PSMA-11 PET was significantly limited for Black patients, compared to non-Hispanic white patients, by a factor of nearly four.

The ways in which crucial intermediary steps in health care delivery between patient presentation and health care outcomes, such as advanced diagnostic imaging, contribute to disparities in health outcomes, are poorly understood across many disease types and imaging modalities. Disparities in health care imaging have been previously described, somewhat extensively in the field of mammography, and more generally with regard to the frequency of missed care opportunities, as well as differences in wait times to receive advanced imaging *(12-18*). A more recent study of the follow-up of incidental findings on abdominal imaging demonstrated that elderly patients and emergency department patients were less likely to complete follow-up imaging and that insurance status and race may also contribute to differences in follow-up rates (*19*). However, the literature examining disparities in radiology remains sparse. The current study demonstrates the essential need for more studies of this kind in radiology as a critical precondition for developing policies and procedures that can identify and eliminate structural barriers to equitable care delivery.

The exact factors that contributed to disparities in use of imaging in this study are unclear. As with disparities in prostate cancer health outcomes, different aspects of social determinants of health may play a role. Our nSES index included a range of variables including multiple measures of education, income, employment, and housing. The study population was more affluent than average with 66.6% of patients belonging to the highest statewide nSES tertile and also had a higher percentage of non-Hispanic white patients (78.8%) compared to regional census data (52.5%) (*20*). Neighborhood socioeconomic status was not a significant

covariate in our analysis, suggesting that additional factors contributed to the disparities that were observed. However, fewer Black patients belonged to the highest nSES tertile (40.0%) compared to non-Hispanic white patients (68.6%), and a larger percentage of Black patients belonged to the lowest nSES tertile than any other group (27.5%). The combined effect of these demographic patterns may have contributed to our results in ways that could not be directly demonstrated through our specific regression analysis. Additionally, of note, a recent study of the use of ^{18}F-fluciclovine in a separate tertiary academic medical center suggested possible under-referrals of Black patients for molecular imaging and similar trends may have occurred at our medical center. More work is needed to better understand the complex social and regulatory factors, including unconscious bias, that may influence imaging access (*21*).

While historically both imaging agents have been used for similar prostate cancer populations at the study institution, the most glaring difference between the routine use of each of these agents is that ^{68}Ga-PSMA-11 has only been available through research trials, while ^{18}F-fluciclovine is covered by both government and commercial payors, secondary to its FDA approval in 2016. Remarkably, despite the requirement for study participation and the possibility of self-pay, nearly six times as many patients in this study were imaged with ^{68}Ga-PSMA-11 compared to ^{18}F-fluciclovine. Thus, the current study's findings highlight potential disparities in access to imaging research trials for Black patients. This problem is common to many clinical trials but often can be difficult to detect, particularly in radiology trials, as many enroll relatively fewer patients (*22*). As we improve our understanding of how bias and racism may limit health care access, more work is needed to develop enrollment strategies designed to promote equitable recruitment, including novel digital marketing interventions, revised screening processes, and sliding scale financial reimbursement.

While this study draws meaningful conclusions, there are several limitations worth noting. For one, this is a single site retrospective study, therefore the study sample may not be representative of all patients for whom molecular imaging may be considered. The regression analysis did not adjust for disease attributes such as Gleason score or prostate specific antigen (PSA) laboratory value. However, current institutional-specific practice is that both of these modalities are used similarly and the use of exhaustive and relatively large study cohorts help to mitigate this potential confounder. Additionally, differences in individual drivers of nSES, such as income or wealth, may have contributed to the differences that we identified in our study if obscured by the larger neighborhood socioeconomic status composite.

Despite these limitations this study has several strengths. This study had a large sample size, which increased the ability to detect differences between the characteristics of patients who received each type of imaging study. The clear discrepancy highlights the need for more innovative and equitable recruitment strategies, as well as the important role that government regulatory agencies can potentially play in facilitating health equity. Data from ^{68}Ga-PSMA-11 PET trials is currently under FDA review and potential approval in the near future could increase the availability of this drug to more patients.

Finally, at many institutions, ^{68}Ga-PSMA-11 PET has only been available in clinical trials through a cost recovery mechanism, by which the FDA allows centers to pay for the cost of the radiotracer if no corporate entity is developing the drug (*23*). As ^{68}Ga-PSMA-11 was not patented, academia took the initiative in development and most trials were performed under cost-recovery. Through this mechanism, patients often would be financially liable for the direct cost of the radiotracer and possibly the cost of the technical component of the PET imaging, which

could pose a significant barrier to low income groups. Additionally, there may be variability in how individual institutions approved cost recovery across institutions.

CONCLUSION

The current study demonstrates that at one tertiary medical center, access to ^{68}Ga-PSMA-11 PET/CT was significantly limited for Black patients, compared to non-Hispanic white patients, by a factor of nearly four. Disparities in access to research trials and concerns about potential financial burden from the cost recovery mechanism may have contributed to differences in imaging rates. More studies evaluating potential disparities in utilization of imaging technologies, related to known social determinants of health, are essential for building equitable systems of health care delivery.

DISCLOSURE

No disclosures to report. All authors declare no conflicts of interest.

KEY POINTS

QUESTION: Are there disparities in PET imaging access for patients with suspected biochemical recurrent or persistent prostate cancer?

PERTINENT FINDINGS: A multivariate logistic regression analysis of 1756 patients who received ^{68}Ga-PSMA-11 or ^{18}F-fluciclovine PET imaging for prostate cancer at a tertiary academic medical center in the US, demonstrated that access to ^{68}Ga-PSMA-11 for Black patients was limited, compared to non-Hispanic white patients, by a factor of nearly four.

IMPLICATIONS FOR PATIENT CARE: Disparities in the use of PET imaging may contribute to disparities in health outcomes and more work is needed to better understand causative factors, including the role of bias and access to clinical trials.

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Figure Legends

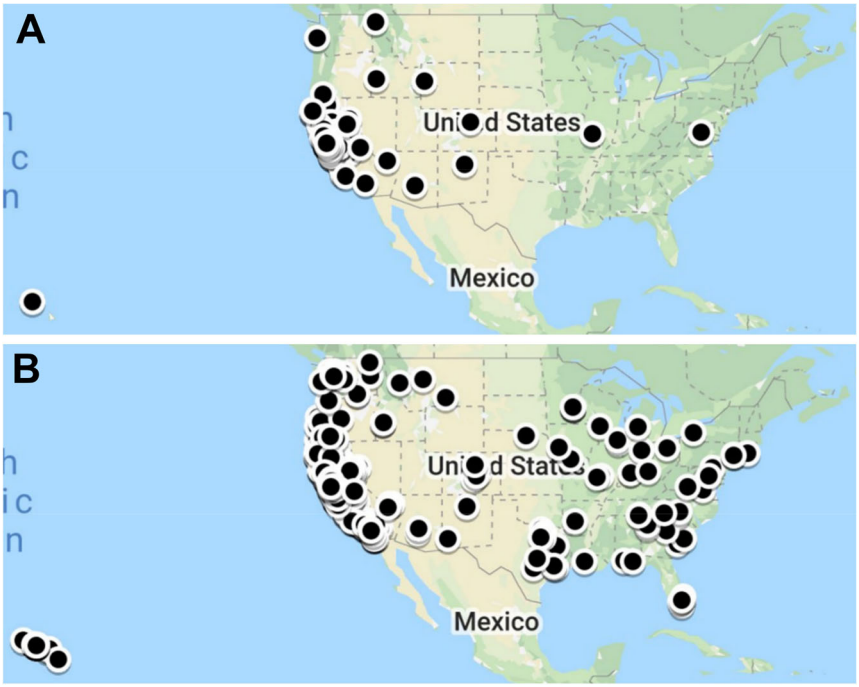

Figure 1. Mapped distribution of zip codes of patients receiving A) ^{18}F-fluciclovine or B) ^{68}Ga-PSMA-11.

Tables

Table 1: Demographic characteristics of patients undergoing ^{18}F-fluciclovine versus ^{68}Ga-PSMA-11 for prostate cancer and results of multivariate regression analysis.

	^{18}F-fluciclovine	**^{68}Ga-PSMA**	**OR (95% CI)**	**p-value**
All patients	254	1502		
Age (mean ± SD)	69.8 ± 7.9	69.6 ± 7.7	1.01 (0.99-1.04)	0.097
BMI (mean ± SD)	28.1 ± 4.0	27.7 ± 4.5	1.00 (0.97-1.04)	0.761
Race				
Non-Hispanic White	182 (71.6%)	1201 (80.0%)	1.00	
Black or African-American	17 (6.7%)	24 (1.6%)	3.88 (1.90-7.91)	<0.001
Hispanic	13 (5.1%)	45 (3.0%)	1.79 (0.84-3.81)	0.131
Asian American or Native Hawaiian/Other Pacific Islander	22 (8.7%)	87 (5.8%)	1.64 (0.95-2.85)	0.073
Unknown	20 (7.9%)	145 (9.6%)	1.06 (0.55-2.02)	0.87
Preferred Language				
English	246 (96.9%)	1474 (98.1%)	1.00	
Not English	8 (3.1%)	28 (1.9%)	1.29 (0.53-3.13)	0.581
Insurance Type				
Commercial	87/238 (36.6%)	478 (31.8%)	1.00	
Government	149/238 (62.6%)	929 (61.9%)	0.70 (0.48-1.01)	0.06
Unknown	2/238 (0.8%)	95 (6.3%)	0.39 (0.09-1.73)	0.215
Neighborhood Socioeconomic Status				
Highest tertile	143/235 (60.9%)	855/1263 (67.7%)	1.00	
Middle tertile	67/235 (28.5%)	303/1263 (24.0%)	1.27 (0.89-1.81)	0.194
Lowest tertile	25/235 (10.6%)	105/1263 (8.3%)	1.08 (0.62-1.91)	0.78

*Note: For any categories in which demographic information was missing from patient records, the new denominator is noted (Insurance Type and Neighborhood Socioeconomic Status).

Table 2. Distribution of neighborhood socioeconomic status (nSES) by race/ethnicity.

	Highest tertile	**Middle tertile**	**Lowest tertile**
All patients	998	370	130
Non-Hispanic White	808 (68.6%)	277 (23.5%)	93 (7.9%)
Black or African-American	16 (40.0%)	13 (32.5%)	11 (27.5%)
Hispanic	26 (51.0%)	12 (23.5%)	13 (25.5%)
Asian American or Native Hawaiian/Other Pacific Islander	74 (74.0%)	23 (23.0%)	3 (3.0%)
Unknown	74 (57.4%)	45 (34.9%)	10 (7.7%)