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Patient-Reported Financial Toxicity Associated with Contemporary Treatment for Localized Prostate Cancer

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Purpose: Contemporary treatment modalities for localized prostate cancer provide comparable overall and cancer-specific survival. However, the degree of financial burden imposed by treatment, the factors contributing to that burden, and how different treatments compare with regard to financial toxicity remain poorly understood.

Materials and Methods: The Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study enrolled men with localized prostate cancer from 2011 to 2012. Questionnaires were collected at 6, 12, 36, and 60 months after enrollment. Differences in patient-reported financial burden were compared between active surveillance, radical prostatectomy, and external beam radiotherapy using multivariable logistic regression.

Results: Among 2,121 patients meeting inclusion criteria, 15% reported large or very large burden of treatment costs within 6 months, declining to 3% by year 5. When controlling for age, education, income and other covariates, external beam radiotherapy was associated with greater financial burden than active surveillance and radical prostatectomy at 1 year (OR 2.2, 95% CI 1.2–4.1 and OR 1.5, 95% CI 1.0–2.3, respectively) and 3 years (OR 3.1 95% CI 1.1–8.8 and OR 2.1, 95% CI 1.2–3.7, respectively). Radical prostatectomy and active surveillance had similar rates of financial burden at all time points. Age, race, education, and D'Amico risk group were associated with financial burden.

Abbreviations and Acronyms

ADT = androgen deprivation therapy
AS = active surveillance
EBRT = external beam radiation therapy
EPIC-26 = Expanded Prostate Index Composite questionnaire
HMO = health maintenance organization
RP = radical prostatectomy
SF-36 = Medical Outcomes Study Short Form Survey
TIBI-CaP = Total Illness Burden Index for Prostate Cancer
VA = Veterans Affairs

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Conclusions: External beam radiotherapy was associated with the highest financial burden, even when controlling for age, education and income. Prospective studies that directly measure out-of-pocket and indirect costs and account more thoroughly for baseline socioeconomic differences are warranted in order to identify those most at risk.

Key Words: prostatic neoplasms, costs and cost analysis, patient reported outcome measures

With long-term overall and cancer-specific survival similar between most treatment options for clinically localized prostate cancer,[1] discerning health related quality of life outcomes has become essential to better counsel men with newly diagnosed disease. Financial toxicity can be defined as the distress or hardship experienced by patients due to the cost of cancer treatment. Despite evidence of the profound impact of financial toxicity associated with cancer treatment in the United States, little is known about the comparative financial burden experienced after contemporary treatment modalities for localized prostate cancer.

In the United States, 42% of patients with a new cancer diagnosis report depleting their entire life assets within 2 years of diagnosis, and nearly 10% of patients with breast, colon, lung and prostate cancer decline recommended cancer treatments due to concerns with cost.[2,3] As treatments become more technologically advanced, the costs associated with treatment continue to rise. Similarly, as we improve our ability to achieve longer lasting oncologic outcomes, patients may live longer and thus risk incurring greater costs of long-term care and surveillance. Despite improved attention to direct and indirect costs in recent years, patient-reported financial burden among men with localized prostate cancer treated with surgery, radiation, and active surveillance remains under-studied and poorly understood.

Utilizing the prospective, population-based Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study, we aimed to test the hypothesis that the patient-reported financial burden associated with prostate cancer treatment would vary by treatment modality. We also sought to determine patient factors associated with financial burden in order to better identify those most at risk and guide shared decision making.

METHODS

Study Cohort

The CEASAR study is a prospective, longitudinal, multicenter population based cohort study that enrolled men with clinically localized prostate cancer from 5 Surveillance, Epidemiology, and End Results (SEER) registries as has been previously described.[4] This study included men 80 years of age or younger who were diagnosed with clinically localized prostate cancer (cT1-cT2, PSA <50 ng/dl) in the 6 months prior to enrollment. Surveys were collected at baseline and at 6, 12, 36 and 60 months after enrollment. Institutional review board approval was obtained from each study site, and all participants provided informed consent.

We included all patients who underwent active surveillance, radical prostatectomy, or external beam radiation therapy with or without androgen deprivation therapy. Patients who received primary ADT or cryoablation were excluded. Patients receiving low dose brachytherapy were also excluded due to low representation in the cohort.

Outcomes

The primary outcome of this study was the degree of patient-reported financial burden at each time point after diagnosis, based on 4 questions that assessed the direct and indirect costs of treatment (supplementary Appendix, https://www.jurology.com). These questions were adapted for the prostate cancer population by the study methodologist/psychometrician (SHK) from a disease burden scale developed for the Medical Outcomes Study and used in the diabetes Patient Outcome Research Team study, among others.[5–7] For the purpose of analysis, financial burden was expressed as a binary variable grouping those who reported a "large burden" or "very large burden" vs those who did not.

Exposure

The primary exposure of interest was treatment with AS, RP or EBRT. We performed subgroup analyses to investigate EBRT patients treated with and without ADT, and RP patients treated robotically and open. Patients who crossed over from active surveillance to RP or EBRT within 1 year of diagnosis were re-classified on the date of treatment.

Covariates

Surveys captured patient-reported age, race/ethnicity, education, employment status, and marital status. The Total Illness Burden Index for Prostate Cancer was used as a measure of medical comorbidities.[8] Health insurance type was reported as Medicare, private/HMO, VA/military, Medicaid, other insurance or none. Patients with both private and Medicare insurance were classified under Medicare. We combined patients with VA/military, Medicaid, other insurance or no insurance due to small numbers of patients within each group.

Due to a high proportion of retired men in this population, patient-reported income was deemed an unreliable measure of baseline socioeconomic status. Instead, median household income from the patient home zip code, based on data from the American Community Survey, was used as a surrogate measure, as has been reported previously.[9]

Tumor characteristics were abstracted from health records and cancer registry data. Patients were categorized

into D'Amico low risk disease (clinical stage ≤T2a, Gleason score ≤6, and PSA <10 ng/dl), intermediate risk (cT2b or Gleason score 7 or PSA 10-20 ng/dl) or high risk (cT2c or higher, Gleason score ≥8 or PSA >20 ng/dl).[10]

The validated 26-item Expanded Prostate Index Composite questionnaire measuring sexual function, urinary incontinence, and urinary irritative, bowel, and hormonal function was utilized to evaluate patient-reported, disease-specific function at all time points.[11] The validated Medical Outcomes Study 36-Item Short Form Survey was utilized to evaluate general health related quality of life including domain scores for physical functioning, emotional well-being, energy and fatigue.[12] Questionnaires additionally utilized validated instruments to assess social support and participatory decision making style, and these covariates were included in the model to evaluate their effect on subjective financial burden.[13,14]

Statistical Analysis

Patient baseline demographic, socioeconomic, and clinical characteristics were summarized with median and interquartile range (IQR, continuous variables) or frequency and percentage (categorical variables) by treatment groups (RP vs EBRT vs AS). Differences among treatment groups were assessed using Kruskal-Wallis or Pearson chi-square tests. The proportions of patients who reported large or very large burden were compared between treatment groups at each study time point using Pearson chi-square test. To evaluate the trends of financial burden over time using the longitudinal survey data, we first fit logistic regression including treatment, time since treatment, and their interactions and then produced the trajectory of trends of burden for each treatment group. In the multivariable analyses, we further controlled for time since treatment (continuous, restricted cubic splines), age (continuous, restricted cubic splines), race, insurance status, zip code based median household income, education, marital status, D'Amico risk group, TIBI-CaP, study site, SF-36 scores (continuous, linear), social support (continuous, linear), participatory decision making index (continuous, linear), and preceding EPIC-26 domain scores (continuous, linear). In all models, we used the Huber-White method[15,16] that was implemented by *robcov* function in *rms* R package (R Foundation for Statistical Computing, Vienna, Austria) to estimate the variance-covariance matrices to account for the correlation due to repeated measurements collected on the same subjects from multiple time points. In order to allow for variable estimation of financial burden at different time points since initial treatment, we included the interaction terms between treatment group and time since initial treatment. Odds ratios and associated 95% confidence intervals were reported. All missing covariate values were imputed 10 times using multiple imputation using chained equations implemented by *aregImpute* function in *rms* R package. Statistical significance was considered for all 2-sided p values <5%. All analyses were conducted using R version 3.6.[17]

RESULTS

Altogether, 2,121 patients met the inclusion criteria, had available baseline zip code data, and completed at least 1 post-baseline survey (fig. 1). Patients treated with EBRT were older, had higher TIBI-CaP scores, higher risk disease and lower rates of private insurance, employment and income (all p <0.001, table 1). Among RP patients, 18% underwent open and 66% underwent robotic RP (16% had no approach documented). Of EBRT patients 76% were treated with IMRT, and conventional fractionation was used in 95%.

Longitudinal, unadjusted trends in financial burden between treatment groups revealed that the proportion of patients reporting financial burden due to treatment costs in this cohort was relatively low and decreased over time from 15% at enrollment to 3% at 5 years (fig. 2, supplementary table 1, https://www.jurology.com). EBRT was associated with the highest financial burden due to treatment costs and general finances at 6 months, 1 year, and 3 years (11%, 9%, 5% with respect to treatment costs, respectively; supplementary table 1, https://www.jurology.com). RP had the next highest financial burden, but was similar to AS after 1 year. The proportion of patients reporting

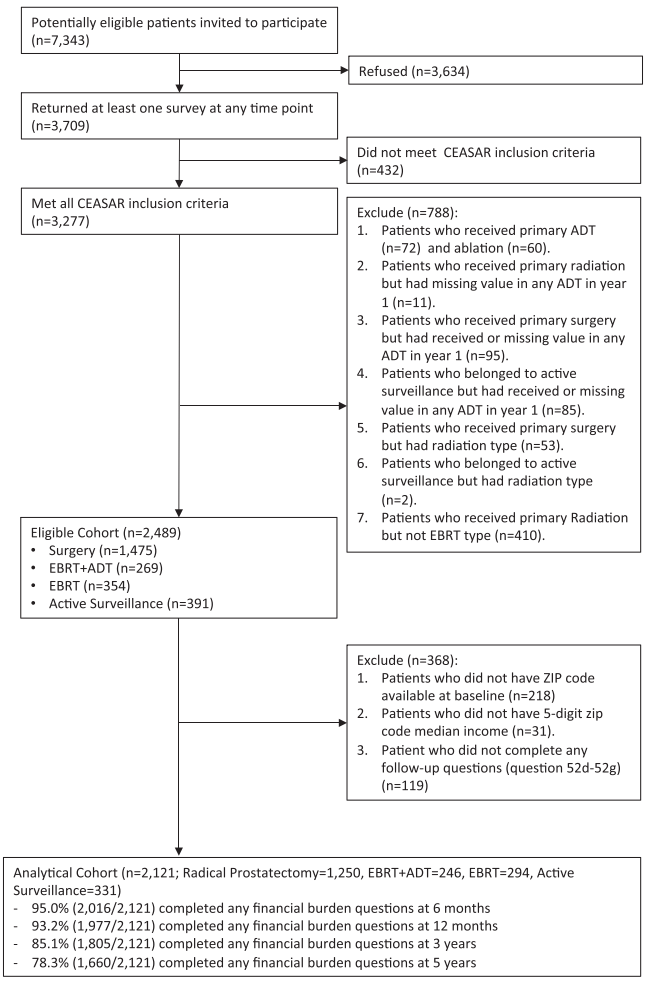

Figure 1. CEASAR study analytical cohort with 5-year data

Table 1. *Demographics and baseline characteristics of study cohort*

	No. Pts*	RP	EBRT	Active Surveillance	p Value
No. pts		1,250	540	331	
Median yrs age (IQR)	2,121	62.0 (57.0–66.0)	69.0 (64.0–73.0)	67.0 (61.0–73.0)	<0.001
No. race (%):	2,118				0.012
NonHispanic White		940 (75)	379 (70)	258 (78)	
Black		151 (12)	101 (19)	40 (12)	
Hispanic		105 (8)	35 (6)	20 (6)	
Asian		37 (3)	20 (4)	8 (2)	
Other		14 (1)	5 (1)	5 (2)	
No. education (%):	2,024				<0.001
<High school		99 (8)	84 (16)	24 (7)	
High school graduate		245 (21)	108 (21)	62 (19)	
Some college		265 (22)	116 (22)	66 (20)	
College graduate		280 (24)	105 (20)	74 (23)	
Graduate/professional school		292 (25)	107 (21)	97 (30)	
No. married (%)	2,019	991 (84)	386 (74)	258 (80)	<0.001
No. TIBI-CaP comorbidity index (%):	2,031				<0.001
0–2		405 (34)	90 (17)	84 (26)	
3–4		515 (43)	215 (41)	130 (40)	
5 or more		265 (22)	218 (42)	109 (34)	
No. health insurance type (%):	2,120				<0.001
Medicare		400 (32)	375 (69)	189 (57)	
Private/HMO		791 (63)	135 (25)	125 (38)	
VA/military		8 (1)	5 (1)	5 (2)	
Medicaid		14 (1)	11 (2)	3 (1)	
Other		18 (1)	5 (1)	3 (1)	
None		18 (1)	9 (2)	6 (2)	
No. employment (%):	2,107				<0.001
Full time		693 (56)	118 (22)	106 (32)	
Part time		91 (7)	40 (7)	36 (11)	
Retired		403 (32)	342 (64)	175 (53)	
Unemployed		56 (5)	34 (6)	13 (4)	
No. median household income by zip code (%):	2,121				<0.001
$30,000 or Less		46 (4)	44 (8)	11 (3)	
$30,001–$50,000		317 (25)	178 (33)	98 (30)	
$50,001–$100,000		775 (62)	274 (51)	189 (57)	
More than $100,000		112 (9)	44 (8)	33 (10)	
No. D'Amico risk group (%):	2,115				<0.001
Low risk		568 (46)	157 (29)	256 (78)	
Intermediate risk		514 (41)	246 (46)	65 (20)	
High risk		166 (13)	135 (25)	8 (2)	
No. site (%):	2,121				<0.001
1		340 (27)	217 (40)	92 (28)	
2		118 (9)	14 (3)	56 (17)	
3		171 (14)	45 (8)	35 (11)	
4		396 (32)	132 (24)	118 (36)	
5		225 (18)	132 (24)	30 I (9)	
Median baseline EPIC-26 score (IQR):					
Sexual function	2,008	78 (38–95)	58 (18–80)	75 (43–90)	<0.001
Urinary incontinence	2,037	100 (79–100)	100 (79–100)	100 (85–100)	0.44
Urinary irritative	2,027	88 (75–100)	88 (75–94)	88 (75–94)	0.1
Bowel function	2,071	100 (96–100)	100 (92–100)	100 (96–100)	0.008
Hormonal function	2,032	95 (85–100)	90 (80–100)	95 (85–100)	<0.001
Median SF-36 score (IQR):					
Physical function	2,040	100.0 (85.0–100.0)	90.0 (68.3–100.0)	95.0 (80.0–100.0)	<0.001
Emotional well-being	2,072	84.0 (68.0–92.0)	84.0 (68.0–92.0)	84.0 (72.0–92.0)	0.053
Energy/fatigue	2,073	75.0 (60.0–85.0)	70.0 (55.0–85.0)	75.0 (60.0–85.0)	<0.001
General health	2,115	80 (60–80)	60 (60–80)	80 (60–80)	<0.001
Median social support scale (IQR)	2,106	95.0 (70.0–100.0)	95.0 (70.0–100.0)	95.0 (70.0–100.0)	0.162
Median participatory decision making scale (IQR)	2,085	85.7 (71.4–92.9)	78.6 (63.8–89.3)	85.7 (67.9–96.4)	<0.001

* Number of nonmissing covariates out of 2,121 total eligible patients.

financial burden at 5 years was low (1%–3%) and similar between all groups. Similar trends were seen in the burden due to other health care costs and health insurance costs, with EBRT associated with the greatest frequency of financial burden at all time points through 3 years. On subgroup analysis of conventional vs hypofractionated EBRT there were no significant differences in burden at any time point.

We used our multivariable model to assess differences between treatment groups at specific time points, controlling for all covariates. EBRT was associated with greater burden of treatment costs than AS at 1 year (OR 2.2, 95% CI 1.2–4.1, p=0.01) and 3

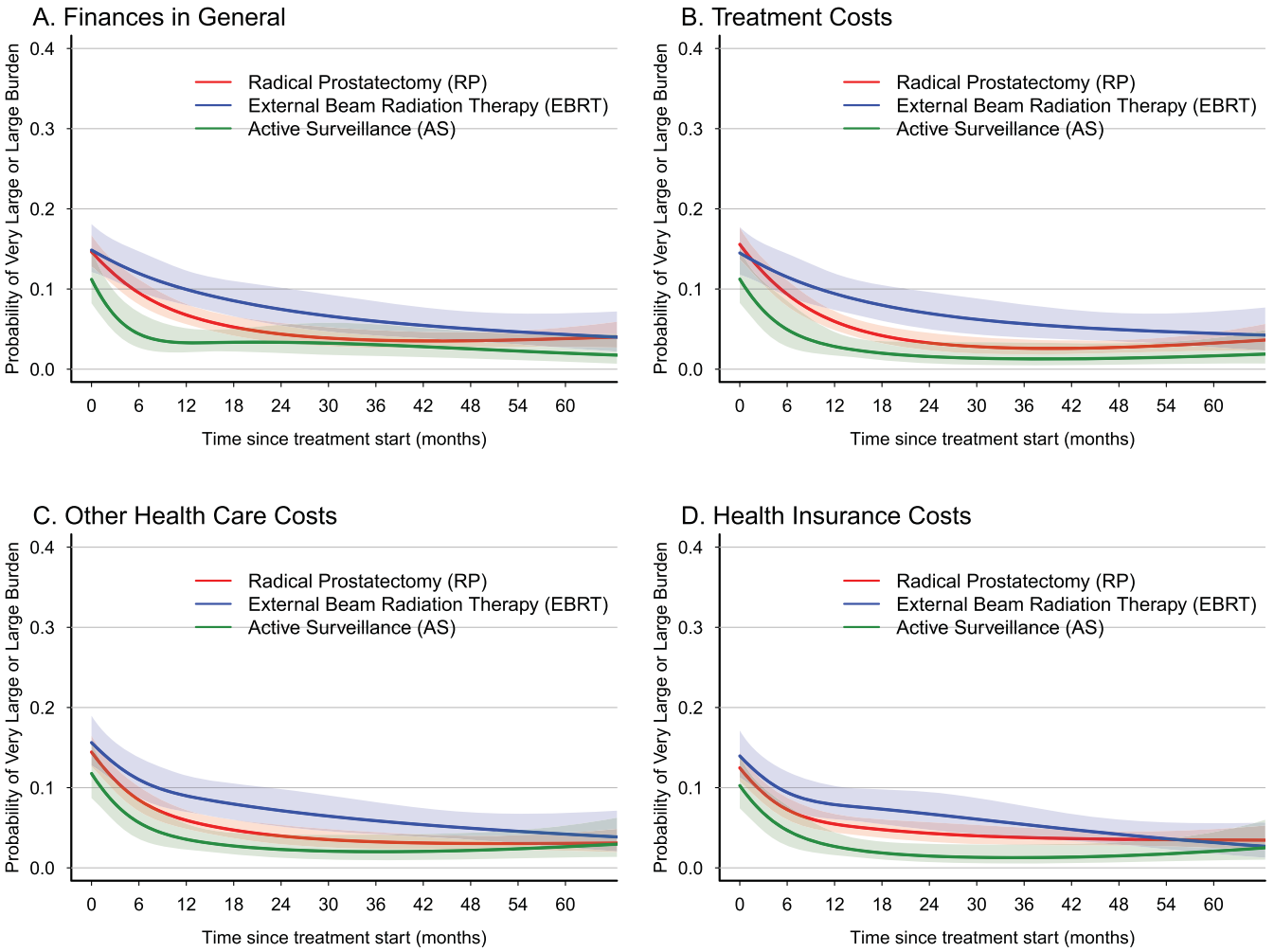

Figure 2. Unadjusted trends in financial burden by treatment groups over time

years (OR 3.1, 95% CI 1.1–8.8, p=0.034, table 2). EBRT was also associated with greater burden of treatment costs than RP at 1 year (OR 1.5, 95% CI 1.0–2.3, p=0.049) and 3 years (OR 2.1, 95% CI 1.2–3.7, p=0.015). RP and AS had no significant differences due to the burden of treatment costs at any time point.

Using our multivariable model we found that intermediate or high D'Amico risk group, younger age, nonWhite race and lower educational attainment were all independently associated with higher financial burden (table 3). The EPIC-26 hormonal domain score was the only functional outcome associated with subjective financial burden (OR 0.78. 95% CI 0.69–0.89).

In a subgroup analysis comparing EBRT alone vs EBRT+ADT, there were no significant differences between the 2 groups at any time point. The relationships between these 2 groups and the other treatments were similar to those seen in the model

Table 2. *Association of treatment choice with financial burden*

	6 Mos		1 Yr		3 Yrs		5 Yrs	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Due to finances in general								
EBRT vs RP	1.2 (0.8–1.8)	0.29	1.4 (1.0–2.0)	0.088	1.6 (0.9–2.9)	0.088	1.3 (0.7–2.5)	0.42
EBRT vs AS	3.0 (1.3–7.0)	0.011	2.2 (1.3–3.9)	0.005	1.4 (0.6–3.0)	0.45	1.9 (0.7–4.8)	0.20
RP vs AS	2.4 (1.1–5.6)	0.037	1.6 (0.9–2.8)	0.098	0.8 (0.4–1.8)	0.62	1.4 (0.6–3.3)	0.40
Due to treatment costs								
EBRT vs RP	1.2 (0.8–1.8)	0.35	1.5 (1.0–2.3)	0.049	2.1 (1.2–3.7)	0.015	1.5 (0.8–2.9)	0.20
EBRT vs AS	1.7 (0.7–4.4)	0.24	2.2 (1.2–4.1)	0.01	3.1 (1.1–8.8)	0.034	2.0 (0.7–5.6)	0.19
RP vs AS	1.4 (0.6–3.5)	0.44	1.5 (0.8–2.7)	0.20	1.5 (0.5–4.1)	0.44	1.3 (0.5–3.4)	0.57

Table 3. *Multivariable logistic regression analysis of financial burden due to treatment costs*

Covariate	OR (95% CI)
Median household income by zip code	0.89 (0.70–1.13)
Age quartile	0.61 (0.46–0.80)
Insurance status:	
Private/HMO	Reference
Medicare	0.73 (0.50–1.07)
VA/military/medicaid/other/none	0.84 (0.47–1.51)
Race:	
White	Reference
Black	1.59 (1.06–2.38)
Hispanic	3.02 (1.67–5.46)
Asian	2.26 (1.0–5.11)
Other	1.25 (0.34–4.61)
Education:	
<High school	Reference
High school graduate	0.72 (0.48–1.09)
Some college	0.48 (0.31–0.76)
College graduate	0.36 (0.22–0.59)
Graduate/professional school	0.33 (0.19–0.55)
Married	0.92 (0.65–1.32)
TIBI-CaP comorbidity index:	
0–2	Reference
3–4	1.14 (0.78–1.66)
≥5	1.09 (0.72–1.66)
D'Amico risk category:	
Low risk	Reference
Intermediate risk	1.50 (1.07–2.10)
High risk	1.58 (1.04–2.39)

Model controlled for SF-36 general health and physical function scores, social support, participatory decision making style, EPIC-26 domain scores and study site.

using the aggregated EBRT group (supplementary table 2, https://www.jurology.com). In a subgroup analysis comparing open vs robotic RP, there were no significant differences between the 2 groups.

DISCUSSION

In this longitudinal population based cohort study, we found that the proportion of men reporting a large or very large financial burden after treatment for localized prostate cancer is relatively low overall; less than a fifth of survey participants reported financial burden within the first 6 months, and this proportion declined over time. Men treated with EBRT experienced greater financial burden compared to RP or AS even after adjusting for age, education, income and other baseline patient characteristics. We found no difference in financial burden between RP and AS. Higher risk disease, younger age, Black or Hispanic race and lower educational attainment correlated with increased financial burden, suggesting patients with these characteristics may be at higher risk for financial burden.

Altogether, these longitudinal data indicate that EBRT is associated with a more prolonged burden of cost compared to surgery and AS. This is in line with a previous study by Jayadevappa et al who compared patient-reported out-of-pocket and indirect costs in a cohort of 512 men treated with RP or EBRT at a VA hospital and academic center.[18] They found surgery had higher mean out-of-pocket and indirect costs at 3 months vs EBRT ($5,576 vs $2,010) but lower medication and overall out-of-pocket and indirect costs at 24 months of followup. Notably, their study lacked an AS comparison group and did not assess the subjective experience of financial burden associated with the reported costs. Much of the remaining literature in the United States has utilized cost modeling to compare relative expense to the health care system between treatment modalities rather than direct costs to patients.[19–22]

The association of financial burden with socioeconomic factors such as race and education is in line with the results of previous studies in the United States and worldwide.[23–25] A 2010 observational study found 7% of patients with prostate cancer reported a "large amount of distress" from the cost of cancer care and that subjective burden was higher in patients with lower annual income.[3] While the study by Jayadevappa et al found that costs were inversely correlated to health related quality of life outcomes,[18] we found that the EPIC-26 hormonal domain score was the only functional outcome associated with financial burden. This finding may contribute to the association of financial burden with D'Amico high risk disease, in particular those receiving EBRT +ADT. We additionally found that younger age was associated with higher financial burden, which may be due to younger patients having higher rates of employment and inherently more indirect costs (eg opportunity cost of missed work) than those incurred in an older, predominantly retired population. Our findings of higher financial burden in Black and Hispanic men and in those with lower educational attainment should prompt further studies aimed at addressing disparities in prostate cancer care. Surprisingly, we did not find a significant effect of zip code based median household income, suggesting it may be a poor surrogate for the patient financial resources.

This study must be interpreted with several limitations in mind. First, the available data did not include a robust measure of patient financial resources at baseline, which raises the possibility of unmeasured confounding driving some of the observed differences. Second, we did not measure actual out-of-pocket costs or objective actions taken to address costs (eg selling assets, filing for bankruptcy), so the outcome measure, patient-reported financial burden, is somewhat subjective. Other aspects of financial toxicity such as treatment nonadherence and changes in work participation will be important to assess in future studies.[26] Nevertheless, while the questionnaire utilized to measure financial burden has not been validated in a

prostate cancer population, it was developed with methodological rigor and has been used in other populations. Third, although it was important to include underinsured patients in the final analysis, the small number of patients with VA/military, Medicaid, other or no insurance precluded accurate and precise estimates of the effect of these insurance types on our primary outcome. Finally, we did not include brachytherapy, an additional modality that may be associated with its own distinct trends in financial burden, given low accrual, and the low numbers of patients receiving hypofractionated EBRT also precluded meaningful multivariable analysis. Despite these limitations, our study captures a population based, ethnically diverse sample of men treated with contemporary modalities. The prospective, longitudinal cohort study design further enables us to evaluate changes in burden over time while limiting the effect of recall bias. This cohort also includes patients with various types of insurance as opposed to other studies that have utilized claims data and thus suffer from poor generalizability. Financial toxicity is dependent upon the health care system in which a patient receives care, and further study is warranted to evaluate this subject in other countries.

While we cannot ascertain from the available data why EBRT patients reported greater financial burden than other groups, differences in direct/indirect costs, variable perception of financial burden or residual confounding remain possibilities. Altogether, this study helps quantify the proportion of patients reporting significant financial burden associated with prostate cancer treatment and serves as a basis for further investigation into differences between treatments and identification of patients at risk for a high degree of burden.

CONCLUSIONS

For men with clinically localized prostate cancer, treatment with EBRT was associated with higher self-reported financial burden compared to RP and AS, both in aggregate and longitudinally. Patient level risk factors for financial burden include younger age, Black or Hispanic race, and lower educational attainment. Prospective studies, with robust measures of baseline financial resources and actual out-of-pocket costs, are needed to identify patients at risk for undue financial distress, which will better allow for shared decision making.

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