



Impact of Age and Life-expectancy on Treatment Receipt in High-risk Prostate Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. Authors KF, JJJ, SS, and NAB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KF, SS and NAB managed the analyses of the study. Authors JJJ and SS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background/Objectives: The incidence of Prostate cancer is increasing with age and active treatment of high-risk prostate cancer improves survival. However, it is uncertain how the age as contrasted with life expectancy impact treatment decision-making for men with clinically significant prostate cancer. The aim of this study was to determine whether age or life expectancy affected the treatment receipt.

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Participants: 541 men with high-risk localized prostate cancer (Gleason \geq 8 or PSA > 20) diagnosed between 2007 and 2013 were recruited to the study.

Measurements: Outcome variables included treatment underuse and type of definitive therapies such as radical prostatectomy, radiotherapy, androgen deprivation therapy and cryotherapy. Life expectancy was assessed according to Schonberg Prognostic Index.

Results: Among the 541 high-risk prostate cancer patients, older men (\geq 65 years) received definitive therapy at similar rates as younger men (97% vs 98%; $p=0.2$), while younger men were more likely to accept surgery compared with older men (95% vs. 72%, $p<0.001$). Age affected treatment choice depending on the patient's life expectancy. Among men with higher life expectancy, age did not affect surgery receipt (OR=0.62; 95%CI: 0.18-2.20). But among men with lower life expectancy, older age (OR=0.15; 95%CI: 0.06-0.38), black race (OR=0.27; 95%CI: 0.10-0.77), comorbidity (OR=0.31; 95%CI: 0.13-0.76) and non-commercial insurance (OR=0.12, 95%CI: 0.05-0.28) were associated with lower rate of surgical receipt.

Conclusion: Although most high-risk prostate cancer patients undergo definitive therapy, both age and life expectancy affected the type of treatment. Clinical decisions appear to be based on patients' medical condition and long-term outlook, rather than simply age. Non-clinical factors such as race and insurance play a role in treatment decision-making.

Keywords: Prostate cancer; radical prostatectomy; radiotherapy; cryotherapy; life expectancy.

1. INTRODUCTION

Despite its generally indolent nature, prostate cancer remains the second leading cause of cancer death among men in the United States (US). Older men are more likely to be diagnosed with clinically significant high-risk prostate cancer, and such cancers account for half of all prostate cancer deaths in the US [1]. For men with clinically significant prostate cancer, treatment can improve survival [2], yet even older prostate cancer patients with a good life expectancy, they often do not receive treatment similar to younger men [3].

A recent analysis of men with clinically significant non-metastatic prostate cancer showed that only 10% of men aged 75-80 with a 52% probability of living an additional 10 years received potentially curative treatment (radical prostatectomy or radiotherapy), suggesting that age rather than life expectancy affected treatment decisions making [3]. However, this work, based in Sweden, did not report race different, a known risk factor for more aggressive prostate cancers, treatment disparities and higher mortality rates [4,5]. Similarly, according to CaPSURE (Cancer of the Prostate Strategic Urologic Research), a longitudinal, observational registry of 13,805 US men with localized prostate cancer, of whom 10% were black, and older men were much less likely to receive local treatment [6]. However, only one-fifth of CaPSURE patients had clinically significant cancer. Although the most recent study showed a significant benefit of radical prostatectomy over radiotherapy among young

(age \leq 65) men [7], several other studies found that radiation therapy was as effective as radical prostatectomy for high-risk cancer treatment [8,9]. Despite the debate over the benefit of these definitive treatments, whether there is a treatment preference among older men is not well documented.

Based on the improvement of oncological care among older adults [10], the effectiveness of treatment in older men with high-risk tumors [11,12] and literature report of age and racial disparities in prostate cancer treatment, we tried to assess current treatment patterns among a group of high-risk prostate cancer patients to determine how patient age and life expectancy affect receipt of definitive treatment and evaluate whether there is a racial disparity in treatment receipt based on age or life expectancy. We focus on clinically significant prostate cancer, the type for which treatment has been proven to improve survival [8].

2. METHODS

2.1 Patient Selection

This study used data collected for a parent study on race and quality of prostate cancer treatment in which we included 637 cases of prostate cancer (PCa) from an academic tertiary referral center (2007-2012) and an urban municipal hospital (2007-2013). Cases were identified from pathology reports and the tumor registry to allow for the inclusion of all diagnosed cases regardless of treatment receipt. White patients

with similar age and Gleason score as black patients identified were selected into the study to ensure power. As we seek to identify cases in which treatment could significantly improve survival, we excluded metastatic disease at presentation (n=58). We also excluded patients due to factors that might have confounded treatment decision making and represented clinical exceptions, such as a history of previous cancer (n=26), or for whom treatment might not improve survival such as patients with poor prognosis in which office notes documented severe comorbidities such as end-stage renal disease or class IV heart failure (n=6) and cases where it was clear they were seen for the second opinion only (n=6). Second opinion cases were excluded because these patients sought treatment elsewhere. All cases identified as treatment underuse were called to participate in focus groups to assess reasons for treatment decision [13,14] reducing the chance that men identified with underuse were misclassified due to lack of documentation. This study only included PCa patients with high-risk cancer as defined by the D'Amico index (Gleason 8-10, pre-treatment PSA > 20, or pathological or clinical stage $\geq 2c$) [15]. Institutional review board approvals were obtained from both institutions.

Medical records of the remaining 541 men were reviewed and data abstracted for clinical characteristics including comorbidities, demographics, body mass index (BMI), Gleason score, prostate-specific antigen (PSA) level, smoking history, hospitalization in the prior year, and descriptors of functional status. D'Amico prostate cancer risk was calculated for each patient [15].

2.2 Estimated Life Expectancy, D'Amico Risk and Comorbidity

We estimated each PCa patient's overall prognosis using the 9-year Schonberg Prognostic Index [16], a validated tool to predict the likelihood of living 9 years among community-dwelling older adults based on age, gender, smoking history, history of cancer, diabetes, independence in instrumental activities of daily living and hospitalizations over the past year. Given the nature of chart data, former smoking status, self-rated health, and the number of overnight hospitalizations were frequently not available. With these missing data, our measure of the 9-year Schonberg Prognostic Index slightly overestimates patient life expectancy overall. There was no difference in missing data between

younger and older men. Life expectancy was dichotomized at the median, with those having $\geq 84\%$ 9-year survival based on the Schonberg Index classified as having a higher life expectancy. We used the Charlson Comorbidity Index to adjust for comorbid conditions [17] as this index assesses the risk of mortality.

2.3 Types of Treatment Received & Underuse of Definitive Treatment

Definitive PCa treatment was defined as having either received surgery (open, laparoscopic or robotically-assisted radical prostatectomy), radiotherapy (external beam radiotherapy and/or brachytherapy), cryotherapy, or androgen deprivation therapy (ADT) alone (if diagnosed before the publication of the seminal article establishing radiotherapy with ADT as the standard of care in 2009) [18] aligned with 2012 National Comprehensive Cancer Network (NCCN) guidelines [19]. In addition to definitive treatment overall, we examined factors affecting receipt of surgery vs less aggressive definitive treatment such as radiotherapy, cryotherapy, or ADT among high-risk patients.

2.4 Statistical Analyses

We dichotomized the study population into younger (< 65 years) and older groups (≥ 65 years) to assess whether there were age differences in receipt of definitive treatment and specifically, surgery. T-tests and chi-square tests were used, as appropriate, to compare patient characteristics between older and younger men and between those with higher vs. lower life expectancy. We used multivariable logistic regression models to determine which clinical and demographic factors most affected a patient's likelihood of receiving definitive treatment and of undergoing surgery. Interaction terms between age and life expectancy were added to assess whether there was effect modification by life expectancy on different age groups. Other interaction terms and collinearity were tested for the models, but none was significant in the final models.

3. RESULTS

3.1 Study Demographics

The mean age of our study population was 59.6 (± 8.3) years; 54% were black and 46% white (Table 1). Rates of public insurance were higher among the older men (19% Medicare only and 11% Medicaid for those in the older age group

vs. 1% Medicare only and 4% Medicaid among younger men; $p < .0001$). Older men were more likely to have at least one comorbidity (31% vs. 15%; $p < .0001$), higher PSA scores (13.3 ± 22.7 vs. 8.0 ± 8.8 ; $p = 0.01$), and lower life expectancy (67% vs. 35%; $p < .0001$). Black men were more likely than white men to have multiple comorbidities (27% vs. 10%; $p < .0001$), had lower life expectancy (50% vs. 39%; $p = 0.01$), and were less likely to have commercial insurance (73% vs. 89%; $p < .0001$) (not shown in tables).

3.2 Treatment Underuse and Types of Treatment Received

Among clinically significant high-risk PCa patients, 98% received definitive treatment, and younger and older men were equally likely to have received definitive treatment (98% vs. 97%, $p = 0.2$), but this difference was not statistically significant (Table 1). The 11 (2%) patients who did not receive definitive treatment were all black men who did not have commercial insurance. Patients who did not receive definitive treatment were more likely to have comorbid

Table 1. Patient characteristics by age groups

	Age < 65 y N=382 (71%)	Age ≥ 65 N=159 (29%)	p-value
Demographics			
Age, mean±SD (IQR [†]), years	56±6 (51-60)	69±5 (66-71)	-
Race			0.5
Black	201 (53%)	89 (56%)	
White	181 (47%)	70 (44%)	
Insurance			<.0001
3 rd party commercial	333 (87%)	102 (64%)	
Any Medicaid	15 (4%)	17 (11%)	
Medicare Only	4 (1%)	30 (19%)	
Self-pay	18 (5%)	3 (2%)	
Unknown	12 (3%)	7 (4%)	
Clinical characteristics			
Charlson Comorbidity Index ≥ 1	56 (15%)	49 (31%)	<.0001
Current Smoker ^{††}	52 (15%)	12 (8%)	0.06
PSA prior to diagnostic biopsy [†]	8.0 (8.8)	13.3 (22.7)	0.01
Gleason Sum			0.002
7	341 (89%)	123 (77%)	
8	20 (5%)	14 (9%)	
9+	21 (5%)	22 (14%)	
Stage ^{††}			0.002
IIA	0	5 (4%)	
IIB	259 (70%)	88 (67%)	
III	109 (30%)	38 (29%)	
Schonberg 9 Year Life expectancy			<.0001
High expectancy (≥84%)	247 (65%)	53 (33%)	
Low expectancy (<84%)	135 (35%)	106 (67%)	
Treatments Received			<.0001
Surgery (Radical Prostatectomy)	363 (95%)	115 (72%)	
Radiation Therapy(External Beam or Brachy)	11 (3%)	29 (18%)	
ADT alone before 2009	1 (0.3%)	10 (6%)	
ADT alone after 2009	1 (0.3%)	3 (2%)	
Cryotherapy	1 (0.3%)	0	
Active surveillance	0	0	
No treatment	5 (1%)	2 (1%)	
Underuse of definitive Rx ^{†††}	6 (2%)	5 (3%)	0.2

[†] IQR: Inter Quartile Range

^{††}Smoking status, PSA prior to diagnosis, and stage have missing data

^{†††}Underuse of definitive Rx is without surgery, radiation therapy, cryotherapy, ADT before 2009

conditions (64% vs. 18%, p=0.001) and lower life expectancy (73% vs 44%, p=0.07) than patients who received definitive treatment.

Among these high-risk PCa patients, 88% received surgery, and younger men were more likely to undergo surgery than older men (95% vs. 72%, p<.0001) (Table 1). Age was associated with the type of treatment received by patients with lower life expectancy but had no impact on patients with higher life expectancy (Table 2). Older men with lower life expectancy were significantly less likely than younger men with lower life expectancy to have undergone surgery (94% vs. 62%; p<0.001).

3.3 Factors Predicting Treatment Underuse and Receipt of Surgery

Multivariate logistic model adjusting for comorbidity found that treatment underuse was not associated with age (odds ratio [OR]=1.06; 95% confidence interval [CI]: 0.98-1.15) or lower life expectancy (OR=0.99; 95%CI: 0.19-5.16), but was associated with comorbidity (OR=6.26; 95%CI: 1.48-26.51).

In multivariate logistic regression model assessing factors associated with receipt of surgery, we found older age associated with lower odds of getting surgery (OR=0.24, 95% CI: 0.12-0.48) after adjusting for comorbidity, black race, insurance and life expectancy (Table 3). Life expectancy did not appear to be independently associated with receipt of surgery.

We found a borderline significant interaction between life expectancy and age (p=0.08), indicating there may be an effect modification by life expectancy across age groups. Thus, we stratified the analysis by life expectancy.

In stratified logistic models (Table 3), non-commercial insurance coverage was associated with a lower likelihood of receiving surgery (OR=0.22; 95%CI: 0.07-0.70 among patients with higher life expectancy; OR=0.12; 95%CI: 0.05-0.28 among patients with lower life expectancy). Among patients with higher life expectancy, black race and comorbidities were not associated with the likelihood of receiving surgery; but among patients with lower life expectancy, black race (OR=0.27; 95%CI: 0.10-0.77) and comorbidities (OR=0.31; 95%CI: 0.13-0.76) were associated with a lower likelihood of surgical treatment. Older age was not associated with receipt of surgery among patients with higher life expectancy (OR=0.62; 95%CI: 0.18-2.20) but was associated with a lower likelihood of receiving surgery among those with lower life expectancy (OR=0.15; 95%CI: 0.06-0.38).

4. DISCUSSION

Overall, we found that underuse of definitive treatment among high-risk PCa patients was very low. After controlling for sociodemographic and clinical factors, age and life expectancy did not affect definitive treatment receipt among high-risk PCa patients, based on qualitative interviews,

Table 2. Age and type of treatment by life expectancy

Primary treatment received	Age Group		P-value
	Age < 65 y (N=382; 71%)	Age ≥ 65 y (N=159; 29%)	
Higher life expectancy[†]			
Surgery (Radical Prostatectomy)	236 (96%)	49 (92%)	0.26
Radiation Therapy (External Beam, Brachytherapy)	8 (3%)	3 (6%)	
ADT alone before 2009	0	1 (2%)	
ADT alone after 2009	0	0	
Cryotherapy	0	0	
No treatment	3 (1%)	0	
Lower life expectancy^{††}			
Surgery (Radical Prostatectomy)	127 (94%)	66 (62%)	<.0001
Radiation Therapy (External Beam, Brachytherapy)	3 (2%)	26 (25%)	
ADT alone before 2009	1 (1%)	9 (8%)	
ADT alone after 2009	1 (1%)	3 (3%)	
Cryotherapy	1 (1%)	0	
No treatment	2 (1%)	2 (2%)	

[†]Higher life expectancy: Schonberg prognostic index estimated 9-year survival ≥ 84%

^{††}Lower life expectancy: Schonberg prognostic index estimated 9-year survival < 84%

Table 3. Factors associated with receipt of surgery

	Over all			High life expectancy [†]			Low life expectancy ^{††}		
	N=541			N=300			N=241		
	OR	95% CI		OR	95% CI		OR	95% CI	
Age ≥ 65 years	0.242	0.122	0.479	0.62	0.18	2.20	0.15	0.06	0.38
CCI* ≥ 1	0.33	0.161	0.678	0.26	0.05	1.19	0.31	0.13	0.76
Black race	0.319	0.146	0.697	0.43	0.13	1.49	0.27	0.10	0.77
Non-commercial insurance	0.142	0.074	0.274	0.22	0.07	0.70	0.12	0.05	0.28
Low life expectancy	0.65	0.302	1.397	-	-	-	-	-	-

*CCI: Charlson Comorbidity Index

†High life expectancy: Schomberg prognostic index estimated 9-year survival ≥ 84%

††Low life expectancy: Schomberg prognostic index estimated 9-year survival < 84%

11 patients were underuse of definitive treatment due to loss of follow-up [14]. Current guidelines recommend that men with clinically significant, high-risk PCa and a life expectancy independent of PCa of > 10 years should be considered for definitive treatment [20]. Previously, studies found that older men were more likely to receive conservative treatment, regardless of their disease characteristics or life expectancy [3,6,21]. In contrast, we found that after adjusting for cancer risk and comorbidities, older men had similar rates of receiving definitive treatment to younger men.

Decisions about the type of treatment in PCa patient are impacted by both age and life expectancy [6]. Among our patients with higher life expectancy, age did not appear to influence the type of treatment received. However, we found that older men with higher life expectancy were more likely to accept surgery compared to those with lower life expectancy, who tended to receive less aggressive treatment such as radiotherapy and ADT. Our findings are consistent with current guidelines for treating clinically significant prostate cancer in older men. The International Society of Geriatric Oncology recommends that treatments should be tailored to the individual's health status, driven mainly by the severity of comorbid conditions and functional status, as well as PCa progression risk [11].

Our results suggest that physicians and patients are tailoring their cancer treatment decisions based more on function, life expectancy benefit, and disease characteristics rather than historic concerns of stereotyping and limiting options by age [22]. To those with high-risk PCa patients and the—treatments are known to increase survival, we may have found higher treatment

rates than other reported in the literature. The high treatment rates we found support a growing trend of appropriate, more aggressive treatments being offered to and accepted by older cancer patients [10].

Our study also identified non-clinical factors that predict the use of less aggressive therapies, particularly among men with lower life expectancy. While the race did not appear to affect the type of treatment received in those with higher life expectancy, men with public insurance were significantly less likely to receive surgical treatment compared to men with private commercial insurance, especially black men. Physician recommendations and patient preferences are previously reported [13,14]. Qualitative studies revealed that black men preferred radiotherapy due to lower immediate risks of urinary incontinence and sexual dysfunction [23], a preference echoed among the men participating in this study [13]. As insurance significantly affects receipt of surgical treatment among patients with both lower and higher life expectancy, and race significantly affects the receipt of surgery among patients with lower life expectancy, it is worth noting that nonclinical factors continue to exert an impact on clinical decision-making [24].

As our parent study was to assess racial disparity in prostate cancer care, our sample patients were selected by matching on age and Gleason score for the equal number of black and white patients. This enabled us to have a large percentage of black patients with enough power to detect clinical and other non-clinical differences by race.

Our study is unique in which we were able to compute the life expectancy estimates use the information available to us. Other studies

evaluated the age differences in high-risk PCa treatment, which were only able to adjust for comorbidities [6,25] here we were able to adjust for both comorbidities and other factors included in Schonberg Prognostic Index that could be considered in PCa treatment decision making. The Schonberg Prognostic Index was developed among community-dwelling older adults, which has not been routinely applied to PCa patients or individuals younger than 65 years. However, this index is commonly used in clinical practice to aid physician decision-making [26,27].

Our study is limited in that we are unable to determine whether the differences in receipt of surgery between older and younger men, in terms of patient preference or physician recommendations. Our sample was limited to men treated at two urban medical centres so may not be generalizable to PCa patients treated in other settings. We did, however, include both a tertiary referral centre and a municipal hospital where nearly one-quarter of patients were publically insured or uninsured. Furthermore, the low numbers of patients who experienced underuse limited power to find significant associations. We may have also overestimated life expectancy due to missing data. As there were no differences in missing data in age group, it is unlikely that missing data exerted a differential effect. The Schonberg Prognostic Index was developed in community-dwelling older adults and is typically used to aid with the decision making of whether or not to perform screening tests, rather than to estimate overall life expectancy [28]. This index also has not been routinely applied to PCa patients or individuals younger than 65 years. However, it is commonly used in clinical practice to aid physician in decision-making [26,27].

In summary, underuse of definitive treatment among high-risk PCa patients is very low, and neither age nor life expectancy plays a role in receiving of definitive treatment after adjusting for other clinical factors. Age affects decision-making regarding the type of treatment (surgical vs other less aggressive definitive treatment) among patients with lower life expectancy but does not affect the surgical treatment received among patients with higher life expectancy. Surgery is likely considered as a riskier procedure and thus may be used less often to treat older PCa patients with lower life expectancy. Non-clinical factors (i.e. insurance and race) play a role in treatment

decision-making. Physicians and patients should discuss the risks and benefits of different treatment types, especially for older patients with lower life expectancy due to functional status or other comorbidities.

5. CONCLUSION

This study shows that underuse of definitive treatment among high-risk prostate cancer patients is very low, and the underuse is not associated with patients' age or life expectancy. However, the type of definitive treatment patient received is associated with patients' age and life expectancy. The clinical decision of the type of treatment appears to be based on patients' medical condition and long-term outlook, rather than age alone. Non-clinical factors such as race and insurance status remain to be factored in treat-decision making. These may serve as important information as to how different type of treatment affect patient outcome continues to unfold.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical permission approved by Institutional review board.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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