

# Individualized Decision-Making for Older Men With Prostate Cancer: Balancing Cancer Control With Treatment Consequences Across the Clinical Spectrum

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Prostate cancer (PCa) is the most prevalent non-skin cancer among men and is the second leading cause of cancer death in men. PCa has an increased incidence and prevalence in older men. Age-associated incidence is on the rise due to increased screening in the older population. This has led to a sharp rise in the detection of early stage PCa. Given the indolent nature of many prostatic malignancies, a large proportion of older men with PCa will ultimately die from other causes. As a result, physicians and patients are faced with the challenge of identifying optimal treatment strategies for localized PCa, biochemically recurrent PCa and later-stage PCa. Age-related changes can impact tolerance of hormonal therapy and chemotherapy in men with metastatic disease and shift the risk-benefit ratio of these treatments. Tools such as the Comprehensive Geriatric Assessment (CGA) can help estimate remaining life expectancy and can help predict treatment-related morbidity and mortality in older men. Application of CGA in older men with PCa is important to help individualize and optimize treatment strategies. Research that integrates multidisciplinary and multidimensional assessment of PCa and the patient's overall health status is needed.

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**C**omprehensive, personalized care for older adults with chronic disease is the cornerstone of geriatrics. Geriatrics strives to understand the biological, clinical, and psychosocial heterogeneity related to the aging process, all of which influence patient health and challenge physicians regarding decision-making for diagnosis and treatment.<sup>1</sup> Too often, high-quality data from well-designed clinical trials are lacking for older adults, leaving physicians to make management decisions without adequate information to guide them. This can lead to both overdiagnosis and overtreatment of older adults with comorbidities or cognitive impairment where harms outweigh the benefits of therapy, as well as to underdiagnosis and undertreatment for otherwise healthy older adults based

on age alone. Yet, physicians must act in the face of this complexity and uncertainty. We offer a framework for individualized decision making for older men with prostate cancer (PCa) using principles from geriatrics, focusing on the most common, but critical, clinical situations when decisions for these men are most acute and challenging.

Geriatrics care principles emphasize a multidisciplinary approach to evaluating multiple illnesses, cognitive-behavioral factors, social circumstances and late-life psychiatric challenges.<sup>2</sup> One crucial principle in decision-making for older adults is accurate estimation of remaining life expectancy (RLE) (Table 1). RLE varies by age, gender, comorbidities, patients' self-assessed health status, functional disability, and cognitive impairments. Each of these is a standard aspect of the Comprehensive Geriatric Assessment (CGA).<sup>3</sup> In addition, a diagnosis of cancer adds vulnerability<sup>4</sup> and gives rise to complex decisions for older patients and their families. The management of cancer in the older adult should be guided by individual estimates of RLE rather than by chronological age. One way to simplify the decision-making framework is to consider patients' RLE in three potential situations: (1) RLE without cancer (and no cancer-related treatment); (2) RLE with cancer and no cancer-related treatment; and (3) RLE with can-

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**Table 1. Upper, Middle, and Lower Quartiles of Life Expectancy for US Men**

Quartile	Age (yr)					
	70	75	80	85	90	95
Top 25%	18.0	14.2	10.8	7.9	5.8	4.3
50th percentile	12.4	9.3	6.7	4.7	3.2	2.3
Lowest 25%	6.7	4.9	3.3	2.2	1.5	1.0

Data from Walter L, Covinsky K. Cancer screening in elderly patients: a framework for individualized decision making. *JAMA*. 2001;285:2750.

cer and cancer-related treatment. This approach is the cornerstone of an individualized approach to care for older cancer patients, including PCa.

PCa is the prototypical age-associated disease. PCa incidence increases with age, peaking at 70 to 74 years, with a median age of patients living with the disease of 79 years.<sup>1</sup> It is the most common noncutaneous malignant disease and the second-leading cause of cancer death in American men,<sup>5</sup> and it is a major cause of suffering and healthcare expenditure for men in developed countries.<sup>6</sup> Due largely to the use of more sensitive diagnostic techniques, particularly prostatic-specific antigen (PSA) testing, PCa is now diagnosed more frequently and at earlier stages.<sup>7</sup> However, the majority of older men who develop PCa die from other causes and there is a gap between PCa incidence and mortality, with eight times as many men being diagnosed each year as compared to those dying from the disease.<sup>8</sup> Older men are more likely to be diagnosed with low- or intermediate-grade localized PCa, which may not impact their RLE.<sup>9</sup> As a consequence, the prevalence of PCa in older men is high, with many older patients living with the disease and the effects from treatment for many years.

The long latency period of PCa coupled with a high prevalence of indolent tumors in older men imposes a challenge on decision-making for the efficacy of screening and various treatment interventions.<sup>10</sup> Consequently, it is essential to identify which older men with PCa are most likely to suffer from PCa progression and a negative effect on survival within their RLE versus those patients who either have more indolent cancers and/or health conditions that limit RLE apart from the PCa diagnosis. In addition, it is crucial to understand the likely side effects of PCa treatments in these vulnerable older patients. In this article, we present and describe specific situations that older men and their physicians commonly face that are challenges for individualized decision making for PCa: (1) deciding whether or not to screen for PCa; (2) choosing among options for treating localized disease; (3) choosing when to initiate treatment for treating biochemical PCa

recurrence (BCR); (4) choosing among options for treating castrate-resistant disease, and (5) deciding whether to enroll in a clinical trial. The decision to screen or treat PCa should be based on high-quality data from studies that identify which subset of patients would most likely derive improved clinical outcomes.

## FRAMEWORK FOR INDIVIDUALIZED DECISION-MAKING FOR OLDER MEN WITH PROSTATE CANCER

A decision framework addressing the dilemma of PCa treatment in older men should contain two considerations. First, is the patient likely to derive survival benefit from management of his PCa in his RLE? By using known measures for estimating RLE, one can ascertain if benefit from the intervention is likely to be achieved within the patient's RLE. Patient comorbidities, functional impairments, and geriatric syndromes (including cognitive impairment) provide clinically useful, reasonably accurate estimates of RLE.<sup>11</sup> Second, in patients with limited RLE, where the chance of dying from non-PCa-related causes is higher, will intervention improve patients' quality of life (QOL)? Answers to these questions should be considered in the light of shared decision-making among physicians, patients, and families in choosing whether and when to screen, to initiate therapy, to continue or discontinue ongoing therapy, and when to shift to a primarily palliative focus. In this section, we will show how to estimate RLE in older men with PCa, applying commonly used geriatric assessment tools.

### Geriatric Assessment and Intervention Decisions in the Older PCa Patient

Given that older PCa patients often carry a high comorbidity burden, it is crucial to "stage the aging"—to assess the patient's physiological age as opposed to chronological age—when making treatment decisions.<sup>12</sup> Older patients are also more likely to be vulnerable or frail, and to have age-associated conditions that place them at higher risk of having health problems, either due to biological dysfunction or to social dependency. Frailty is a well-characterized geriatric condition with physiological underpinnings, defined clinical manifestations, and associated adverse outcomes, including falls, disability, hospitalization, and death.<sup>13</sup> An accepted operational definition of frailty is a syndrome in which three or more of the following are present: significant unintentional (lean) weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity.<sup>13</sup> This leads to accelerated functional decline and death, often within 2 to 3 years.<sup>14</sup> There are also biological markers of frailty, particularly those reflecting low-level inflammation such as interleukins (eg, IL-6), albumin, chole-

terol, and C-reactive protein (CRP) that have been used prognostically in older adults. Increases in IL-6 and CRP, and decreases in cholesterol and albumin, are associated with a decline in physical performance, reduced muscle strength, and increased mortality.<sup>15</sup> Complicating matters, cancer itself has been shown to independently increase vulnerability and frailty.<sup>16</sup>

Screening for a “geriatric” risk profile in older PCa patients is essential to estimate morbidity and mortality. The National Comprehensive Cancer Network (NCCN) Guidelines recommend that all cancer patients 70 years and older undergo some form of geriatric assessment.<sup>17</sup> Several screening tools have been developed to provide a validated global assessment of health in older cancer patients (Table 2). The multidimensional CGA provides an overarching measurement of multiple health dimensions, including functional status, medical comorbidities, cognition, nutritional status, social status, physiological factors, and medications.<sup>16,18–20</sup> Recent data demonstrate an independent impact of functional loss, depression, comorbidity, and cognition on prognosis, independent of Eastern Cooperative Oncology Group (ECOG) performance status or American Society of Anesthesiology (ASA) scoring.<sup>19,21</sup>

Recent studies clearly show a benefit in using CGA for older cancer patients. Unfortunately, wider adoption of these tools has been slowed due to limited clinic time and the difficulty for oncologists in easily interpreting results and implementing interventions in busy oncology practices. Development and validation of screening tools to identify those needing CGA that can be easily applied in busy oncology clinical practices is ongoing. One such instrument is the Vulnerable Elders Survey (VES-13), a 13-item self-reported questionnaire that assesses age, functional impairments, and self-rated health that has clear cut-off values associated with 3-year mortality prediction.<sup>22</sup> A small study (N = 43) of older breast cancer patients showed a strong correlation between a VES-13 frailty score >3 and CGA deficits.<sup>22</sup> In a cross-sectional observation study of men with PCa on androgen deprivation therapy (ADT) (n = 50), VES-13 score  $\geq 3$  had sensitivity of 0.87 for identifying impairment compared to CGA<sup>23</sup> (Table 3). In a multicenter, observational study of patients 70 and older with cancer (N = 419), the VES-13 had a sensitivity and specificity of 0.87 and 0.62, compared with CGA of 0.97 and 0.70, for predicting functional impairments.<sup>24</sup> Recent studies continue to validate the high sensitivity and specificity of VES-13 in predicting functional impairment and recommend its preliminary application as a tool to identify patients that require full CGA.<sup>24</sup> Overall, while the VES-13 is a promising candidate to serve as a screening instrument for CGA, it awaits larger, high-quality, randomized studies in multiple tumor types to support its widespread adoption (Table 3).

Decision-making for older men with PCa is complex

due to the disease’s often indolent biological nature, the potential for treatment-related toxicities, and the typically older patient age at diagnosis. Since the advent of PSA-based screening, the incidence and prevalence of PCa has risen dramatically. An estimated 217,730 new cases of PCa were diagnosed, and there were 32,050 PCa-related deaths in the United States in 2010.<sup>25</sup> Between 1995 and 2001, an estimated 91% of new cases of PCa were diagnosed at local or early stages, with 5-year survival now approaching 100%.<sup>26</sup> This long, often indolent disease course presents challenges in selecting those older men who would most benefit from screening and treatment for PCa. Competing causes of death are major contributors to mortality in PCa patients, particularly for those with low-risk disease.<sup>27</sup> In a study of Medicare beneficiaries with PCa, only 39% were found to have died from PCa.<sup>27</sup> Causes of death among PCa patients not dying from PCa were similar to the non-PCa decedents, primarily cardiovascular disease and other cancers. Even more importantly, initial treatment influenced the underlying cause of death in men with PCa. Men aggressively treated with radiation therapy with or without ADT had an adjusted odds ratio (OR) of cancer cause-related death 51% higher (OR 1.51; 95% confidence interval [CI], 1.08–2.10) than their non-PCa counterparts, while adjusted odds were 34% lower (OR 0.66; 95% CI, 0.47–0.93) in men who underwent watchful waiting.<sup>28</sup> So, not only do men with PCa die more often from other causes, but aggressive PCa therapy in those with multiple comorbidities may increase the chances of death from other causes due to treatment toxicities. In the Ohio Cancer Incidence Surveillance System, only 12% of older men with PCa were without comorbidity, disability, or geriatric syndromes.<sup>29</sup> In another study, half of men older than 70 years with PCa who were on ADT had abnormal scores on the VES-13, which identified them as being at risk for functional decline.<sup>23</sup> CGA subsequently revealed impairments in multiple domains: 19% in activities of daily living (ADL), 42% in instrumental activities of daily living (IADL), 56% in abnormal Short Physical Performance Battery (SPPB) scores, and 22% had fallen in the last 3 months.<sup>23</sup> These data suggest that ADT may be pushing older men with PCa toward frailty and vulnerability.

The decision to intervene and treat patients with PCa should be based on estimating RLE using CGA (Table 2). Following a CGA, patients can then be assigned to one of three groups: fit, vulnerable, and frail.<sup>30</sup> Fit men have no ADL or IADL impairments and no geriatric comorbidities (eg, dementia). Vulnerable older men are dependent in one or more IADLs, have stable comorbid conditions, and may possess mild cognitive impairment or depression without other significant geriatric syndromes. Frail older men have one of the following characteristics: age above 85, dependence on one or more ADLs, three or more comorbid-

**Table 2. Common Geriatric Assessment Tools**

Mini Nutritional Assessment (MNA)	The MNA is a validated nutrition screening and assessment tool that can identify geriatric patients aged 65 and above who are malnourished or at risk of malnutrition.
Mini Mental State Examination (MMSE)	The MMSE is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, and to follow the course of cognitive changes in an individual over time.
Geriatric Depression Scale (GDS)	This scale represents a basic screening measure for depression in older adults.
Activities of Daily Living (ADLs)	ADLs are measures of a person's daily functioning, the things we normally do in daily living like dressing, eating, transferring from bed to chair, bathing, bowel, and bladder control.
Instrumental Activities of Daily Living (IADLs)	IADLs are measures not necessary for fundamental functioning, but they let an individual live independently in a community including of light housework, preparing meals, paying bills, using the telephone and shopping for groceries.
Barthel Index	10 items measuring person's daily functioning, specifically ADLs and mobility.
ECOG Performance Status	Criteria used to assess how a patient's disease is progressing and to assess how the disease affects the daily living abilities of the patient.
Cumulative Illness Rating Scale for Geriatrics (CIRS-G)	The Cumulative Illness Rating Scale (CIRS) measures comorbidity. It measures the chronic medical illness burden while taking into account the severity of chronic diseases. The CIRS was developed and was later revised to reflect common problems of elderly people and renamed the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Then a modified CIRS version was developed and validated in an older residential population.
Euro-QoL 5D (EQ-5D)	EQ-5D is a standardized instrument used to measure health quality of life. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.
Pain Visual-Analogue Scale	A pain measurement instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured.
Short Physical Performance Battery (SPPB)	An objective assessment tool developed by the National Institute on Aging (NIA) for evaluating lower extremity functioning in older persons.
Vulnerable Elders Survey (VES 13)	A simple function-based tool for screening community-dwelling populations to identify older persons at risk for health deterioration, which includes one question for age and 12 items for self-rated health.
Senior Adult Oncology Program (SAOP2)	A screening tool to identify elderly persons at risk for disabilities.
Minimum Data Set (MDS) Suite	Suite of instruments built on a common set of assessment items that is considered important in all care settings of older patients.
Comprehensive Geriatric Assessment (CGA)	A tool providing an extensive assessment of multiple geriatric domains, namely, ADL, IADL, CCI, social valuation (Gijon),* cognitive evaluation (Pfeiffer test),† NSI scale, and number of medications.
Charlston Comorbidity Index (CCI)	A method to identify risk of death from comorbid disease for longitudinal studies. Scores range from 0 for least risk of 1-year mortality to 5 for highest risk for 1-year mortality.
Triage Risk Screening Tool (TRST)	A measure to calculate risk of institutionalization by looking at cognitive and social domains, fall risk, recent hospitalization, poly-pharmacy, and functional impairment.

Data from Balducci B, Colloca G, Cesari M, Gambassi G. Assessment and treatment of elderly patients with cancer. *Surgical Oncology* 2010;19(3):117–123.

\*Social valuation (Gijon): Gijon's Social-Familial Evaluation Scale (SFES) used to assess risk of institutionalization in older adults based on social support and community participation.

†Nutritional Screening Initiative.

**Table 3. Predictive Value of Vulnerable Elders Survey-13 Scores  $\geq 3$  for Identifying Impairment Compared With the Comprehensive Geriatric Assessment and Component Geriatric Domains**

Test	Score Range	Abnormal Score	Percentage Impaired				
			Sensitivity	Specificity	PPV	NPV	
CGA	NA	Deficits in $\geq 2$ tests	60	72.7	85.7	88.9	66.7
ADL	0–16	$\leq 14$ (dependence in any ADL)	24	83.3	60.5	40	92
IADL	0–14	$\leq 12$ (dependence in any IADL)	42	76.2	69	64	80
SPPB	0–12	$\leq 9$	50	72	72	72	72
Comorbidity score	0–54	$> 10$ or $\geq 2$ Comorbidities that interfere “somewhat” with daily function	34	76.4	63.6	52	84
No. of medications	0– $\infty$	$> 5$	46	69.6	66.7	64	72
MOS Social Support	0–5	Average score $< 4$	18	33.3	46.3	12	76
Short Portable Mental Status Questionnaire	0–10	$\geq 3$ Errors (mild cognitive impairment)	24	75	57.9	36	88

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; CGA, Comprehensive Geriatric Assessment; NA, not available; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; SPPB, Short Physical Performance Battery; MOS, Medical Outcomes Study.

Data from Mohile SG, Bylow K, Dale W, et al. A pilot study of the Vulnerable Elders Survey-13 compared with the comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who receive androgen ablation. *Cancer* 2007;109:802–10.

ties, or at least one significant geriatric syndrome (eg, falls).<sup>30</sup> Fit men should receive a level of care similar to younger patients. Vulnerable patients are divided into those with reversible or irreversible impairments. Men with reversible impairments should have their conditions treated prior to receiving care at a level similar to their younger counterparts. Vulnerable men with irreversible impairment and frail elders should receive modified interventions only if their risk of cancer-related mortality exceeds their mortality risk from existing comorbidities. Tailoring intervention by careful evaluation of the health status of the patient, using RLE and geriatric assessment methods to assess vulnerability and frailty, is key to ensuring individualized, appropriate, and effective treatment decisions in older men with PCa. We use the remainder of this paper to apply these principles to four key management decisions in older men: (1) screening, (2) localized disease, (3) biochemical recurrence, (4) the development of castrate-resistant disease, and (5) whether to enroll in a clinical trial.

### DECISION 1: TO SCREEN OR NOT TO SCREEN?

Screening decisions in PCa are challenging due to conflicting screening guidelines for men of all ages combined with conflicting data from randomized screening trials that include older men. Two large randomized trials, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of

Screening for Prostate Cancer (ERSPC), begun 10 years ago to determine whether screening for PCa using PSA led to decreased PCa-specific mortality, have failed to produce consistent results (Table 4). While the PLCO trial showed no difference in PCa-specific mortality after a 10-year screening follow-up, the ERSPC trial showed a 20% decrease in PCa-specific mortality in the screening group.<sup>8,31,32</sup> Of note, neither of these trials enrolled men over the age of 74. Furthermore, men aged 55 to 74 years with low baseline serum PSA levels (0.0–1.9 ng/mL) have limited benefit from continued and aggressive treatments.<sup>33,34</sup>

The new trials regarding the utility of PSA tests for screening have resulted in varying recommendations, explicitly tied to estimates of RLE and careful counseling of patients. The American Cancer Society (ACS) recommends that men over 50 years of age with a RLE of at least 10 years should be considered for screening.<sup>35</sup> The American Urological Association (AUA) recommends that men over 40 with a RLE of at least 10 years be considered for screening.<sup>36</sup> The American Geriatrics Society (AGS) suggests the decision to recommend PSA screening be individualized based on RLE without age considerations.<sup>37</sup> The US Preventive Services Task Force (USPSTF) says there is insufficient evidence to recommend for or against screening for men under 75 with at least 10 years RLE, and that men over 75 should not be screened regardless of RLE.<sup>38,39</sup> In summary, guidelines have relied on age and physician estimates of RLE to determine PCa screening appropriateness.<sup>40</sup>

**Table 4. Comparison of PLCO and ESPRC Trials**

	PLCO (10 years follow-up)	ESRPC (9 years follow-up)
N	76,693	162,387
Age (yr)	55–74	55–69
Centers	10 US	7 European countries
PSA cut-off (ng/mL)	4	3
Lead time (yr)	2	4.5
PCa mortality	174 (0.23%)	540 (0.33%)
Total = screen/control	(92/82)	(214/326)
PCa detected (N)/screening group	3,452/38,343 = 9%	5,900/72,890 = 8.2%
PCa detected (N)/control group	2,974/38,350 = 7.8%	4,307/89,353 = 4.8%
PCa detected/total(N)	6,426/76,693 = 8.4%	10,290/162,387 = 6.3%
Noncompliance	15%	18%
Contamination*	52%	20%
Relative reduction in PCa mortality	Insignificant	20%
Absolute reduction in PCa mortality	Insignificant	7.1/10,000

Abbreviations: PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; ERSRPC, European Randomized Study of Screening for Prostate Cancer; PSA, prostate-specific antigen; PCa, prostate cancer.

\*Contamination = serum PSA testing in the control population.

Correctly weighing the potential harms and benefits of PCa screening for individual older men in a clinical setting remains challenging. Older men with a poor health status and/or other significant comorbidities are often overscreened, and therefore experience harms related to PCa evaluation and treatment without a gain in RLE. For example, data from the Veterans Affairs health system show that more than half of men over 70 with more than four comorbidities, who have RLE significantly less than 10 years, still received annual PSA tests.<sup>41</sup> Conversely, older men with excellent health status who might benefit from early treatment of aggressive PCa may be underscreened. In 2005, nearly one third of men over 75 with a RLE of over 10 years did not receive an annual PSA test. It therefore remains unclear whether age and clinical factors related to RLE are being consistently applied in making screening recommendations.

Decision-making is further complicated by uncertainty regarding effective screening practices among men 75 and older owing to lack of randomized controlled trials in this age group.<sup>9</sup> The current trials do not adequately address individual patient characteristics such as comorbidities, functional status, and cognitive status, all of which can influence the likelihood of experiencing harm or benefit from screening, evaluation, and treatment. Clinicians continue to face challenges in offering effective strategies to men being screened for PCa, balancing screening results and treatment interventions.

Recognizing the uncertainty regarding benefits versus harm of screening for PCa in healthy older men, less fit

older men are faced with even more complex questions. Recognizing that older men have multiple comorbidities and are more likely to have functional and cognitive impairment, screening for this often indolent cancer will commonly subject these men to invasive testing and treatments with unclear mortality gains and greater morbidity burdens. Therefore, the fundamental question should not be when and how frequently these men should be screened but whether a specific older adult is likely to gain morbidity and mortality benefit from screening. Once again, an appropriate approach would be to assess the patient's RLE, including accounting for their comorbidity burden, cognitive impairment, and functional status. An otherwise healthy 75 year old man has an estimated life expectancy of 17 years, and he would potentially benefit from PSA screening.<sup>42</sup> In contrast, a 75-year-old man with multiple comorbidities and functional loss has an estimated life expectancy of 6.8 years and should not be screened. Clinicians should discuss the uncertainty regarding the benefits and risks from PCa screening, allowing men to make shared informed screening decisions. In addition, public policy should neither promote nor discourage its use without a firm evidence base.<sup>43,44</sup>

## DECISION 2: LOCALIZED PCa TREATMENT IN OLDER MEN

As the use of screening PSA has expanded, an increasing number of men are being diagnosed in earlier stages of PCa, when the disease is localized and the patient is asymptomatic.<sup>45</sup> In fact, the vast majority of

PCa is diagnosed when it is localized, with 91% of PCa cases in the Surveillance Epidemiology and End Results (SEER) database in 2000–2004, having localized PCa at the time of diagnosis.<sup>45</sup> Management decisions in older men with localized PCa are challenging in part because PCa is often an indolent, low-grade tumor and over half the affected population dies from other causes.<sup>26</sup> In general, there are similar mortality outcomes for radical prostatectomy (RP) compared with external-beam radiation therapy (EBRT) with or without ADT and active surveillance (AS). A recent randomized study explored survival outcomes based on serum PSA, Gleason score (GS), and clinical stage post-EBRT or RP.<sup>46</sup> Men were classified as low risk if: PSA <10 ng/mL, tumor GS ≤6, clinical stage ≤ T2a; intermediate risk if PSA 10–20 ng/mL, tumor GS 7, clinical stage T2b; and high risk if PSA >20 ng/mL, tumor GS 8–10, clinical stage ≥T2c.<sup>46</sup> It was found that PCa recurred in less than 25% of patients with low-risk disease, 25% to 50% with intermediate disease, and more than 50% with high-risk disease. Men older than 70 years had significant PCa-specific mortality only if they had high-risk PCa prior to presumed definitive treatment. In contrast, a randomized controlled trial of 695 men, age 65 or older, with early PCa randomized to RP or watchful waiting (WW), demonstrated reduced PCa-specific mortality in men with RP but no differences in overall survival between surgery and WW.<sup>47</sup> In a retrospective analysis comparing 767 men with localized PCa treated with WW versus primary ADT (PADT), the 15-year mortality rate was similar in both groups, slightly favoring WW over PADT.<sup>48</sup>

For low-grade localized PCa diagnosed early, the emerging management strategy of choice for older men is (pro)active surveillance (AS). AS allows close monitoring in men with favorable tumor characteristics (low-grade, small-volume disease) by serial PSA testing and repeating prostate biopsies. The choice between AS and active treatment depends on disease progression (increase in GS on histopathology and decrease in PSA doubling time [PSADT]).<sup>49</sup> AS continues to be an underutilized method of treatment for localized PCa, even though it has been shown to have similar survival outcomes compared to other treatment modalities. In a population-based Swedish study with 223 men of mean age 72 years, 5-year progression-free survival rates for men on AS were 83%, 50%, and 27% in those with well-, intermittent, and poorly differentiated malignancies, respectively.<sup>50</sup> Disease-specific mortality rate in men with well-differentiated disease was only 2.5%, signifying that AS achieved outcomes similar to invasive treatment in this subgroup.<sup>50</sup> A recent decision-analysis supports AS as the most cost-effective option for treating low-risk PCa.<sup>51</sup>

Despite these studies showing similar outcomes with AS, early intervention with RP or EBRT is the norm. In 2003, a review of the Cancer of the Prostate

Strategic Urological Research Endeavor (CaPSURE) database found that only 17% of men chose AS as initial treatment for low-grade, localized disease.<sup>52</sup> Patient anxiety about living with cancer for a significant period of time likely plays a significant role in the treatment decisions made.<sup>53</sup> A reasonable approach for guiding AS in fit older men is by correctly identifying low-risk (PSA <10, GS ≤6), low-volume disease (<3 cores, <50% of core involvement), and conducting 3- to 6-month PSA and Digital Rectal Examination (DRE) testing along with a scheduled repeat biopsy within one year of beginning AS.<sup>49</sup>

RP may be an effective treatment option for some older men with localized disease. To date, the two randomized controlled trials comparing WW and RP are the Scandinavian Prostate Cancer Group Study No.4 (SPCG-4) and The Veterans Administration Cooperative Urological Research Group Study (VACURG). SPCG-4 randomized 695 men with RLE greater than 10 years to RP versus WW.<sup>54,55</sup> Compared to WW, RP reduced all-cause mortality, disease-specific mortality (10% *v* 15%; *P* = .01) and metastasis (15.2% *v* 25.4%; absolute risk difference was 10.2% [CI, 3.1%–17.2%]).<sup>54</sup> VACURG was conducted in the early 1980s (before the PSA era) with 142 patients, and showed similar median survivals (10.6 years *v* 8.0 years).<sup>55</sup>

With newer laparoscopic surgical techniques, ensuring minimal nerve damage and faster postoperative recovery, excellent surgical outcomes have been reported in men of all ages. The most common complications include urinary incontinence (13%), urethral stricture (2%), and impotence (30%).<sup>56,57</sup> A study comparing outcomes in men categorized into young and old age groups (<55, 55–59, 60–64, 65–69, and 70+ years) after RP showed similar treatment outcomes by age.<sup>58</sup> Interestingly, multivariate adjusted, PCa-specific mortality was found to be lower in men over the age of 70 (Relative Risk (RR) 0.53; 95% CI, 0.30–0.90) while risk of progression was lower in the remaining age groups (RR 0.57–0.62). Despite recent studies showing favorable outcomes post-RP in older men, RP is not usually offered to men over age 70 independent of RLE due to perceived perioperative mortality risk.<sup>59</sup> Similar rates of postoperative complications are found in men between ages 65–69 and 70–74 after RP, but men 75 and older have been reported to have slightly higher rates of complications.<sup>60</sup>

EBRT is the most commonly offered treatment for older men with localized PCa.<sup>61</sup> There is a paucity of data comparing the two most commonly used treatment modalities, RP and EBRT. A randomized controlled trial involving 106 men with localized PCa (tumor state T1 or T2) conducted during the pre-PSA era showed superiority of RP over EBRT in preventing 5-year disease recurrence and incidence of distant metastasis.<sup>62</sup> Technologic advances in EBRT have improved treatment outcomes, especially related to tox-

icity. Commonly associated toxicities include erectile dysfunction (with increased numbers in men who received adjuvant ADT), radiation proctitis, nocturia and urinary frequency. The incidence of severe toxicities (grade 3 and above) is less than 5%.<sup>62</sup> Although EBRT and RP have similar survival outcomes, EBRT is usually preferred due to its minimally invasive nature.<sup>63</sup>

Brachytherapy, a treatment sometimes suggested to men with low-risk disease, involves radioactive seed placement at the tumor site, thereby providing higher local radiation doses than standard EBRT. The use of this treatment modality is limited due to paucity of data on long-term efficacy.

ADT, in which testosterone is lowered to undetectable levels, is achieved by orchiectomy or use of gonadotropin-releasing hormone (GnRH) agonists.<sup>64</sup> ADT is often given as primary therapy to older men with localized disease because they are often considered nonsurgical candidates based on age and comorbidity.<sup>65</sup> A cohort study reporting on 19,271 men aged 66 and older with localized PCa showed similar 10-year survival in men undergoing PADT versus conservative management (30.2% *v* 30.3%; hazard ratio 1.00; 95% CI, 0.96–1.05). In healthy older men with localized (T1–T2) PCa, the likelihood of death from competing causes exceeds the risk of death from PCa.<sup>65</sup> No randomized trials have compared PADT to other treatment categories.

ADT also has been studied and advocated for use as neoadjuvant or adjuvant therapy in combination with RP or EBRT. Of the four randomized control trials comparing RP with ADT versus RP alone, PCa-specific mortality, BCR, or distant metastases rates were similar.<sup>66–68</sup> Adjuvant ADT with EBRT has demonstrated improvement in overall and disease-specific mortality in men with high-risk localized PCa (PSA  $\geq$ 10 and GS  $>$ 6) compared to EBRT alone. However, the use of ADT was associated with increased side effects, including cardiovascular disease, in men with competing comorbid conditions.<sup>69,70</sup> Additionally, ADT with EBRT has shown a reversal in mortality risk in men with moderate to severe comorbidities.<sup>71</sup> Although these studies document disease-specific mortality, data on other clinically relevant outcomes, such as adverse events and QOL, are lacking.

When initially introduced, ADT was considered to have an acceptable trade-off of mortality gain for lowered QOL. However, it is now recognized that toxicities from ADT may lead to premature morbidity and mortality. ADT has been shown to significantly increase the risk of incident diabetes, coronary heart disease, myocardial infarction, and ventricular arrhythmias and sudden cardiac death.<sup>72</sup> In addition, duration of ADT has been significantly associated with increased fracture risk, sarcopenia, obesity, and frailty.<sup>72</sup> Clinicians are constantly faced with complex decision-making challenges in trading-off morbidity and mortality from

cancer control versus morbidity and mortality from ADT toxicity (Table 5).

Deciding between treatment options for localized PCa presents a major challenge due to lack of head-to-head RCTs comparing “optimal” treatments individualized to patient characteristics. Research is ongoing to develop tools aimed to assist with decision-making throughout the course of the disease. D’Amico et al, in 1998, proposed risk stratifying men for biochemical recurrence free-survival (BRFS) based on low, intermediate, or high risk of BCR based on serum PSA, GS, and tumor stage.<sup>73</sup> This classification has been adopted by several investigators when conducting head-to-head comparisons of treatment options for localized PCa. A study involving 6,652 men undergoing RP for localized disease randomized to no neoadjuvant or adjuvant ADT before BCR showed a 5-year BRFS of 84.6% overall and 94.5%, 76.6%, and 54.6% for low-, intermediate-, and high-risk groups ( $P < .001$ ).<sup>74</sup> However, men undergoing RP for high-risk disease were only a small fraction of the overall patient population (4.9% of high-risk patients in RP group *v* 67.7% in the low-risk group). Therefore, although this classification can give valuable information regarding men at higher risk for recurrence, a shift toward a low risk group (using D’Amico’s criteria) over time limits the clinical relevance of this classification.<sup>74</sup> The use of nomograms, which are algorithms based on clinical parameters used to predict probability of a primary end point, can help guide therapy. Many nomograms exist for localized PCa. Kattan nomograms, which focus on risk of long-term disease progression after localized therapy with RP, EBRT, and brachytherapy, have been developed and patients have been followed up to 7 years post-procedure (for RP).<sup>75</sup> However, nomograms often fail to include information on underlying health status and QOL. In addition, constant updating is also necessary as new prognostic information becomes available.<sup>76</sup> Decision analyses comparing four treatment strategies—RP, EBRT, WW, and delayed ADT—showed a 1-year quality adjusted life expectancy (QALE) benefit from RP or EBRT as compared to WW in men aged 60 to 65 years.<sup>77</sup> Conversely, the study showed harm from invasive interventions in men over age 70 years.<sup>77</sup> The importance of balancing cancer control with harms from therapy for older men is highlighted by such findings.

Despite extensive data to assist with individualized treatment options for older men with PCa, no single optimal treatment currently exists. To date, little is known regarding health outcomes (overall survival, disease-free survival), the comparative effectiveness (adverse effects, costs, quality of life) and ethical disparities associated with therapy for localized PCa. In the near future, studies such as the Prostate Cancer Intervention versus Observation Trial (PIVOT) will provide valuable additional insight into comparative effectiveness of therapy in an ethnically diverse popula-

**Table 5. Potential Complications of Prostate Cancer Treatment in Older Men**

Active surveillance	Disease progression Anxiety
External-beam radiation therapy	Nocturia Urinary frequency Impotence Radiation proctitis
Radical prostatectomy	Perioperative mortality Impotence Incontinence
Androgen deprivation therapy	Hot flashes Adverse quality-of-life effects: decreased sense of well-being and vitality Fatigue Impotence and decreased libido Sarcopenia and decreased muscle strength Declines in physical performance Declines in cognitive abilities Depression Osteoporosis and fractures Anemia Increased risk for diabetes and worsening of cardiovascular health
Chemotherapy	Fluid retention and weight gain Febrile neutropenia Anemia Fatigue Neuropathy Hyperglycemia Anorexia and weight loss Cardiovascular toxicity (with mitoxantrone)

Adapted with permission from Mohile et al. Management of prostate cancer in the older man. *Semin Oncol* 2008;35:597–617.

tion.<sup>78</sup> PIVOT is a large multicenter study, comparing RP or EBRT with AS in men with localized disease.<sup>78</sup> The study closed in January 2010 after 10 years of accrual, and results are awaited. Treatment choices often are based on institutional preference and expertise, physician referral, patient demographics, and social factors such as ease of transportation (favoring EBRT over RP). Older men are at greatest risk for undertreatment based solely on chronological rather than physiological age, as much as overtreatment.<sup>79</sup> This is likely a result of both, physician- and patient-related factors. Whereas the physician may suggest conservative measures based on age, older men with less anxiety also opt for less aggressive interventions.<sup>80</sup>

### DECISION 3: BIOCHEMICAL RECURRENCE— IS EARLY TREATMENT WITH ADT ADVISABLE?

ADT is the standard of care for metastatic PCa.<sup>44</sup> Treatment for BCR with ADT, although commonly used, remains controversial and is another decision that should be carefully individualized to the patient. In one

study, 303 patients with BCR selected from the CaPSURE registry were studied for significant predictors of time to initiate secondary therapy. PSA level, GS, and time to PSA failure were found to have a significant correlation with the development of progressive disease.<sup>81</sup> Of the men diagnosed with BCR, 57% received ADT and 43% received EBRT. ADT was the likely treatment given to men with higher PSA and seminal vesicle invasion.<sup>81</sup>

Once men are diagnosed and treated for localized PCa, assessment of disease response is determined primarily by serum PSA. BCR is defined by a rise in serum PSA after primary treatment prior to the development of clinical signs and symptoms of metastasis.<sup>82</sup> The PSA value that determines BCR depends on the previous treatment received. Men who received RP as primary treatment are considered “disease-free” if PSA is undetectable 6 weeks post-surgery; BCR after RP is defined by a PSA level of 0.4 ng/mL or higher.<sup>83</sup> Defining BCR in men treated with EBRT is challenging due to the presence of residual PSA-producing, noncancerous

prostate tissue. The American Society for Therapeutic Radiation Oncology (ASTRO) has defined PSA failure as a rise in three consecutive PSAs after a nadir is achieved.<sup>83</sup> Owing to various criticisms, alternative definitions have been proposed and a PSA level greater than nadir plus 2 ng/mL is now defined as BCR.<sup>84</sup>

While ADT is the cornerstone treatment for recurrent PCa, it is unknown if ADT improves mortality in men with BCR.<sup>85</sup> In a study of 1997 men treated with RP, 15% of men developed BCR 15 years after surgery.<sup>82</sup> Of these, 34% of men developed overt metastatic disease and the median survival time from the development of metastatic disease was 5 years.<sup>82</sup> In an observational study, BCR patterns were followed in 623 veterans post-EBRT and RP. Follow-up at 5, 10, and 15 years showed higher mortality in men with BCR. However, only a minority of men died from PCa regardless of the type of primary treatment (48% and 37% of patients, respectively) after 15 years of follow-up.<sup>85</sup>

The decision to treat with ADT should be individualized to the patient. In order to answer the critical question of whether ADT confers a survival advantage for BCR, it is imperative to identify the subset of patients, with the most aggressive disease and therefore the highest likelihood of benefit. Survival benefit has been observed in men with tumor-node-metastasis (TNM) stage T3 PCa<sup>86</sup> and in men with nodal metastasis treated with RT and pelvic lymphadenectomy followed by ADT.<sup>87</sup> These results should be interpreted with caution and may not apply to the group of men with BCR.

Patient characteristics that identify men with a higher risk for progression to clinical metastasis and death are GS, PSADT, and time to recurrence. Cancers with GS of 8 to 10 have a 75% recurrence risk within 5 years and are associated with worse overall outcomes.<sup>88</sup> PSADT of less than 6 months post-RP is associated with a higher risk of PCa death.<sup>89</sup> Patients with a PSADT of greater than 6 months after RP have a better 3-year metastasis-free survival rate than those with a shorter PSADT.<sup>89</sup> Shorter PSADTs (<12 months) also have been linked to PCa-specific death after EBRT.<sup>90</sup> D'Amico et al illustrated that PSADT of <3 months was a surrogate for PCa-specific death after EBRT or RP.<sup>91</sup> A less than 2 year time to PSA recurrence after RP is associated with worse PCa-specific mortality rates.<sup>92</sup>

Numerous nomograms and models that use pretreatment and/or pathologic factors in an attempt to identify men at a high risk of BCR after curative-intent therapy have been developed. These models may help with identifying those men most likely to benefit from early ADT. Pretreatment PSA, GS, presence of extraprostatic extension, positive surgical margins, and preoperative PSA velocity all have been correlated with BCR and have been included in nomograms.<sup>93</sup> Other important factors include pathologic stage, tumor volume, race, angiogenesis (measured by immunohisto-

chemistry using the monoclonal antibody CD34),<sup>94</sup> and a variety of molecular markers.<sup>95</sup> Although it is clear that the combination of multiple factors can better predict BCR and PCa-specific mortality, the accuracy of these combinations must be validated in different populations.

Changes in the type of ADT available have shifted significantly over the decades largely due to patient preferences rather than demonstrated improvement in outcomes. Bilateral orchiectomy has fallen out of favor due to a perceived negative psychological impact on men. Medical castration can be achieved through complete androgen blockade with the use of GnRH agonists combined with an anti-androgen therapy to prevent an initial testicular testosterone "surge."<sup>96</sup> Complete androgen blockade is a common approach to treatment of BCR; however, wide practice variation exists due to conflicting data. The largest experience, from the Prostate Cancer Trialists' Collaborative Group, demonstrated a small (2.9%) but in significant improvement in 5-year survival for maximal androgen ablation compared to single-agent castration alone.<sup>97</sup> Other groups report a larger benefit, although the value of combination therapy for asymptomatic patients with BCR remains unproven.<sup>98-100</sup> To date, studies have failed to show a significant survival advantage of complete androgen ablation versus castration alone, and single-agent blockade with a GnRH is the standard of care.

The timing of when to initiate ADT for BCR also has been the subject of debate. A large study evaluated outcomes of 1,352 men with BCR who were administered early ADT or late ADT.<sup>101</sup> Men in the early ADT group received ADT after PSA recurrence without evidence of clinical metastasis, whereas men in the late ADT group received ADT after clinical metastasis. The primary endpoint was development of clinically overt metastatic disease. Early ADT in men with a Gleason score of 7 or greater and a PSADT of 12 months or less was associated with a delay in clinical metastasis (hazards ratio 2.12,  $P < .01$ ). However, there was no effect on the overall prevalence of clinical metastasis in the total cohort. Nevertheless, the use of early ADT in men with high-risk PCa is often recommended due to studies that have noted a survival benefit for patients with tumor characteristics associated with aggressive disease.<sup>102</sup>

Once initiated, ADT is typically continued life-long, and many men live with the toxicities from ADT for many years.<sup>82</sup> Commonly recognized adverse effects include hot flashes, decreased libido, and erectile dysfunction. The impact of ADT on osteoporosis including risk of fracture has been well described, with bone loss rates from 1.0% to 4.6% yearly in men on ADT for nonmetastatic disease.<sup>103</sup> Men on ADT are 13% to 30% more likely to develop a fracture as compared to PCa patients not on ADT.<sup>104</sup> More recently, ADT has been linked in observational studies to worsening of certain

comorbidities, including diabetes and cardiovascular disease, especially in those patients who had these underlying conditions prior to initiation of treatment. In large population-based studies, ADT increased the risk of cardiovascular morbidity by approximately 30%.<sup>12</sup> Physical and cognitive problems, what geriatricians call “frailty,” are prevalent in an at-risk population of elderly PCa patients undergoing treatment with ADT.<sup>105</sup> ADT is associated with loss of lean body mass, or sarcopenia. Sarcopenia in the elderly is linked to a greater risk of falls, functional dependence, and frailty.<sup>105-107</sup> Although there are no studies that clearly demonstrate a causal effect between ADT and cognitive impairment, 20% to 25% of older men on ADT score in the “impaired” range on cognitive screening tests.<sup>108</sup> Due to the potential interactions between age and ADT, it is imperative to recognize those toxicities that can differentially affect the QOL and function of elderly men with PCa and develop an approach to management that accounts for these issues.<sup>109</sup>

#### DECISION 4: TREATMENT FOR PATIENTS WITH CASTRATE-RESISTANT PCa

Although most older men with PCa do not die from this disease, PCa still remains the second leading cause of male cancer-related death. Despite the initial efficacy of treatment, it is accepted that over time, patients with metastatic PCa on ADT will develop hormone-resistant progressive disease. This transition represents an important clinical landmark of an evolving disease that correlates with an increased risk of death and morbidity, even for a patient who is asymptomatic. This change is described as a progression in the clinical states model used to describe PCa evolution.<sup>110</sup> More recently, the Prostate Cancer Clinical Trials Working Group has established the working terminology and operational guidelines for patients with castration-resistant prostate cancer (CRPC). Essentially, CRPC is defined as progression of disease despite castrate levels of testosterone (<50 ng/dL). This definition includes a wide phenotypic range of patients from those with very indolent, but nonetheless progressive disease by PSA, to patients with rapid symptomatic and radiographic progression despite optimal ADT. In the context of the individualization of PCa care for older men, we will further subdivide the decision-making process for CRPC into several key questions.<sup>111</sup>

#### Does the Patient Need Cytotoxic Chemotherapy?

Historically, PCa was considered a malignancy that did not respond to cytotoxic chemotherapy. Chemotherapy now has a role in the treatment of CRPC and is an option for selected older patients. Mitoxantrone was the first chemotherapy drug approved and gained FDA

approval for its palliative benefits in men with symptomatic CRPC.<sup>112,113</sup> Two studies evaluated mitoxantrone with prednisone (*v* prednisone alone) and mitoxantrone with hydrocortisone (*v* hydrocortisone alone) for CRPC. These studies included a significant proportion of older patients with median age around 70 years. In both studies, improvements in QOL were noted and toxicity was low. In one study, patients treated with mitoxantrone had significant pain relief 29% of the time, compared to 12% with prednisone alone ( $P = .01$ ). Although neither study demonstrated a survival benefit with mitoxantrone, the FDA approved mitoxantrone for palliative treatment of hormone-resistant PCa.

Following FDA approval of mitoxantrone, chemotherapy was considered strictly palliative and was reserved for the latest stages of disease. The current standard of care for first-line chemotherapy for CRPC is docetaxel.<sup>114,115</sup> Two pivotal phase III studies demonstrated improved survival with docetaxel in combination with estramustine or prednisone compared to mitoxantrone plus prednisone in men with CRPC.<sup>115,116</sup> The Southwest Oncology Group (SWOG 9916, N = 674) study demonstrated a significant improvement in survival with the combination of docetaxel (60-70 mg/m<sup>2</sup> every 3 weeks) and estramustine, compared to mitoxantrone and prednisone (17.5 months *v* 15.6 months,  $P = .02$ ). The median age of the study population was 70 years, and 90% of patients in the docetaxel arm had a performance status of 0-1. The TAX 327 study compared two schedules of docetaxel 35 mg/m<sup>2</sup> weekly (n = 334) and docetaxel 75 mg/m<sup>2</sup> every 3 weeks (n = 315) plus prednisone versus mitoxantrone plus prednisone (n = 337) and demonstrated a significant survival benefit for the docetaxel treatment. In subgroup analyses, including those in older patients, a survival advantage of docetaxel over mitoxantrone persisted (hazards ratio 0.80 for men  $\geq 75$  years of age).<sup>116</sup>

Despite proven survival and palliative benefits of chemotherapy, the decision of when to start chemotherapy and in whom remains a major concern for patients with CRPC, especially for older men. Older patients were included in the pivotal TAX 327 study. The median age was 68 years, and with approximately 20% of those treated aged  $\geq 75$  years. Although docetaxel is typically well tolerated, even in older adults, it does have well-known side effects. Significant fatigue is seen in the majority of patients and grade 3/4 neutropenia, diarrhea, and neuropathy are all seen in approximately one third of patients treated. In a recent review of patients older than 75 years of age treated with docetaxel for metastatic CRPC, nearly 50% had grade 3 or 4 toxicities, 40% had at least one nonhematologic grade 3/4 toxicity, and treatment-related mortality was significant at 2.5%.<sup>117</sup> Furthermore, the vast majority of the patients studied in the landmark do-

docetaxel studies had significant pain.<sup>115-117</sup> Taken together, it is reasonable to reserve chemotherapy for the older patients that are most fit for chemotherapy, and therefore least at risk from the known toxicity, and for those in need of disease palliation (ie, those with symptoms). Studies to determine who is “fit” for chemotherapy are still needed, although general guidance from CGA is a reasonable starting point (Table 2). For the most part, RLE for patients with CRPC is limited by progression of the cancer rather than other medical or functional problems. Generally, chemotherapy for metastatic, symptomatic CRPC should be considered for all patients given that the agents are well tolerated and efficacious. Those patients who are more vulnerable or frail by CGA criteria may require dose-reduction, additional supportive measures (eg, growth factor support), and close attention to other health status and social support issues.

### If Not Chemotherapy, Then What?

There is a subset of patients, including older men, that warrant other therapeutic considerations. These patients include those with minimal or no symptoms from PCa despite progression of disease while castrate, or those in whom their fitness or comorbidities preclude chemotherapy. For years, secondary, tertiary and even quaternary hormonal maneuvers have been attempted in this population with variable success.<sup>118</sup> These included secondary anti-androgens (eg, nilutamide post bicalutamide), adrenalytic therapies (eg, ketoconazole), corticosteroids, and estrogenic compounds. While none have proven efficacy in regards to survival, disease control based on PSA and imaging is seen in 30% to 40% of patients.<sup>118</sup> These therapies also carry an increased risk of toxicity in older men, and should be used with careful consideration of the patient's other health problems and use of other medications. For example, ketoconazole at high doses can cause significant gastrointestinal toxicity and can interfere with the hepatic metabolism of other medications. Diethylstilbestrol is an estrogenic compound that carries a risk of cardiovascular and thromboembolic events (grade 3 or higher seen in approximately one third of patients).<sup>119</sup> It is therefore critical that the benefits of all therapeutic considerations, even non-chemotherapy, be carefully weighed with the risks in older patients with competing medical comorbidities, especially in patients who are on multiple medications.

The “pre-chemotherapy” CRPC niche is a disease space that is currently under vigorous therapeutic development and the options for these patients are likely to expand greatly. This process has begun with the recent FDA approval of the immunotherapy agent sipuleucel-T. The phase III trial of this therapy that led to its approval demonstrated that sipuleucel-T therapy meaningfully prolongs overall survival for men with

minimal or asymptomatic PCa with little significant toxicity.<sup>120</sup> However, it did not change progression-free survival and its mechanism of action remains quite controversial. It remains to be seen how sipuleucel-T, other emerging immunotherapies (eg, ProstVac, Bavarian Nordic, ipilimumab, anti-PD-1) and novel, potent hormonal therapies (eg, MDV 3100, abiraterone, TAK-700, ARN-509, TOK-001) will impact the decision-making process for older patients with CRPC.

### What Do We Do After Docetaxel?

As stated above, docetaxel is the current standard of care for progressive, symptomatic CRPC. The “post-docetaxel” patient population will include patients with no response to the therapy, those who benefitted but have discontinued therapy due to toxicity, and those who achieve initial benefit but have progressed while receiving docetaxel. The major next decision is whether or not to pursue further anti-cancer therapy (eg, more chemotherapy, ADT), and this decision is complex, especially in patients of advanced age or with other age-associated conditions. The decision-making process for further therapy for these patients will vary and will depend on the reasons for discontinuation of docetaxel. According to the TAX 327 data, the median survival from the onset of docetaxel therapy is 19.2 months, with a median duration of treatment of 9.5 cycles (21 days each).<sup>114</sup> Thus, the approximate median survival following discontinuation of docetaxel treatment is approximately 1 year. In the older adult, a reassessment of the patients' fitness for additional therapy, their underlying medical conditions, and the patients' individual RLE is thus critical. Furthermore, as PCa progresses, morbidity from disease burden, particularly increasing pain and fatigue, is a crucial consideration. Supportive care should be maximized. Currently, there is only one agent that has been proven to offer a survival advantage for men with CRPC after failure of docetaxel. A randomized study of cabazitaxel versus mitoxantrone in this population reported a median survival on cabazitaxel of 15.1 months versus 12.7 months on mitoxantrone ( $P < .001$ ).<sup>121</sup> Approximately 60% of the patients on the trial were 65 years of age or older, and the benefit persisted in this population. However, toxicity was significant, with 57.4% of cabazitaxel-treated patients having some grade 3 or higher toxicity, 7.5% having grade 3 or higher febrile neutropenia, and 4.9% having toxicity-related mortality. Consequently, the package insert for cabazitaxel recommends prophylactic granulocyte colony-stimulating factor (G-CSF) be administered to all patients aged 65 years and older.<sup>122</sup> In addition to chemotherapy, there are multiple “intense” hormonal agents in advanced stages of development for patients with CRPC post-chemotherapy (eg, abiraterone, MDV-3100, TAK-700). The phase III trial of the adrenal androgen synthesis

inhibitor abiraterone in this setting has been completed and the data monitoring committee for the trial has recommended that all patients on the placebo arm be offered abiraterone, indicating that the trial will likely demonstrate clinical benefit. Although not as toxic as chemotherapy, hormonal agents such as abiraterone also have significant toxicities, including hypertension and fatigue, which may interact with pre-existing comorbidities.

## DECISION 5: WHEN IS A CLINICAL TRIAL APPROPRIATE?

Despite recent advances in systemic therapies for PCa, there remain many unmet medical needs in older men affected by this disease in its latest stages. In CRPC, there are currently three approved therapies as noted above: docetaxel, sipuleucel-T, and cabazitaxel. The survival advantage from each of these agents is under 5 months and there is no overwhelming impact on death or morbidity from CRPC. Given this, many oncologists consider referral of PCa patients to ongoing clinical studies at various stages of disease. In CRPC, this decision is divided into the pre-chemotherapy and post-chemotherapy space. Decision-making in these areas for older men is significantly complicated by interactions of the disease, previous treatment, health status and competing comorbidities. Multiple studies show less frequent participation of older individuals in clinical trials. However, it is not clear from any of the completed and available data that advanced age (controlling for other comorbidities) suggests poorer outcome from treatment, although older adults do tend to have higher rates of toxicity. A number of novel approaches continue to be explored including signal transduction inhibitor therapies focused on molecular targets including VEGF/VEGFR, HGF/MET, SRC, AKT, and mTOR; epigenetic approaches such as histone deacetylase inhibitors, pro-apoptotic agents; and novel cytotoxic therapies (sagopilone, patupilone, ixabepilone, picoplatin, nedraplatin). Advancing trends in treatment suggest that nontraditional methods such as isolated PSA assessments be used to measure anti-cancer efficacy.<sup>111</sup> As such, clinical studies will require aggressive support and the populations studied should include patients in older age groups who may derive as much if not more benefit from novel interventions. We strongly recommend discussion of clinical trials for patients with CRPC without particular emphasis on age provided that medical comorbidity, performance status, and functional impairment do not preclude participation. For those who do not qualify or choose not to pursue further treatment, appropriate palliative and hospice care should be provided.

From this discussion, it is clear that multiple opportunities present for CGA are appropriate as a patient progresses through the continuum of the PCa experi-

ence. As demonstrated from the Scher states model, consideration must be given to the phase of the disease where disability or death from PCa will outpace that from other illnesses. However, the CRPC-related decisions, before, during and after chemotherapy in the older adult are complex and need to be thoughtfully individualized.

## SUMMARY

Individualized decision-making for older men for PCa is challenging. RLE plays a central role in deciding benefits from treatment in older men with PCa. Tools such as the CGA can help identify the subset of men with PCa most likely to derive a benefit from therapies. There are specific clinical time points when careful decision-making is essential, including screening for PCa, and treatment for localized PCa, BCR, and CRPC. RLE and geriatric assessments should drive goals of care discussions between physicians and patients in conjunction with standard of care and practice guidelines.

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