Current clinical challenges in prostate cancer

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Abstract: Prostate cancer is the most common malignancy and the second leading cause of cancer death in men in the United States. Close to $12 billion are spent annually on the treatment of prostate cancer in the US alone. Yet still there remain tremendous controversies and challenges that exist in all facets of the disease. This review and discussion will focus on issues and challenges for clinicians and patients diagnosed with the disease.

Appropriate risk stratification for men with newly diagnosed prostate cancer is an appropriate first step for all patients. Once risk-stratified, for those with low-risk of death, it is increasingly recognized that overtreatment creates an unnecessary burden for many patients. This is particularly evident when put in the context of competing comorbidities in an elderly population. For those with advanced or high-risk localized disease, under-treatment remains too common. For those with a high-risk of recurrence or failure following primary treatment, adjuvant or salvage therapies are an option, but how and when to best deploy these treatments are controversial.

Recently, tremendous progress has been made for those with advanced disease, in particular those with metastatic castrate-resistant prostate cancer (mCRPC). Within the last 4 years, five novel FDA approved agents, acting through distinct mechanisms have been FDA approved for mCRPC. With the introduction of these new agents a host of new challenges have arisen. Timing, sequencing and combinations of these novel agents are welcomed challenges when compared with the lack of available therapies just a few years ago.

In this summary of current clinical challenges in prostate cancer we review critical recent studies that have created or shifted the current paradigms of treatment for prostate cancer. We will also highlight ongoing issues that continue to challenge our field.

Keywords: Prostate neoplasms; active surveillance (AS); chemotherapy; castrate-resistance; hormone therapy; survival

Introduction

Prostate cancer is a highly heterogeneous disease, often with a long natural history. Nearly 240,000 men in the United States are newly diagnosed with prostate cancer annually, and more than 90% of these patients have local disease at diagnosis (1). Though statistics are variable, some autopsy reports indicate that the majority of men over age 50 harbor detectable prostate cancer after careful microscopic examination of the prostate (2). Although this data would

suggest that prostate cancer follows an indolent course, it results in the death of nearly 30,000 American annually and approximately 2.7% of men in the United States are estimated to die from prostate cancer in their lifetime (3). The incidence/mortality ratio for prostate cancer is approximately 8, making it distinct from any other major cancer (*Table 1*) (1). This perplexing series of dichotomous facts were eloquently summarized by the late the late Dr. Whitmore, "when a cure is possible is it necessary? And when it's necessary is it possible?" Reconciling this data

involves stratifying patients by their risk of progression and offering appropriate therapy (or non-therapy) based on the risk of disease, comorbidities and life expectancy. After cancer progresses, additional challenges are encountered. Only radiation and surgery have been shown to reliably cure patients and when these modalities fail, additional management problems ensue within each disease state that follows. Much progress has been made in metastatic castrate-resistant disease of late and this progress is highlighted herein. This summary is an introduction to many of the pertinent clinical challenges that face clinicians in treating and managing this complex and multi-faceted disease.

Risk-classification and disease categorization

It is now customary to divide localize prostate cancer into low-, intermediate-, and high-risk categories (*Table 2*). These categories were initially proposed by D'Amico and colleagues and are now endorsed by the National Comprehensive Cancer Network (NCCN) and the American Urologic Association (AUA). Disease classification is based on the clinical stage, PSA, and digital rectal examination results. Despite the relatively simplistic nature of these categories, they have stood the test of time and continue to be relevant in therapeutic discussions. Low-risk prostate has a Gleason score of 6 on prostate biopsy, clinical stage of T1a, T1c, or T2a and a PSA <10 ng/mL. Intermediate risk prostate cancer can have a Gleason of 7, or a PSA of 10-20 ng/mL, or a

clinical stage of T2b or T2c. High-risk localized cancer has a Gleason score between 8 and 10, or a PSA of >20 ng/mL, or a clinical stage of T3a. Patients with T3b or T4 disease are classified as locally advanced.

The D'Amico/NCCN risk (4) classification for categorical distinctions in risk stratification in those initially diagnosed with prostate cancer is one of many that now have been published. More sophisticated models evaluating similar variables in a continuous model such as the UCSF-CAPRA (5) score or Kattan nomograms (6) allow better discrimination of individual risk of progression but are more complex.

The clinical challenges in prostate cancer are many and depend on the disease category at presentation as well as a number of other factors including previously administered treatments. In order to best understand prostate cancer it can be viewed from a disease state model which was originally put forth by Scher and colleagues and subsequently modified many times (*Figure 1*) (7). It is helpful to view prostate cancer in a series of distinct clinical categories as these categories will define not only the appropriate treatments, but also the current clinical challenges.

PIVOT: critical review of treatment versus no treatment

There has only been one trial of PSA detected localized prostate cancer that has looked at a cohort of prostate cancer men that were treated with radical prostatectomy, or not treated, and followed for a minimum of 10 years. This trial termed PIVOT deserves special comment (8). The PIVOT trial was performed primarily in Veterans Administration centers in the United States along with some academic centers. Inclusion criteria required age less than 75 with a PSA ≤50 and the trial was initiated in 1994. Any Gleason score was allowed and a total of 731 patients were randomized with a mean age of 67. About 75% of men presented with a PSA elevation or rise as the primary

Table 1 Incidence: mortality ratio for various cancers in 2013 (1)

Cancer	Incidence:mortality ratio
Prostate	8.04:1
Female Breast	5.86:1
Colon	2.02:1
Lung	1.43:1
Pancreas	1.18:1

Table 2 Risk assessment per NCCN guidelines (NCCN.org)

	Low risk	Intermediate	High risk	Locally advanced
Gleason	6	7	8-10 or	Any
Clinical stage	T1c/T2a	T2b or T2c	T3a or	T3b or T4
PSA	<10 ng/mL	10-20 ng/mL	>20 ng/mL	Any

Note: low risk patients must have Gleason 6 and PSA <10 and clinical stage T1c or T2a. For intermediate and high risk categories the Gleason scores or PSAs or clinical stages can result in categorization.
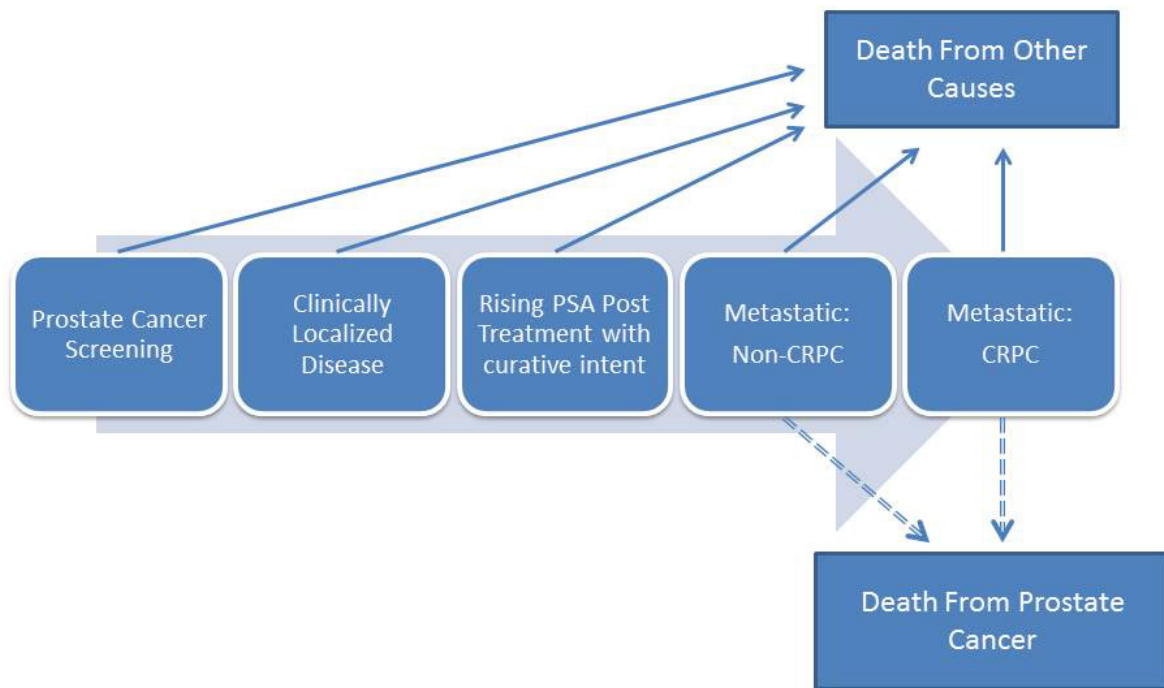
Figure 1 Clinical disease states of prostate cancer [adapted from Scher (7)].

indication for biopsy, making it distinct from other studies (i.e., Scandinavian Prostate Cancer Group Study-4) where PSA detection drove diagnosis only in a small minority.

In PIVOT, 40% of the men had low-risk, 34% intermediate-risk, and 21% high-risk prostate cancer (about 5% were missing data). After 10 years median follow-up, 77% of the men randomized to surgery underwent surgery and 20% of the men randomized to observation had definitive treatments with curative attempt. Over the course of the study 48.4% of the men died but only 7% died from prostate cancer. Given that it is generally accepted that men need to survive at least 10 years to benefit from surgery, this clearly indicates that the population was not ideal for this type of study.

There were no differences in prostate cancer specific mortality noted between the surgery and observation groups and a number of subsets were underpowered. Within the low-risk prostate cancer group, 62 deaths out of 148 were noted in the surgery arm and 54 out 148 men died in the observation arm. The hazard ratio (HR) for overall survival (OS) for low-risk disease was 1.15 (95% CI: 0.80-1.66). The intermittent- and high-risk diseases had favorable HRs for surgery with the HR for OS at 0.69 (95% CI: 0.49-0.98) and 0.74 (95% CI: 0.49-1.13), respectively, despite being underpowered with regard to subset analysis. Those with a

PSA of >10 ng/mL also had as HR of 0.67 (95% CI: 0.48-0.94) favoring surgery. Thus some subsets favored surgery and some did not in the OS analysis.

In PIVOT, approximately 40% of the men had died by 10 years of followup indicating that either the age or comorbidity was suboptimal in this trial which has been characterized as being a trial of surgery in men appropriate for watchful waiting (instead of a trial of observation in men appropriate for surgery). It is clear that OS was suboptimal for a surgical-treated population and there was inadequate power to accurately assess various subsets. Regardless, the data indicate that patients with low-risk disease had no benefit from treatment. Of men in the low-risk category treated by surgery (N=148), 6 men died from prostate cancer, whereas in the observation group (N=148), 4 men died from prostate cancer. Taken together there was a strong trend toward benefit in men treated with surgery for those with intermediate and high risk disease but no trend toward benefit in low risk disease at 10 years of followup in a population which included many men who died less than 10 years after randomization. This trial points to the importance of risk stratification in decision making but also demonstrates that our current stratification schemes are imperfect. Better risk stratification is one of the key challenges for prostate cancer research going forward.

Table 3 Treatment of prostate cancer by risk category: adapted from Cooperberg *et al*. (16)

Risk category	Watchful waiting (%)	Radical surgery (%)	Brachytherapy (%)	External beam (%)	Cryotherapy (%)	Androgen deprivation (%)
Low	9.2	56.8	16.0	7.3	3.1	7.6
Intermediate	4.8	52.9	13.5	12.3	4.5	11.9
High	3.2	32.2	7.5	18.1	6.1	32.8

Note: watchful waiting and active surveillance or not distinguished herein. Radical surgery is radical prostatectomy.

Life expectancy in prostate cancer management

The ability to predict an individual patient's life expectancy is critical for screening, diagnosis, and/or treatment of localized prostate cancer (9). This is particularly important and difficult for prostate cancer patients due to the cancer's variable and generally long natural history coupled with its prevalence in older men with competing comorbidities. Physicians are poor at predicting overall life expectancy. Several tools are available to assist in predicting life expectancy (10). The first are actuarial life tables, which represent an average number of remaining life years based on the age/sex of a group of individuals. While actuarial tables are easily accessible (11) and rapidly provide a reasonable estimation, they fail to account for individual medical comorbidities. The second tool available for life-expectancy calculations are comorbidity indices, perhaps the best known is the Charlson comorbidity index (12). This index assigns weights to 19 medical conditions and adjusts life expectancy based on those weights. The tool is limited in that patient's comorbidities are dichotomized rather than considered in a continuous fashion and it may over emphasize the importance of some medical conditions. Nomograms for life expectancy that incorporate multiple variables are also available. Such nomograms, predict 10 years life expectancy following treatment for localized prostate cancer with a predictive accuracy in the range of 69-84% (13-15). Nomograms to predict life expectancy in patients electing active surveillance (AS) are currently under development.

Low-risk localized prostate cancer: concepts and challenges

Unfortunately there has largely been a failure of clinicians to meet the challenges of low risk prostate cancer with the great majority of patients receiving aggressive therapy (see *Table 3*) regardless of age or disease risk (16,17). Patients with low risk disease have a much greater probability of dying from causes other than prostate cancer, even 20 years after diagnosis (18). Clearly many patients with low-risk prostate cancer will not benefit from active treatment.

While there may be multiple reasons for the over treatment of low-risk disease, perhaps the most difficult to overcome is the fear, on the part of both the clinician and the patient, of missing the opportunity for high probability of cure with therapeutic intervention. Watchful waiting (WW) refers to conservative management of prostate cancer until the development of local or systemic progression at which point palliative measures are employed. A recognized alternative to WW or active treatment is AS; a therapeutic strategy that involves actively monitoring the patient's disease with the expectation to intervene with intent to cure if the cancer progresses. AS is a recognized strategy that has emerged in the past decade and is endorsed by the NCCN, the American Urological Association (AUA), and the European Association of Urology (EAU) for select patients.

Although multiple ongoing clinical studies are evaluating the effectiveness of AS, existing data is largely from non-randomized, immature single institution with follow-up of less than 10 years. All agree that followup is suboptimal. Inclusion criteria are typically based on predictors of progression of disease and vary somewhat from study to study. Inclusion criteria include pathologic assessment of prostate biopsy with a particular emphasis of Gleason grading, clinical staging via digital rectal exam of the prostate, various measures of volume of cancer within the prostate (based on the number biopsy cores with cancer and the length of cancer in those cores), total PSA, and (to some extent) PSA adjusted for the size of the prostate (PSA density). More recently studies have assessed use of novel bio- and genetic-markers as part of AS cohorts, however determining which markers to use and how to best incorporate them is currently is investigational (19). Unfortunately all of these predictors of progression have significant limitations and better characterization of the extent and aggressiveness of disease at the time of diagnosis remains a challenge. Clinical staging with DRE is subjective and lacks precision. PSA or PSA density reflect not only the burden of cancer but the volume

of benign prostatic hyperplasia and/or the presence of inflammation. PSA levels may fluctuate and a single test may be unreliable (20). Gleason score is subjective and dependent on the interpretation of individual pathologists. Biopsies fail to sample the entire gland and changes in Gleason grading from biopsy to radical prostatectomy have been demonstrated to be 36% at tertiary care centers with expert dedicated genitourinary pathologists examining both specimens (21). Perhaps most controversial of all is determining volume of disease; the number of biopsy cores containing cancer may depend in part on the total number of cores taken, and the length of the core containing cancer, but biopsy techniques are not standardized among urologists and methods of measurement not standardized amongst pathologists.

Several studies, despite nuanced differences in inclusion criteria, and intensity of follow up, have confirmed that, in well-selected patients with low-risk prostate cancer undergoing AS there is a low rate of cancer-specific death, but longer follow-up is needed before definitive conclusions can be reached (22-30). The randomized PIVOT trial is consistent with these observations as well as the SPCG-4 study (31). Both studies emphasized that long term followup is key to understanding cancer-specific survival (8,31). What is novel is that patients in these AS studies have undergone repeat evaluation including prostate biopsy and were offered curative treatment upon evidence of progression.

Two important and largely unresolved clinical challenges emerge from the AS studies; first is how do we define progression? Defining progression is challenging because the prostate is incompletely sampled on biopsy and it is unclear if increases in grade or volume on subsequent biopsies is a result of de-differentiation of the original tumor(s) or merely a result of more/better sampling (30). Most progression of tumors usually comes in the form of upgrading and occurs in first two years of enrollment in AS, supporting the theory of better sampling. One study demonstrated that immediate repeat biopsy prior to enrollment in AS resulted in upstaging or upgrading in 27% of patients (28). More follow will be needed to determine if rates of progression begin to rise as the cohorts are followed for longer periods. Better biopsy schemes (MRI-guided) have been proposed and this may help to answer some of the questions related to under-grading of biopsies (32). It is clear that conventional prostate biopsies are "blind" and that imaging plays little role in current standard of care.

The second major challenge with AS is to determine whether intervention for patients who experience progression (however it is defined) have outcomes that approximate their initial projected outcome? If patients who experience progression on AS protocols have worse prognosis, earlier intervention may be of benefit. Two randomized studies aimed to address these issues by randomly assigning men with low risk prostate cancer to AS or radical intervention; the ProtecT (Prostate testing for cancer and Treatment) has completed accrual at nine centers in the United Kingdom and the Surveillance Therapy Against Radical Treatment (START) which has recently been terminated due to poor accrual. Results for both are many years away.

High risk localized prostate cancer

High-risk clinical localized prostate cancer shares many of the same challenges with low risk prostate cancer; appropriate risk stratification based on an imprecise physical exam, limited random sampling of the prostate, and a variation in PSA. However, that is where the similarities end. While the primary challenge associated with low-risk prostate cancer is often an over treatment of disease, the primary challenge of high-risk prostate cancer is often under treatment. Many patients with high-risk disease who are likely to benefit from aggressive local therapy with curative intent only receive palliative treatment with androgen deprivation therapy (ADT). The CaPSURE database, a provider-based registry from a number of community based urology practices has demonstrated that 41% of high-risk patients receive ADT alone, compared with 24% and 28% that undergo RP and RT respectively (17,33).

The cause for this under treatment is not completely clear, but is likely based on the erroneous belief that treatment offers little benefit as these patients are likely to fail and die of disease. However, depending on the definition of high-risk disease, local treatment with either RP or RT results in progression free probability (PFP) of 49-80% (34,35). Perhaps even more convincing are several randomized trials which have demonstrated improved survival in men with high-risk prostate cancers who have received active treatment compared with observation or ADT alone. In PIVOT, men with intermediate- and high-risk prostate cancer had a strong trend toward improved OS with RP compared with observation (8). Similar findings were reported in the SPCG-4 study randomizing men with non-PSA detected prostate cancer to RP or observation (31). Finally, the randomized trial SPCG-7 for high-risk prostate cancer, demonstrated improvement in OS with external

beam radiation plus ADT compared with ADT alone (36). Although no adequately powered randomized trial has determined the best active treatment for high-risk localized prostate cancer, monotherapy with ADT has the potential for significant harms, reduces QoL, and is not indicated for patients with asymptomatic localized prostate cancer. Its persistent use as monotherapy represents a challenge for the field (37).

Death from prostate cancer post-radical prostatectomy

A large data-base study consisting of over 11,000 patients (and confirmed in a data set of over 12,000 patients) with projected 15 years of followup from a series of excellent cancer centers around the country indicated that Gleason 8 or higher, seminal vesicle invasion, and lymph node positivity were particularly associated with a higher risk of prostate cancer death, regardless of the age group examined (37). The 15-year prostate cancer specific mortality risk was estimated as being 0.8% to 1.5%, 2.9% to 10%, 15% to 27% and 22% to 30% for organ confined cancer, extra-prostatic extension, seminal vesicle invasion, and lymph node metastasis, respectively. Nomograms have been developed to assess prostate cancer-specific mortality risks with long term follow-up (38). This study emphasizes the very low risk of death from prostate cancer in patients with low-risk disease, while demonstrating the potentially aggressive nature of other tumors in a manner that can be quantitated over time.

Adjuvant radiation therapy post-radical prostatectomy

With regards to the utilization of adjuvant radiation therapy, there is a randomized prospective Southwestern Oncology Group (SWOG) trial which supports the concept of OS benefit for adjuvant radiation therapy in individuals with pathologic T3a and T3b post-surgery (39). The data however are somewhat controversial in that there is a substantial proportion of these patients who will never recur post-operatively and the use of adjuvant radiation therapy may clearly be associated with over treatment. An important European trial (EORTC 22911) looked at adjuvant radiation therapy and demonstrated no survival benefit despite a PSA recurrence benefit (40). The clearest conclusions to be reached are that the PSA benefit was not translatable into a life expectancy benefit

because so many of the patients who have a PSA recurrence post-prostatectomy are not destined to die from their disease. This emphasizes that PSA recurrence does not equate to death, a finding clearly demonstrated in careful analyses of the Johns Hopkins database (41).

Salvage radiation post-radical prostatectomy

One problematic area that has been not carefully examined in the context of the current clinical prostate cancer debate is the issue of salvage radiation and whether or not hormones may provide an additional positive benefit to external beam radiation (42). Although hormonal therapy in the context of radiation for localized intermediate or high-risk disease is certainly standard of care (43), the utility of hormonal therapy in combination with salvage radiation in the post-prostatectomy setting is not clear. The RTOG trial 0534 is addressing this issue in a prospective randomized manner with an accrual goal of nearly 1,700 patients (42). To date well over 1,000 patients have been accrued and this trial should be definitive in terms of answering the question of whether or not ADT adds value to salvage radiation for those with a PSA rise post-radical prostatectomy.

Timing of hormonal therapy

Another controversy in prostate cancer management is the timing of hormonal therapy for people who have failed primary treatment with curative intent and who have a rising PSA. To date there have been no trials that clearly indicate that earlier therapy is better for this particular patient population.

The data demonstrating that early ADT in combination with external beam radiation is superior to radiation alone, is plentiful and the original studies performed by the EORTC lead by Bolla and colleagues have stood the test of time (43). The use of hormonal therapy in the absence of radiation, as compared to hormonal therapy plus radiation, clearly leads to an inferior outcome (36).

In one trial, important though very small, patients with lymph node metastases detected at the time of radical prostatectomy were randomized to receive ADT for life or observation. In this context the hormonal therapy was found to be better with regards to OS as well as other intermediate endpoints (44). Unfortunately, the small size of this trial, and the lack of additional prospective randomized trials supportive of these conclusions, are problematic.

In a prospective study that utilized hormonal therapy

early or later for those deemed to be unsuitable for definitive local therapy (EORTC 30891), there was slight improvement in OS for immediate androgen deprivation but quite oddly the prostate cancer specific mortality was not improved (45).

A retrospective study performed in hospitals associated with the US Department of Defense, found overall that there was no difference in bone-scan radiographic progression-free survival for early as compared to later ADT for patients with a PSA rise post-radical prostatectomy (46). However, when considering those patients with a Gleason 8 or higher disease, or those patients with a pre-ADT PSA doubling time (PSADT) of <12 months, there was an improvement in bone scan progression-free survival for those with a PSA of <5 ng/mL as opposed to >5 ng/mL, or for those with a PSA of >10 ng/mL as opposed to those with a PSA of <10 ng/mL. It is possible that lead-time bias represents the explanation for this finding. Given the lack of randomization here, one cannot view these data as being definitive but the finding that men with a PSADT of more than one year and a Gleason of 7 or less did not benefit from early ADT may be important.

Taken together, although ADT and radiation yields results that are superior to radiation alone in both intermediate and high risk disease, the use of early hormonal therapy for those with other disease states is considered controversial at best and no clear consensus can be drawn from the literature for those with a PSA rise after definitive therapy.

Intermittent versus continuous hormonal therapy

The use of hormonal therapy in an intermittent or continuous fashion is a current debate in our literature. For patients who have had a PSA recurrence after definitive radiation without evidence of metastatic disease, at 6.9 years of follow-up, both the intermittent and continuous therapeutic approach using ADT were not distinct when it comes to OS (47). However, there are improvements seen in the several quality of life parameters for patients treated with an intermittent approach, consequently many people now regard intermittent hormonal therapy as standard of care for individuals who have a non-metastatic PSA recurrence. Though this study convincingly shows that intermittent and continuous ADT showed no significant difference in OS for this population, the more important question regarding the timing of ADT (when should it begin) was not settled by this study (48).

A large SWOG trial addressed patients who were treated for initial metastatic disease with an intermittent versus continuous ADT regimen but unfortunately the conclusions were equivocal (49). In a non-inferiority analysis, the intermittent arm had a HR slightly worse (HR: 1.1; 95% CI: 0.99-1.23) but the confidence intervals overlapped both 1.0 and the pre-specified upper boundary of 1.2 thus the study concluded that intermittent ADT in this setting was not non-inferior. There was much about this trial that was suboptimal and notably there were little difference between the intermittent versus continuous regimens in terms of overall quality of life. While most individuals continue to regard continuous ADT as the standard of care for metastatic patients intermittent may be a reasonable alternative.

Non-metastatic CRPC (mCRPC)

No definitive studies demonstrate any agents offer survival advantage for patient with non- mCRPC. Modest improvements in bone-scan free survival were reported for denosumab therapy as compared to placebo but OS was not distinct and the incidence of osteonecrosis of the jaw was significantly higher in denosumab treated patients (50).

Overview of mCRPC

The summary and sequence of overall FDA approvals in mCRPC can be seen in *Tables 4,5*. The first drug to prolong survival in this setting was docetaxel in 2004. Prior to that, various FDA approvals involved pain or other non-OS endpoints. The progress in metastatic castrate resistant prostate cancer has been phenomenal since 2010 when two drugs, sipuleucel-T and cabazitaxel where both approved after demonstrating a prolongation of OS. Additional trials demonstrating prolongation of OS have subsequently been demonstrated for abiraterone, enzalutamide and radium. It is possible to classify these trials into different categories based on whether they were "front line" or post-docetaxel. The cabazitaxel approval in 2010 was in the post-docetaxel space, the first abiraterone approval in 2011 was in the post-docetaxel space, as was enzalutamide in 2012. Abiraterone was given a second approval for those individuals treated with for asymptomatic disease in the pre-docetaxel space in 2012. Sipuleucel-T in 2010 was approved in the asymptomatic or minimally symptomatic setting without regard for prior docetaxel treatment. The latest approval, radium-223 was approved in 2013 in

Table 4 FDA approvals in metastatic CRPC by year of approval and key endpoints

Agent	Year FDA approval	Key endpoint/setting	Class of drug
Estramustine	1981	Response	Estrogenic action
Strontium-89	1993	Bone pain	Radiopharmaceutical/beta emitter
Mitoxantrone/prednisone	1996	Pain	Chemotherapy/anthracenedione
Samarium-153 EDTMP	1997	Bone pain	Radiopharmaceutical/beta emitter
Zoledronic acid	2002	Skeletal related events	Bisphosphonate
Docetaxel/prednisone	2004	Survival	Chemotherapy/taxane
Sipuleucel-T	2010	Survival	Autologous cellular immunotherapy
Cabazitaxel/prednisone	2010	Survival	Chemotherapy/taxane
Denosumab	2010	Skeletal related events	Monoclonal/anti-RANK ligand**
Abiraterone/prednisone	2011	Survival	Androgen synthesis inhibitor
Enzalutamide	2012	Survival	Anti-androgen
Abiraterone/prednisone	2012	Radiographic PFS*/survival	Androgen synthesis inhibitor
Radium-223	2013	Survival	Radiopharmaceutical/alpha emitter

*PFS, progression free survival; **Receptor activator of NF-Kappa B.

Table 5 Key trials in mCRPC demonstrating a survival benefit

Trial	Disease state (all mCRPC)	Trial design and comparator arm	HR	Survival (months)
TAX 327 (51) N=1,006	With or without symptoms	Docetaxel/prednisone *vs.* mitoxantrone/prednisone	0.76	18.9 *vs.* 16.5
IMPACT (52) N=512	Minimal symptoms	Sipuleucel-T *vs.* control	0.78	25.8 *vs.* 21.7
TROPIC (53) N=755	Post-docetaxel	Cabazitaxel/prednisone *vs.* mitoxantrone/prednisone	0.70	15.1 *vs.* 12.7
COU-AA-301 (54) N=1,195	Post-docetaxel	Abiraterone/prednisone *vs.* placebo/prednisone	0.65	14.8 *vs.* 10.9
ALSYMPCA (55) N=921	Bone-metastatic symptomatic both pre- and post-docetaxel	Radium-223/BSC* *vs.* placebo/BSC	0.70	14.9 *vs.* 11.3
AFFIRM (56) N=1,199	Post-docetaxel	Enzalutamide *vs.* placebo	0.63	18.4 *vs.* 13.6
COU-AA-302 (57) N=1,088	Asymptomatic pre-docetaxel	Abiraterone/prednisone *vs.* placebo/prednisone	0.75	NR *vs.* 27.2

*BSC, best supportive care.

symptomatic prostate cancer without visceral metastases. There was no mention of the docetaxel treatment in the radium-223 label as patients with or without docetaxel treatment both had a prolongation in OS in a pre-specified stratified analysis.

There are now a total of seven trials that have been pivotal for FDA approval in the mCRPC space as shown in *Table 5*. These trials all reported HRs for OS between 0.63 and 0.78 (51-58). The OS was quite variable from trial to trial

but considering that some of these trials were conducted predominately in asymptomatic patients with no prior therapy for CRCP (52,57), whereas others were conducted in patients who had progressed post-docetaxel (53,54,56), a direct comparison of survival cannot be performed.

Pivotal docetaxel trials

In 2004, the FDA approved docetaxel/prednisone for

mCRPC. Two trials examined the efficacy of docetaxel in patients with metastatic castrate resistant prostate cancer and served as the basis for the FDA approval. The TAX 327 trial randomized 1,006 men with metastatic castrate resistant prostate cancer to either 12 mg/m^2 mitoxantrone every three weeks, 30 mg/m^2 of docetaxel weekly for 5 out of 6 weeks or to 75 mg/m^2 of docetaxel every three weeks (51). The every 3 weeks schedule of docetaxel demonstrated a survival advantage with a median survival of 18.9 months compared to 16.5 months in the mitoxantrone group and 17.4 months in the weekly docetaxel group. The SWOG 9916 trial randomized 674 men to either docetaxel at 60 mg/m^2 with estramustine every three weeks or to 12 mg/m^2 of mitoxantrone every three weeks (58). Docetaxel demonstrated a survival advantage with a median survival of 17.5 compared to 15.6 months for mitoxantrone. Progression of prostate cancer on docetaxel is an inevitability and presents one of the challenges for the clinician that has been more recently addressed by a series of trials and FDA approvals in the post-docetaxel space (53,54,56).

Immunology therapy: sipuleucel-T

Immunology therapy has been a debatable topic in all of cancer with considerable discussion and little promise until recent years. After initial submission of limited data, and a convoluted review process that did not involve the usual divisions at the FDA, sipuleucel-T was initially not approved. The trials initially submitted included two relatively small randomized trials which were considerably smaller than typical for FDA approvals. The sponsors then designed and implemented a much larger trial called D9902B or the IMPACT study which was conducted in patients with asymptomatic or minimally symptomatic mCRPC. There was no benefit in terms of progression free survival or radiographic response, but the group randomized to initial treatment with sipuleucel-T had better OS compared to the placebo group (52). It has been questioned whether the control group did worse than might have been anticipated however our review of the data do not support this concept and the control group in this study did no worse than patients in other analogous trials.

Abiraterone and enzalutamide

The approvals of abiraterone and enzalutamide challenged commonly held beliefs in metastatic prostate cancer—

specifically, both are hormonal therapies that have shown activity in what has been termed castration resistant disease. Abiraterone works through selective inhibition of CYP17 lyase, and a phase I/II study of the agent highlighted significant activity of the drug in both the pre- and post-docetaxel setting. Two phase III studies of abiraterone ensued, encompassing both of these disease spaces. In the COU-AA-301 trial, a total of 1,195 patients with mCRPC and prior docetaxel therapy were randomized in a 2:1 fashion to receive abiraterone or placebo (both with prednisone) (54). The trial met its primary endpoint, demonstrating an improvement in OS with abiraterone therapy (14.8 *vs.* 10.9 months; P<0.001). Secondary endpoints, including time to PSA progression and PSA response, were also improved with abiraterone. In contrast to COU-AA-301, COU-AA-302 examined a cohort of patients with mCPRC who were docetaxel naïve (57). In this study, patients were randomized in a 1:1 fashion to either abiraterone or placebo (again with prednisone). The study had a co-primary endpoint of improvement in radiographic PFS (rPFS) and OS. Ultimately, PFS was improved with abiraterone (16.5 *vs.* 8.3 months; P<0.0001). Although OS was improved with abiraterone (35.3 *vs.* 30.1 months; P=0.0151), the difference did not meet the threshold established by the O'Brien-Fleming method (P=0.0035). Nonetheless, on the basis of the two studies noted herein, abiraterone has garnered FDA approval in both the pre-docetaxel and post-docetaxel setting.

The mechanism of enzalutamide differs significantly from abiraterone. Specifically, enzalutamide is a potent antiandrogen that inhibits nuclear translocation of the androgen receptor. With phase I/II data showing compelling activity in mCRPC, two phase III programs were launched. In the AFFIRM trial, 1,199 patients with mCPRC and prior docetaxel therapy were randomized in a 2:1 fashion to receive enzalutamide or placebo (55). The study was stopped after a planned interim analysis, where it was determined that enzalutamide was associated with an improvement in OS (18.4 *vs.* 13.6 months; P<0.001). Secondary endpoints such as PSA response and soft tissue response were also improved with enzalutamide. Results from the second phase III study of enzalutamide are highly anticipated—in the phase III PREVAIL study, docetaxel-naïve patients with mCRPC were randomized to enzalutamide or placebo.

The clinical trajectories of abiraterone and enzalutamide have moved in parallel, creating a quandary for investigators. Given the results from COU-AA-301 and AFFIRM, would it be preferable to use abiraterone/prednisone or

enzalutamide in the docetaxel refractory patients? Notably, radium-223 and cabazitaxel (discussed elsewhere in this manuscript) are also options in this setting. Furthermore, if the noted PREVAIL (pre-docetaxel) enzalutamide study is positive, the oncologist is left with additional choices five valid options for first line therapy in mCRPC—sipuleucel-T, docetaxel, enzalutamide, radium-223, and abiraterone.

Cabazitaxel

Cabazitaxel represents the only cytotoxic therapy to demonstrate an OS advantage post-doctaxel (46). The TROPIC trial randomized 755 men who had progressed post-docetaxel were randomized to either 12 mg/m^2 of mitoxantrone every three weeks or to the novel taxane cabazitaxel at 25 mg/m^2 every three weeks (53). Median OS was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group. The use of cabazitaxel represented the first therapy FDA approved for patients whose prostate cancer has progressed post-docetaxel. Febrile neutropenia was 7.5% and caution with regard to treatments in patients with borderline counts or performance status is advised. Given that cabazitaxel was approved in the post-docetaxel space, as was enzalutamide and abiraterone, one might question which drug is best for which patient in this setting. Thus far, we have no comparative trials so conclusions are limited.

Radium-223

The radium-223 approval was based on the ALSYMPCA trial which randomized 921 patients with an OS primary endpoint (55). Inclusion criteria specified at least 2 bone metastatic lesions on bone scan and the presence of some symptoms. Those with visceral disease were excluded. Patients were required to be post-docetaxel, have refused docetaxel, unfit to receive docetaxel, or did not have docetaxel available. Randomization was to intravenous radium at 50 kBq/kg or placebo for six doses with a 2 to 1 randomization. All patients received "best standard of care". The "best standard of care" consists of whatever hormonal treatments might be appropriate in the mind of the investigator (ketoconazole, estrogens, dexamethasone, etc.) but no concomitant chemotherapy, experimental agents, or other radiopharmaceuticals were allowed.

The pre-specified interim analysis was positive for OS and the placebo group patients were subsequently allowed to cross over to radium-223. An updated OS

analysis was presented to the FDA, with median OS at 14.9 months in the radium treated group and 11.3 months in the placebo treated group (49). The HR was 0.695 and the P value was 0.00007. There was also a reduction in symptomatic skeletal events which consisted of radiation to bone, surgery to bone, pathologic fracture, or spinal cord compression. Overall the treatment was well tolerated with a 6% incidence of grade 3/4 thrombocytopenia being the most significant finding; 2% of the patients had grade 3/4 neutropenia.

One of the many challenges regarding radium-223 is an understanding of how best to optimize and integrate this novel therapy into the overall treatment paradigm. The initial clinical trial was conducted prior to the approval of enzalutamide or abiraterone and whether or not combinations of these novel hormonal agents would have provided additive value to radium-223 is untested. Phase I trials with radium-223 and docetaxel have been conducted (59) and phase II trials are now underway utilizing the 50 kB/kg radium dose q six weeks in combination with 60 mg/m^2 of docetaxel q three weeks. Looking at combination therapies with radium-223 may be quite interesting. It is also unclear whether or not the optimal dose and schedule of radium-223 was utilized in ALSYMCA and trials will examine various alternative doses and durations of radium therapy in hopes of defining what may or may not be more optimal doses and schedules.

Selecting appropriate therapies in the mCRPC patient

Front line therapies include docetaxel, sipuleucel-T, abiraterone/prednisone, and radium-223. Therapies available in the post-docetaxel space are abiraterone, enzalutamide, cabazitaxel, and radium-223. The sequence of therapies remains an area of debate but given there are no direct comparisons in clinical trials, the debate is more conjectural than data driven. Some agents are only currently approved post-docetaxel, such as enzalutamide and carbazitaxel—so those agents have a quite defined space. Given that many patients do not receive docetaxel, the issue of how to address these non-docetaxel patients in terms of second-line therapy is not at all clear. The radium-223 trials were the only trials with eligibility criteria that included those who were unfit for docetaxel or for those that refused docetaxel.

There are several tremendous challenges with regard to making appropriate choices as to which drug we should administer to each patient. We currently have very little

Table 6 Summary of retrospective experiences documenting the activity of enzalutamide followed by abiraterone (and vice versa)

Author	N	Sequence	Description of results
Loriot *et al*. (62)	38	Enzalutamide → abiraterone	• All patients had prior docetaxel. Abiraterone efficacy: median PFS: 2.7 months; 3 patients (8%) with PSA response (>50%); 7 patients (18%) with ≥30% PSA decline
Noonan *et al*. (63)	30	Enzalutamide → abiraterone	• All patients had prior docetaxel. Abiraterone efficacy: median duration of treatment: 3.3 months; 3 patients (10%) with ≥30% PSA decline; no radiographic responses
Schrader *et al*. (64)	35	Abiraterone → enzalutamide	• All patients had prior docetaxel. Enzalutamide efficacy: median duration of treatment: 4.9 months; 28.6% PSA decline >50%; 48.6% with no PSA response

data with regards to making appropriate drug choices guided by anything but clinical parameters. Our much studied biomarkers have yet to adequately inform clinicians regarding appropriate steps to take in individual patients. This is a major challenge in our field.

The presence or absence of prior docetaxel treatment is important to consider given some FDA approvals are specifically in this space. Performance status is always critical, as is the location of the metastatic lesions. Poor performance status patients should not receive cytotoxic chemotherapy as a rule. Are the metastatic lesions in the bone, viscera, both, or neither? Taking into account the pace of the disease progression influences clinical thinking. In addition the presence or absence of focal pains (which may be amenable to palliative external beam radiation therapy) is important to assess. Tolerance or intolerance of prior therapies, hematopoeitic function, and the availability of clinical trials are also important to consider (as are various laboratory parameters). Patients' preferences as always are part of the issue, as are out of pocket costs. Many therapies are not administered because out of pocket costs are prohibitive. Cytotoxics such as docetaxel and cabazitaxel required good performance status/blood counts/ liver functions. Sipuleucel-T should be restricted to good performance patients with minimal pain and preferably a relatively low burden/pace of the disease. Radium is for patients with bone-metastatic disease and neither radium nor sipuleucel-T are suitable for patients with extensive visceral disease. Out of pocket costs drive many decisions for oral drugs particularly in the United States.

The post-abiraterone/post-enzalutamide space

The question of what to do with patients who have failed abiraterone for mCRPC is currently subject to debate.

Utilization of docetaxel has been viewed by many as being standard for patients who have not previously received any chemotherapy but results are mixed at best. The de Bono group has published data to indicate that docetaxel activity is diminished in patients' post-abiraterone (60). There are no large trials in this setting so conclusions must be tempered until more data are available.

Fizazi and colleagues studied cabazitaxel/prednisone in patients who had received abiraterone and reported relatively high PSA response rates (61). These data have only been published in abstract form so there is much we more to learn about response durability and characteristics of the treated patients.

Minimal data are available for enzalutamide post-abiraterone (*Table 6*). One series, recently published retrospective analysis indicates that the response to enzalutamide post-abiraterone/post-docetaxel is blunted relative to those patients treated post-docetaxel alone (64). One study noted that 28.6% of men had a PSA decline of >50%. Further, 48.6% of men had no PSA response at all. This is much lower than expected. In the phase I/II trials, 56% of post-docetaxel patients had a PSA decline of >50% and only 17% had no PSA response (65). This German series did not assess PFS in a traditional sense so PFS data are limited.

The finding of *any* responses to enzalutamide post-abiraterone is of interest and implications of this observation are several. It should be clearly noted that post-abiraterone patients are a major challenge in our field. It may be that more androgens are present in the post-abiraterone state than appreciated and this concept is supported by finding that some urinary androgens can be still be detected despite abiraterone use (66). It is also possible that some non-androgenic steroids can engage the androgen receptor (AR) and that enzalutamide can block this interaction. After CYP17 inhibition, progesterone and its metabolites are

increased (58). Given that synthetic progestin withdrawal can be associated with PSA declines (67), we suggest that progestin/AR interactions might be relevant. It is possible that enzalutamide blockade of the putative progestin/AR interactions could be growth-inhibitory. It is known that selected AR mutations can recognize progesterone as an agonist (68) lending plausibility to this hypothesis. Alternatively, it may be that simply post-abiraterone withdrawal, that androgen-synthesis resumes and that simply that intratumoral androgens are effectively blocked by enzalutamide.

Two studies have examined abiraterone effects post-enzalutamide (and also post-docetaxel). Both of these small case series indicated a high degree of cross-resistance between enzalutamide and abiraterone with PSA responses (>50% declines) being less than 10% and the median PFS being less than 4 months (62,63).

Taken together, it is clear that cross-resistance between abiraterone and other agents is an issue and understanding this cross-resistance and devising methods to over-come it, is a top priority in the field of CRPC research. Space limitations preclude the complete discussion on this topic but AR splice variants may also be partially responsible for cross resistance in some instances (69). Devising methods to block ligand-independent AR signaling is a key challenge for progress in CRPC.

Limitations of sequencing therapies in CRPC

We are currently in the "sequencing era" where we administer drug A then drug B and then drug C for patients with mCRPC. It is unusual in other cancers to choose this strategy. In Hodgkin's disease, at curable malignancy, we utilize four drug regimens to cure. In prostate cancer we have only begun to explore combination therapy and this will be a tremendous challenge going forward, particularly given the cost of the various therapies involved. Regardless, combination therapies will likely be necessary to continue to improve patient outcomes.

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Footnote

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