

Prostate Cancer - Seminar

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Search strategy and selection criteria **[feel free to modify]**

Searches were conducted using Medline, PubMed and the Cochrane Library for English-language papers published between January 2000 and October 2020. Search terms were “prostate cancer”, “screening”, “diagnosis”, “treatment”, “genetics”, “molecular markers”, “oligometastases”, “randomised trials” and “review”. We surveyed bibliographies of our search results and recent major meeting programmes. We cited manuscripts that we deem to be practice-changing data or comprehensive reviews in order to meet space constraints here. Feedback from peer review was also incorporated.

Summary (150 words)

The management of men with prostate cancer continues to evolve rapidly...

(5000 word limit)

Introduction

Prostate cancer (PC) is a major health issue in men worldwide. Recent global health burden data estimate that approximately 1.3 million men are diagnosed annually, with around 10 million presently living with a prior diagnosis. The global prevalence of metastatic disease (approximately 700 000 men) ultimately leads to more than 400 000 deaths annually. Death counts are expected to more than double by 2040. In parallel to the mortality figures, a similar number of men are estimated to be living with morbidity from treatment more than 10 years after diagnosis {Disease, 2018 #1;Foreman, 2018 #2}.

Since the previous edition of the Seminar {Attard, 2016 #3}, research efforts have continued to clarify our understanding of PC . Insights into initial development and biological behaviour, our ability to diagnose primary and metastatic cancer, and our treatment options have expanded greatly. This Seminar will focus on more recent developments, how they relate to prior data and their practical implications to the clinician and should be read in the context of the wide variation in health care resources available to PC patients globally {Williams, 2013 #58}.

Biology

PC oncogenesis is associated with complex interactions between inherent germline susceptibility, acquired somatic mutations and environmental factors. Localized PC often contains multiple foci of differing genetic alterations and differential capacity for metastatic seeding and inherent treatment resistance.

Genomic alterations

Early stage PC is associated with few recurrent single nucleotide mutation variants (SNV), but rather have large-scale genomic structural rearrangements (GSR) and copy number alterations (CNA) typically {Fraser, 2017 #7}{Cancer Genome Atlas Research, 2015 #8}. Early genomic aberrations include TMPRSS2-ERG fusions in 50-60%, loss-of-function mutations in the gene encoding the transcriptional repressor speckle-type POZ protein (SPOP) in 5-10% and gain-of-function mutations in the gene encoding forkhead box protein A1 (FOXA1) {Fraser, 2017 #7}{Armenia, 2018 #9}, but rarely alterations in the androgen receptor (AR) gene {Fraser, 2017 #7}. Deletion of PTEN and alteration of TP53 is observed in 10-20% of cases and become more frequent in advanced disease (>50% of cases; see below). Men of Asian heritage have fewer TMPRSS2-ERG fusions and instead are driven in 20-40% of cases by recurrent hot spot mutations in FOXA1, ZNF292 and CHD1 {Li, 2020 #10}. Up to one third of localised PC has increased genetic instability characterised by in-

creased copy number, kataegis (regions of localized gene hypermutations), chromothripsis (regions of chromosome shattering) and chromoplexy (high frequency and genome-wide gene structural rearrangements) which has been associated with disease relapse {Rubin, 2018 #11;Lalonde, 2014 #12;Hieronymus, 2014 #13}. Such genetic instability combined with intratumoural hypoxia is further associated with treatment failure {Lalonde, 2014 #12;Bhandari, 2019 #14}.

Progression to metastatic castration-resistant prostate cancer (mCRPC) is associated with dysregulation of genes implicated in growth control and genetic stability that are rarely seen in localised disease. Homozygous deletions and loss of function mutations in PTEN occur in more than 40% of cases while alterations such as gain of function mutations occur in PIK3CA, PIK3CB or AKT1 in 5% of cases. Activation of the WNT signalling pathway and gain of the MYC oncogene function are also frequent, occurring in 20–30% {Quigley, 2018 #104}, and alterations in TP53 and RB1, are seen in 20-50% of cases {Armenia, 2018 #9}.

The androgen receptor (AR) is clearly important in metastatic disease. Untreated metastatic castration-sensitive prostate cancer (mCSPC) show AR alteration in up to 70% of cases due to amplification of or gain-of-function mutations, increased transcription (mediated by FOXA1) or increased AR signalling {Quigley, 2018 #104}. AR gene alterations may induce expression of AR transcript splice variants (AR-V), which in turn may be constitutively active AR variants, such as AR-V7. Several studies have now addressed the importance of AR-V7 detection in tumour tissue or circulating tumour cells (CTC) and together support AR-V7 as one factor in acquired resistance toward AR-targeting agents {Rebello, 2019 #17}. Collectively, a loss of androgen receptor (AR) signalling dependence occurs in 15%-20% of advanced treatment-resistant prostate cancers and may manifest as transformation to a castration-resistant neuroendocrine PC (CRPC-NE) that is highly treatment-refractory.

DNA damage response (DDR) genes also play a key role in PC. Men with germline *BRCA1/2* mutations have a three- to eight-fold increased lifetime risk of PC which can behave aggressively due to frequent additional c-MYC oncogene activation on top of inhibition of the tumour suppressors TP53 and PTEN {Taylor, 2019 #24;Taylor, 2017 #25}. Furthermore, somatic changes in a range of DDR genes occur in approximately 25% of metastatic prostate cancers - most frequently in *NBS1*, *BRCA1*, *BRCA2*, *PALB2*, *CHEK2* and *ATM* {Arce, 2019 #23}. Such changes along with those in mismatch repair (MMR) or the CDK-12 gene pathway have led to targeted approaches as we will describe subsequently.

The identification of key molecular markers that are predictive of responses to specific therapies heralds the era of personalized therapies. RNA-based prognostic signatures are being validated for their use in predicting disease relapse including commercially-available tests such as Decipher (22 gene RNA-based array), the 12-gene 'Oncotype DX' and the 31-gene 'Prolaris' signatures which give information on the likelihood of distant metastases at 5 and 10 years post therapy although, to date, none have high level evidence supporting their

use to direct therapy {Egger, 2020 #15}. Alterations in RB1, AR, and TP53 are associated more aggressive disease that is less reliant on AR signalling {Nyquist, 2020 #19; Abida, 2019 #20} and a combined genomic (TP53, RB1, CYLD, AR) and epigenomic (hypo- and hypermethylation of 20 differential sites) signature applied to circulating tumour DNA (ctDNA) may identify patients with early features of CRPC-NE {Beltran, 2020 #21}. Other studies have highlighted synergy between transcription factors, such as ONECUT2, and intratumoural hypoxia in driving the CRPC-NE phenotype and emphasize the potential of hypoxia-directed therapy for these patients {Guo, 2019 #22}.

Diagnosis and Staging of Prostate Cancer

Prostate-Specific Antigen (PSA) screening for prostate cancer diagnosis

There have recently been updates to both USA and European studies of PSA-based screening. The American Prostate, Lung, Colorectal and Ovarian (PLCO) study reporting 16 year data and the UK Cluster randomised trial of PSA testing for Prostate Cancer (CAP) at 10 years showed no reduction in mortality in screened men with a concomitant rise in the detection of low risk PC {Pinsky, 2019 #4}. In contrast, the European Randomised Screening for Prostate Cancer (ERSPC) of >182000 men followed for up to 16 years shows an increasing benefit of screening with time, and a significantly reduced rate of PC death in those screened (rate ratio 0.80 [95% confidence interval 0.72-0.89, $p < 0.001$]) {Hugosson, 2019 #5}. Although contaminated by significant levels of screening in the control arm, the PLCO study did show that men with a baseline PSA of <0.49ng/ml had a 0.4% risk of clinically significant PC over 13 years compared to a 29.5% risk for a PSA >4 ng/ml, suggesting that men with a baseline PSA of <1 at age 55-70 may not need further screening and men with a baseline PSA of 1-2 ng/mL could reduce screening frequency {Kovac, 2020 #6}. Accordingly, the United States Preventive Services Task Force (USPSTF) has adjusted the recommendation for PSA-based screening from status D (not recommended) to C, where the decision to undergo PSA testing in men aged 55-69 years old should be individualised based on a possible small reduction in the risk of death from PC against the potential harms of overdiagnosis and overtreatment {Force, 2018 #26}.

Magnetic Resonance Imaging (MRI) for prostate cancer diagnosis

Over the past two decades there has been significant advances in both MR imaging techniques and reporting frameworks that have improved sensitivity for diagnosis {Turkbey, 2019 #27; Barentsz, 2012 #28; Weinreb, 2016 #29}. There is now randomised controlled trial (RCT) evidence that MRI-directed biopsy identifies approximately twice the number of clinically significant cancers (Grade Group 2-5) compared to standard trans-rectal biopsies (93% v 48% sensitivity) {Ahmed, 2017 #30}. This approach allows 1 in 4 men to avoid biopsy and reduces the detection of indolent disease {Kasivisvanathan, 2018 #31}, as confirmed in subsequent

studies {Rouviere, 2019 #32;van der Leest, 2019 #33}. MRI before biopsy should now be considered standard of care {Drost, 2020 #34}, although there are challenges in providing this to a consistent quality across different health systems {Brizmohun Appayya, 2018 #35;Faria, 2018 #36}. The European Association of Urology has now proposed that men have a baseline PSA at age 45 and MRI be the first investigate when the PSA is raised {Gandaglia, 2019 #37}.

	Study			
	PRECISION {Kasivisvanathan, 2018 #31}	PROMISE {Ahmed, 2017 #30}	MRI-FIRST {Rouviere, 2019 #32}	4M {van der Leest, 2019 #33}
Study design (n)	RCT (n=500)	?add in	Paired validating (n=251)	Paired validating (n=626)
Magnet strength / reporting system	1.5T & 3T / Likert		1.5T & 3T / Likert> PI-RADS	3T / PIRADS centralised review
MRI- Biopsy	4 cores per target (max 12)		3 cores per MRI lesion + 2 cores per USS lesion + 12 standard cores	In bore biopsy – 3 cores per patient
Standard biopsy	10-12 cores		12 + 2 cores per hypoechoic lesion	12 core TRUS
Clinically significant PC in MRI –TB (Insignificant PC)	38% (9%)		32% (6%)	25% (14%)
Clinically significant PC rate in standard biopsy (Insignificant PC rate)	26% (22%)		30% (20%)	23% (25%)
Biopsy Avoidance Rate	28%		14%	49%

Table xx. Details of recent seminal studies of multiparametric MRI in prostate cancer.

Molecular imaging of prostate cancer

Molecular imaging utilising positron emission tomography (PET) has gathered considerable traction in directing PC management recently. Early interest in PET tracers based on choline metabolism (using ¹¹C- or ¹⁸F-choline) or amino acid analogs (for example, ¹⁸F-FACBC) has been largely supplanted by small polypeptide ligands to the Prostate Specific Membrane Antigen (PSMA) that is highly expressed on PC. Intra-prostatic primary lesions will be PSMA-PET avid in over 90% of cases, and the avidity correlates with tumour grade {Williams, 2020 #39}. The identification of extra-prostatic disease following definitive treatment has been extensively studied. Meta-analysis shows the sensitivity for identification of recurrent disease after surgery rises from 45% at a PSA range of 0.2-0.49 ng/mL, up to 95% with a PSA>2ng/mL {Perera, 2020 #40}. A prospective trial comparing the FDA-approved ¹⁸F-FACBC (also known as ¹⁸F-fluciclovine) to ⁶⁸Ga-PSMA-11 showed PSMA-PET to have approximately double the sensitivity for all distant disease locations {Calais, 2019 #41} {Calais, 2019 #41}. Similarly, the proPSMA RCT compared the imaging accuracy of conventional imaging (abdomino-pelvic computed tomography and whole body bone scan) against that of ⁶⁸Ga-PSMA-11 for staging newly diagnosed intermediate- or high-risk PC showed improved sensitivity from 38% (95%CI 24-52%)

with conventional imaging to 85% (95%CI 74-96%) with PSMA-PET. Further ⁶⁸Ga-PSMA-11 resulted in lower radiation dose and a shorter imaging duration for patients {Hofman, 2020 #42}.

Management of localised prostate cancer ("Management of the pelvis in PC")

The intensity of treatment offered for the intra-pelvic component of PC is based on the fundamental factors of PSA level, clinical tumour stage and histological grade, with recent reclassification of the Gleason score to the ISUP Grade Group {Epstein, 2016 #44}. The standard division into low-, intermediate- and high-risk PC increasingly incorporates factors such as positive biopsy core number, the length of tumour in the biopsy cores, imaging findings and molecular signatures {Eggerer, 2020 #85}.

Active Surveillance

The context in which active surveillance (AS) is offered and carried out is evolving. A large single institution analysis of Grade Group 1 disease show a risk of metastasis of <1% and PC mortality of 0.1% at 15 years {Tosoian, 2020 #43}. The availability of MRI to assess for clinically significant cancer at baseline has reduced the reliance on confirmatory biopsies. The application of Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria to define the likelihood of significant change on repeat MRIs {Moore, 2017 #47;Dieffenbacher, 2019 #48} informs the intensity of surveillance schedules {Amin, 2020 #49}. Similarly, there is growing interest in overlaying MRI characteristics and genomic markers to improve risk stratification {Herlemann, 2020 #50;Leapman, 2017 #51;Falagarrio, 2019 #52}.

High level evidence now supports the importance of managing the primary lesion in all but the most indolent and advanced PCs. Compared with watchful waiting, radical prostatectomy (RP) extended median overall survival (OS) by 2.9 years in the SPCG-4 randomized trial {Bill-Axelsson, 2018 #53}. Similarly, men with a PSA > 10 ng/mL or other high-risk features benefitted from RP with a relative risk reduction in overall mortality of >30% in the PIVOT trial at a median follow-up of 12.7 years {Wilt, 2017 #55}. Radiation therapy (RT) studies have consistently shown a significant survival advantage when men with high-risk disease were randomised to receive RT to the prostate in addition to androgen deprivation therapy (ADT) rather than ADT alone, with a 9% OS increase at 10 years in the SPCG-7 trial {Widmark, 2009 #86} and 8% at 7 years in the NCIC PR3 study {Warde, 2011 #87}.

Extending this concept to the metastatic setting, the STAMPEDE trial randomised 2,061 men with mCSPC to have radiotherapy or not to the prostate in addition to lifelong ADT plus upfront docetaxel. The study showed no OS benefit in unselected patients, however a pre-specified analysis showed RT resulted in a 8% improvement in OS at 3 years men with low metastatic burden (less than 4 bone metastasis and absence of visceral

metastasis) (HR 0.68; 95%CI 0.52-0.90) {Parker, 2018 #54}. The HORRAD trial showed no OS difference (HR: 0.9 (95%CI: 0.7-1.14) when RT was added to ADT alone (median PSA = 145 ng/dL; most with >5 bone metastases) {Boeve, 2019 #56}. Two further phase III trials (PEACE1 trial and SWOG/NCTN study) are anticipated to read out on this issue RT to the prostate in the setting of mCSPC in 10 years. In the same vein, several randomised trials are presently addressing cytoreductive prostatectomy in metastatic disease.

Approximately 60% of men with high-risk PC who undergo a RP will develop biochemical recurrence and require intensification of treatment. Three RCT's evaluating adjuvant RT following prostatectomy {Wiegel, 2014 #96;Bolla, 2012 #97;Thompson, 2009 #98} have shown that the combined approach results in delayed recurrence {Wiegel, 2014 #96;Bolla, 2012 #97;Thompson, 2009 #98} and potentially impact OS {Thompson, 2009 #98}. A further trio of RCT's that explored the role of immediate adjuvant RT in all patients with risk features (pT3 or margin positive) versus salvage radiotherapy in the setting of a rising PSA >0.2 ng/mL yielded equivalent oncological outcomes and mitigated against unnecessary toxicity {Parker, 2020 #100;Kneebone, 2020 #102;Sargos, 2020 #103} Furthermore, a planned individual patient data meta-analysis of the 2153 patients from these studies also shows no evidence of improved event-free survival with adjuvant RT over early salvage (HR=0.95 95% CI 0.75 to 1.21; p=0.70) {Vale, 2020 #101} reinforcing the importance of patient selection when considering local therapy. (?add in EUA guidelines to further stratify recurrences into low and high risk)

A more sobering view of the value of local therapy comes from the ProtecT study, where 1643 men, mostly low- or intermediate-risk disease, diagnosed by PSA screening without metastases were randomised to active surveillance, radical prostatectomy or radical radiotherapy. At a median of 10 years follow-up, just 62 men had developed metastatic disease, with the active surveillance group having approximately double the metastatic rate of the treatment arms, albeit at just 6.3 metastatic events per 1000 person-years (p=0.004) {Hamdy, 2016 #43}. No impact of local treatment has yet been observed on survival indices, with <10% of deaths being from PC. Patient-reported outcomes showed a significant and often permanent detriment in several quality of life domains in treated patients {Donovan, 2016 #44}. This study demonstrates the critical need to balance patient comorbidities against the need to control the primary disease.

The ideal way to deliver local therapy is constantly being reassessed due to the expansion of therapeutic options. Surgical techniques continue to evolve with robotic-assisted RP (RARP) rapidly gaining popularity due to potential advantages related to its minimally invasive nature. A RCT of 326 men comparing RARP to open surgery showed reduced admission times and blood loss with RARP, but otherwise similar urinary, sexual and quality-of-life outcomes at 24 months {Yaxley, 2016 #56;Coughlin, 2018 #57}. Long-term oncological outcomes between techniques are lacking as yet.

Definitive radiation therapy (RT) to the intact primary prostate cancer continues to be a valid treatment approach with much of the recent focus being into using larger doses per fraction (hypofractionation). More than ten RCT's involving >8000 participants have now compared the conventional approach of 7 to 9 weeks external beam (1.8-2.0 Gy per fraction) with shorter courses (2.5-3.4 Gy per fraction). Summary data shows hypofractionation to have similar overall survival (high certainty) with a possible small reduction in biochemical control in the hypofractionation arm of uncertain clinical significance (HR 0.88, 95% CI 0.68 - 1.13, moderate certainty). Hypofractionation is comparatively well tolerated, with a possible small increase in late gastrointestinal toxicity (RR 1.05, 95% CI 0.93 - 1.18; moderate certainty) without a corresponding quality of life detriment {Hickey, 2019 #45}.

There remains a strong consensus for the addition of ADT to definitive RT for locally advanced or high-risk PC through multiple RCT's. Several meta-analyses show benefits for all clinical endpoints through to overall survival with the addition of ADT to RT in high-risk PC, with an approximate 20% reduction in the rate of death {Jackson, 2020 #88;Roach, 2000 #89;Shelley, 2009 #90;Bria, 2009 #91}. At least 6 months of ADT should be considered for men with GGG3 or more cancers {D'Amico, 2011 #92}, with durations out to 3 years likely to be of benefit in high-grade cancers {Bolla, 2009 #93}. While radiation biological dose escalation with brachytherapy may provide a reduction in biochemical {Morris, 2017 #95} or metastatic failure {Joseph, 2020 #94}, data presently suggest that ADT will continue to be beneficial when combined with such approaches {Jackson, 2020 #88;Joseph, 2020 #94}.

Oligometastatic prostate cancer

The oligometastatic state is usually defined as up to 3-5 metastatic lesions {Battaglia, 2019 #46}, and may be further subdivided by the history and timing of deposits {Guckenberger, 2020 #47} and molecular imaging. A wave of interest has developed in metastasis-directed therapy (MDT) in oligometastatic disease with the advent of more sensitive molecular imaging (such as PSMA PET) that is upgrading previously considered nonmetastatic patients (on standard imaging) to metastatic. The STOMP study (n=62) evaluating MDT versus observation in oligorecurrent PC. The median ADT-free survival was 21 months in the MDT group compared to 13 months in the observed group (HR=0.60, 80% CI 0.40–0.90; p=0.11) with no clear impact on quality of life or OS {Ost, 2018 #50}. The ORIOLE study (n=54) showed a reduction in the rate of progression at 6 months from 61% in the observation arm to 19% in the stereotactic ablative radiotherapy (SABR) arm (P=0.005) {Phillips, 2020 #51}. Finally, the SABR-COMET study (n=16 PC cases of 99 enrolled, randomised 2:1 SABR:observation) has shown a 5-year OS improvement from 17.7% (95% CI 6-34%) untreated to 42.3% (95% CI 28-56%; P = .006) following SABR. Time to development of subsequent metastases was unchanged by SABR, with the predominant effect seen when given to those who had repeated oligoprogression following initial

MDT, suggesting that appropriate patient selection will be critical for success of these approaches {Palma, 2020 #52;Palma, 2019 #53}. Multiple randomised trials are proceeding to address many questions in this space including the clinical utility of SABR in conjunction with systemic therapies.

Castration-sensitive metastatic prostate cancer

Reduction of circulating testosterone via medical or surgical means remains the backbone of systemic therapy for metastatic PC. Of note, androgen receptor targeted therapies (ARPIs) and docetaxel originally developed for men with advanced castration-resistant disease have now been shown to be highly beneficial when brought earlier in the disease course. Potent ARPI such as abiraterone acetate that blocks androgen biosynthesis {Fizazi, 2017 #72}{James, 2017 #73} as well as the potent AR antagonists apalutamide {Chi, 2019 #71} and enzalutamide {Davis, 2019 #70} significantly improve survival when given orally, daily, and continuously with ADT. Docetaxel chemotherapy is an alternative option to ARPI, is given at a dose of 75 mg/m² intravenously every 3 weeks for six cycles; patients are then maintained on ADT alone until evidence of disease progression {Sweeney, 2015 #74}. (Table xx)

The combination of both ARPI and docetaxel upfront, or their sequential use in the metastatic hormone naive setting, has not been shown to be of benefit and may increase toxicity {Davis, 2019 #70}. The choice between ARPI or docetaxel in combination with ADT is typically based on clinical features including volume of disease, comorbidities, drug access and patient preference including funding options. Patients with low volume disease should also be considered for treatment of their primary tumour with RT if not already done.

Non-metastatic castration-resistant prostate cancer (nmCRPC)

Non-metastatic CRPC is defined as rising PSA, castrate levels of serum testosterone and no evidence of metastatic disease on conventional imaging (bone scintigraphy and computed-tomography scan) and variable rates of progression can exist. Therefore, treatment approaches in nmCRPC needs to consider the heterogeneous clinical outlook when weighing up the risk and benefits of adding further systemic treatment. Clinical interest in the state is driven by three phase III placebo controlled randomised trials that evaluated potent ARPIs in poor-risk patients with a PSA doubling time (dt) of <10 months. Each of these studies had very similar designs and have shown remarkably similar outcomes with a primary metastasis-free survival (MFS) endpoint (Table xx).

The PROSPER trial randomised patients to either enzalutamide or placebo. Enzalutamide, resulted in superior metastasis-free survival (MFS) (median 36.6 months for enzalutamide vs 14.7 months for placebo; HR = 0.29; p < 0.0001) and, with subsequent follow-up, a 27% reduced risk of death (HR 0.73; 95% CI 0.61-0.89; P = .0011) equating to a 10.7 month median OS gain {Sternberg, 2020 #66}. The SPARTAN trial randomised men

to apalutamide or placebo showed an improved median MFS (40.5 months vs. 16.2 months, HR 0.28; $p < 0.001$). Similarly, OS has recently been shown to be improved also at a median 52 months of follow-up, with a median OS extension of 14 months (HR 0.78; 95%CI 0.64-0.96; $p = 0.016$) {Smith, 2020 #67}. Darolutamide, evaluated in the ARAMIS trial initially reported an increased the median MFS of 40.4 months versus 18.4 months; HR 0.41; 95% CI 0.34-0.50, and with further follow-up, a significant OS improvement {Fizazi, 2020 #68}. **Need to mention safety / tolerability – yes would make sense to mention best tolerated in class which is useful when given earlier in disease , sorry ran out of time this am.?**

While these agents can be considered for patients with nmCRPC, observation is also a valid option particularly for patients with more indolent PSA dynamics (PSA dt > 10 months). Additionally, it is inevitable that the clinical scenario of nmCRPC will require redefining as imaging improves. Evaluation of 200 men with nmCRPC and PSA dt < 10 months showed that 98% had disease visible on PSMA PET imaging with the majority being extra-pelvic metastases {Fendler, 2019 #69}. Such data drives controversy about the clinical relevance of the endpoint MFS in the setting nmCRPC where MFS implies a delay in the appearance of metastatic disease that is a function of the insensitivity of imaging. Finally, the critical broader implications on quality of life and health economics of early versus later implementation of the same therapeutic strategy in nmCRPC versus mCRPC needs to be assessed.

Metastatic castration-resistant prostate cancer (mCRPC)

AR Targeted Therapy

Next generation AR targeted therapies are well established in the metastatic PC space. Abiraterone acetate, is a potent CYP17A1 inhibitor that blocks androgen biosynthesis in the adrenal gland, tumour and testis {Attard G, 2005}. The phase III COU-AA-301 {de Bono, 2011 #78} and COU-AA-302 {Ryan, 2013 #77} trials showed an approximate 4 month survival advantage over placebo in both the pre- and post-docetaxel disease state (Table x). Abiraterone also improved quality of life, pain control and reduced skeletal related events. The potent AR antagonist enzalutamide that impairs AR nuclear translocation and binding to androgen response elements on the DNA {Tran C, Science 2009} achieved regulatory approval for the same indications as abiraterone acetate, with comparable impact on overall survival and multiple patient reported outcomes in the AFFIRM {Scher, 2012 #76} and PREVAIL {Beer, 2014 #75; Beer, 2017} studies (Table x).

Chemotherapy

Mitoxantrone (with prednisolone) was the first therapeutic agent to be approved for mCRPC based on improved palliation {Tannock IF, JCO, 1996}, subsequently all but replaced by docetaxel. The two large phase III studies of docetaxel against mitoxantrone and prednisolone both showed an approximate 3 month overall

survival advantage, albeit with increased toxicity in the study combining docetaxel with estramustine (Tan-nock IF, 2004; Petrylak DP; 2004). Cabazitaxel, a second-generation semisynthetic taxane, retained a similar efficacy in men who have progressed on docetaxel when compared with mitoxantrone. Cabazitaxel also retained antitumour activity in patients who were resistant to docetaxel or had progressed on abiraterone or enzalutamide (de Bono, Lancet, 2010). The FIRSTANA trial evaluated cabazitaxel at 20 mg/m² or 25 mg/m² over docetaxel as first-line chemotherapy. The OS was comparable across the arms with no survival advantage for cabazitaxel {Oudard S, JCO 2017}.

Treatment Sequencing for mCRPC

A multitude of agents disrupting AR signalling (enzalutamide apalutamide, abiraterone acetate and darolutamide) and taxanes (docetaxel and cabazitaxel) have been approved for the same indication in metastatic PC, making selection of one agent over the other influenced by the safety profile and patient factors. In many regions, APRI constitute the majority of front-line treatments for mCRPC. Recently, a series of Phase II/III trials have provided compelling evidence for significant cross resistance and limited efficacy with uninterrupted switching between APRI and a preference for sequential use of APRI and taxanes {Attard G, 2018; de Wit, 2019 #79; {Khalaf, 2019 #80}. A phase II back to back sequencing study of abiraterone acetate followed by enzalutamide and vice versa in 202 men with mCRPC showed 4 month improvement PSA PFS (median 19.3 months versus vs 15.2 months, hazard ratio 0.66, 95% CI 0.45–0.97, p=0.036) and better PSA responses (36% versus 4%) in the arm receiving enzalutamide followed by abiraterone acetate compared to the other way around but without any survival advantage for either sequence {Khalaf, 2019 #80}. In the control arm of the Phase III Profound trial, the sequential use of abiraterone acetate or enzalutamide or visa versa resulted in a trivial **ORR of 3% a rPFS of approximately x** months. (de Bono, 2020). Finally, the Phase III CARD trail that randomised patients with mCRPC who had progressed on abiraterone or enzalutamide to either the alternate alternative agent or cabazitaxel established an improved median radiological PFS by 4.3 months (HR 0.54, 95% confidence interval, 0.40–0.73; p < 0.001) and overall survival by 2.6 months (HR, 0.64; 95% CI, 0.46 to 0.89; P = 0.008) for the use of cabazitaxel compared with sequential use of abiraterone and enzalutamide {de Wit, 2019 #79}.

The growing shift in practise for upfront use **ARPIs** in newly diagnosed metastatic castration-sensitive disease and nmCRPC raises significant concerns about potential cross resistance and likely limited clinical benefit from second-line **APRI** therapy in the setting of mCRPC when the disease is likely more symptomatic. Collective these data highlight the critical importance of development of other therapies that spare the AR signalling in PC.

Bone-targeting treatments

The alpha-emitting radionuclide $^{223}\text{Radium}$ (^{223}Ra) mimics calcium and is taken up in osteoblastic bone metastasis {Parker, 2013 #58}. The seminal ALSYMPCA trial showed a significant survival and QoL benefit to ^{223}Ra compared with placebo in mCRPC patients (median OS 14.9 months vs 11.3 months; $p < 0.001$) leading to widespread use for this indication. Combining ^{223}Ra with abiraterone acetate plus prednisone, the ERA-223 trial subsequently found more than double the incidence of fracture (28.6% vs 11.4%), suggesting that ^{223}Ra monotherapy should remain the current standard {Smith, 2019 #57}.

Inhibition of osteoclastic activity has been shown to be beneficial in mCRPC, with the bisphosphonate zoledronic acid (4mg every 3 weeks) reducing SREs at 15 months by 11% (44% v 33%; $P = 0.02$) {Saad, 2002 #82}. Denosumab, a monoclonal antibody to the receptor activator of nuclear factor κB ligand (RANKL), further extended the median time to first SRE by 3.6 months when compared with zoledronic acid ($p = 0.008$) {Fizazi, 2011 #81}. Higher rates of osteonecrosis (2% vs 1%) and hypocalcaemia (13% vs 6%) were seen with denosumab, and neither agent has shown an impact on OS {Smith MR, 2013}. Looking to studies in the era of modern APRI that are known to improve SRE's also, post-hoc data suggest ongoing benefit to adding either denosumab or zoledronic acid in mCRPC {Ryan, 2013 #59; Saad, 2015}.

Poly(ADP-ribose) polymerase (PARP) inhibitors

Approximately 23% of mCRPCs harbour loss of function somatic and /or germline alteration in DNA repair genes such as *BRCA2*, *BRCA1*, *ATM*, and *CHEK2* {Robinson D, Cell, 2015}. These homologous recombination defects (HRDs) confer genomic instability and tumour-specific vulnerabilities that can be exploited with a PARP inhibitor (PARPi) to induce synthetic lethality. In heavily pretreated mCRPC patients, the TOPARP study (Part A) showed that 32% of men had a response to PARPi, and of those responders, 88% had homozygous loss of function alterations in HR genes, namely *BRCA1*, *BRCA2*, *ATM* and the *FANC* genes. The Part B validation cohort subsequently showed a response rate of 54% when selected for HRDs with variable antitumour activity based on the genomic aberration {Mateo, 2020 #61; Mateo, 2015 #62}. In the definitive phase III PROFOUND study, men with mCRPC who had progressed on an APRI and had an identified HRD were randomised 2: 1 to olaparib or physician's choice of the alternate APRI. Cohort A ($n=245$) enrolled patients with *BRCA1/2*, and *ATM* gene alterations and Cohort B ($n=142$) patients with other prespecified HRD genes. Cohort A showed a median radiological PFS extension of 3.8 months (HR 0.34; 95% CI 0.25–0.47, $P < 0.001$) and a median overall survival increase from 15.1 to 18.5 months for olaparib over the second APRI despite 80% of patients on the control arm crossing over to the olaparib arm. Improved rPFS and OS was also observed in cohort B {de Bono, 2020 #60}. This study establishes the role of PARP inhibition in mCRPC patients with underlying HRD and ushers in an era of molecularly stratified treatment for mCRPC patients based on genomic testing.

Immune therapies

Despite the immune resistance of PC, the autologous cellular vaccine Sipuleucel-T is became the first FDA-approved vaccine therapy for a solid malignancy in 2010, showing a median survival advantage of 4.1 months {Kantoff, 2010 #83}. The production of the cellular immunotherapy is labour intensive and costly and in the setting of many new therapeutic advances in **PC** the uptake in the community has been limited. Conversely, the PSA-targeted poxviral vector-based immunotherapy PROSTVAC-VF showed no survival advantage in a phase III trial despite promise in early phase studies {Gulley, 2019 #84}.

Upregulation of the key inhibitory regulators of cytotoxic T cell activity Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and Programmed Death-1 (PD-1) and its ligand (PDL-1) provides a means for cancer cells to evade immune responses. While highly successful against other cancers, there is yet to be a clear role for immune checkpoint inhibitors in PC. The monoclonal antibody inhibitor of CTLA-4, Ipilimumab, failed to demonstrate an OS advantage compared with placebo in two phase III trials, in docetaxel pre-treated and chemotherapy naïve minimally symptomatic mCRPC patients (**Kwon ED, 2014; Beer TM, 2017**). Early phase studies of inhibition of the PD-1/PDL-1 axis showed response rates of approximately 15% {Hansen, 2018 #64;**Antonarakis, 2020 #65**}, which combined with the observation of a number of prolonged responses has led to definitive phase III trials with these agents.

Anti-PD-1 combination strategies have resulted in marginally more anti-tumour activity in unselected men with mCRPC. A Phase 2 study involving adding pembrolizumab to enzalutamide for men with mCRPC progressing on enzalutamide reported a $\geq 50\%$ PSA decline in 18% of 28 patients (**Graff J, 2020**). Keynote-365, a phase 2 umbrella study evaluating multiple pembrolizumab combinations in patients with mCRPC shown a PSA response rate of 28%, 31% and 12% for the enzalutamide, docetaxel and olaparib combination arms respectively (**Evan Yu, GU ASCO 2020**). The phase III trial (IMbassador250) of atezolizumab, a monoclonal antibody to PD-L1 given concurrently with enzalutamide versus enzalutamide in 759 mCRPC patients who had progressed on abiraterone acetate did not meet its primary endpoint of OS with a median OS of 15.2 months versus 16.6 months in favour of single agent enzalutamide (**Chris Sweeney, AACR 2020**).

A recent study (Checkmate 650) of ipilimumab and nivolumab in mCRPC patients reported double the objective response rate (25% versus 10%) in mCRPC patients who had not previously been exposed to chemotherapy as opposed to those who had. Intriguingly, and in those with an underlying DNA repair defect the response rate was 50%. These data raises salient questions if immune checkpoint blockade is likely to be more effective in patients that harbour underlying DNA repair deficiencies and when it is delivered at earlier stages of the disease when the cancer is less bulky and heterogenous. Cyclin-dependent kinase 12 (CDK12) aberrations and mismatch repair deficiency are reported to account for higher genomic instability and tumour neoantigens and therefore confer improved responses to immunotherapy (**Abida W, 2019; Rodrigues**

DN, 2018; Wu YM, 2018). Multiple phase III trials are planned or ongoing looking at a variety of checkpoint inhibitor combinations.

PSMA theranostics

The high avidity of PSMA for most prostate cancer makes it an attractive theranostic target for paired imaging and treatment of prostate cancer. Therapeutics leveraging PSMA expression have focussed on PSMA-targeted bispecific molecules, antibody drug conjugates, and antibodies or small molecules conjugated with alpha and beta particle radioisotopes. Amongst these, the short-range β emitter conjugate ^{177}Lu -DOTA-PSMA-617 (LuPSMA) has now had substantial clinical evaluation.

The first phase 2 prospective study of LuPSMA included 50 men with mCRPC who had no further conventional therapy options available. It reported a >50% PSA fall in 64% of cases, and grade 3–4 anaemia, thrombocytopenia, and neutropenia of 10%, 10%, and 6%, respectively {Hofman, 2018 #63}. These promising data launched two randomized trials in mCRPC. Preliminary results from the Phase II TheraP trial (NCT03392428) that randomised 200 patients with mCRPC who progressed on docetaxel and ARPIs to either ^{177}Lu -PSMA or cabazitaxel showed an improvement in PSA responses $\geq 50\%$ compared to cabazitaxel (66% vs. 37%; $p < 0.0001$) (Hofman, ASCO 2020 Proceedings). The Phase III registration VISION trial (NCT03511664) has randomised 750 patients 2:1 to ^{177}Lu -PSMA or physician choice of best supportive treatment with results awaited.

Agree with your assessment – not important for this paper but I have embedded with the refs for your consideration.

With advances in molecularly-directed therapy with PARP inhibitors (for *BRCA2* and other homologous recombination alterations) and immunotherapy (for mismatch repair deficiency, microsatellite instability, and potentially *CDK12* loss), genetic and genomic sequencing in patients with advanced prostate cancer are becoming more routine {Ku SY, 2019}. There a number of available clinical sequencing platforms to investigate genomic alterations using primary or metastatic tissues, and more recently in blood via circulating tumor DNA (ctDNA). While there are still open questions regarding the optimal tissue, test, and timing of assessment, it is clear that testing will become more integrated into care. Beyond informing therapy choice, acquired molecular alterations can provide insights into mechanisms of treatment resistance. *AR* gene mutations, amplification, and splice variants), for instance, are associated with re-activation of AR-signaling in castration resistant disease, and their presence portends unfavorable subsequent responses to currently available potent AR -targeted therapies { Ku SY, 2019; Romanel A, 2015; Antonarakis ES, 2014}. The presence of *RB1* loss has been associated with poor prognosis in metastatic CRPC {Abida W, 2019}, and in combination

with concurrent *TP53* mutation or deletion has been associated with lineage plasticity and the development of AR-independent disease { Beltran H,2016; Ku SY, 2017; Mu P,2017}. This lineage plasticity may manifest clinically as a histologic transformation from a luminally differentiated AR-positive prostate adenocarcinoma to a small cell /neuroendocrine carcinoma { Beltran H, 2019}. Clinically, neuroendocrine transformation is associated with aggressive disease, and sometimes atypical spread in the absence of PSA rise. When suspected, tumor biopsy can confirm the diagnosis, with morphologic characteristics similar to small cell lung cancer and other high grade neuroendocrine carcinomas. In this setting patients may be treated with small cell directed therapies, such as platinum- based chemotherapy {Conteduca V, 2019}. Of note, lineage plasticity and histologic transformation to a small cell carcinoma has also been observed in subset of patients with EGFR mutated lung adenocarcinoma at the time of resistance to EGFR targeted therapies {Sequist LV,2011}.

Conclusion

Lots of points to cover...

mCRPC defined on conv imaging – will change with PSMA

Timing	Study	Agents studied	Number of participants	Hazard ratio (MFS/rPFS)	Hazard ratio (OS)	Overall Survival Indices
Metastatic Post-docetaxel	COU-AA-301 {de Bono, 2011 #78}	Abiraterone/prednisone vs Placebo/prednisone (2:1)	1195	0.67	0.74	Median 15.8 vs 11.2 months
	AFFIRM {Scher, 2012 #76}	Enzalutamide vs Placebo	1199	0.4	0.63 (95% CI 0.53–0.75; p < 0.001)	Median 18.4 vs 13.6 months
Metastatic Pre-docetaxel	COU-AA-302 {Ryan, 2013 #77}	Abiraterone/prednisone vs Placebo/prednisone	1088	0.45	0.79 (p<0.003)	Median OS 34.7 vs. 30.3 months
	PREVAIL {Beer, 2014 #75}	Enzalutamide vs Placebo	1717	0.19	0.71 (95% CI 0.60–0.84; p < 0.001)	Median 35.3 vs. 31.3 months
Non-Metastatic Pre-docetaxel	PROSPER {Sternberg, 2020 #66}	Enzalutamide vs Placebo (2:1)	1401	0.29	0.73 (95% CI 0.61–0.89; P = .0011)	Median 67.0 mo v 56.3 mo
	SPARTAN {Smith, 2020 #67}	Apalutamide vs Placebo (2:1)	1207	0.28	0.78 [95%CI 0.64–0.96; p=0.016)	Median 73.9 vs 59.9 mo
	ARAMIS {Fizazi, 2020 #68}	Darolutamide vs Placebo (2:1)	1509	0.41	0.69 (95% CI, 0.53 to 0.88; P = 0.003)	3yr OS: 83 vs 77%

Table x. Randomised trials of systemic therapy studies in castrate-resistant prostate cancer. All patients had background androgen deprivation therapy in all studies. All results were statistically significant unless labelled non-significant (NS).

Timing	Study	Agents studied	Number of participants	Hazard ratio (MFS/rPFS)	Hazard ratio (OS)	Overall Survival Indices
	STAMPEDE {James, 2017 #73}	Abiraterone/prednisone vs Placebo	1917	0.29	0.63 (95%CI 0.52 to 0.76; P<0.001)	3yr OS 83% vs 76%
	LATITUDE {Fizazi, 2017 #72}	Abiraterone/prednisone vs Placebo	1209	0.47	0.62 (95%CI 0.51 to 0.76; P<0.001)	3yr OS ~66 vs 49%
	TITAN {Chi, 2019 #71}	Apalutamide vs Placebo	1052	0.48	0.67 (95% CI, 0.51 to 0.89; P = 0.005)	2yr OS ~82 vs 74%
	ENZAMET {Davis, 2019 #70}	Enzalutamide vs NSAA	1125	0.40	0.67 (95%CI 0.52 to 0.86; P = 0.002)	3yr OS 80 vs 72%
	CHAARTED {Sweeney, 2015 #74}	Docetaxel + ADT v ADT	790	0.61	0.61 (95%CI 0.47 to 0.80; P<0.001)	Median OS: 57.6 months vs. 44.0 months

Table x. Randomised trials of systemic therapy in castration-sensitive prostate cancer. All patients had background androgen deprivation therapy in all studies. All results statistically significant.

Contributors

SW was responsible for search strategy, overall structure and editing of the Seminar.

CM wrote the section on screening and diagnosis.

RB was primary author of the section on biology.

EC, CM and SW wrote about localised disease

SS, HB and SW wrote the section on advanced disease.

SW wrote about radiation therapy and molecular imaging.

EC and SW wrote about oligometastatic disease.

All authors reviewed and approved the final version of the Seminar and provided feedback on reviewers comments.

Declarations of interests

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