Prostate cancer

Gerhard Attard, Chris Parker, Ros A Eeles, Fritz Schroder, Scott A Tomlins, Ian Tannock, Charles G Drake, Johann S de Bono

Much progress has been made in research for prostate cancer in the past decade. There is now greater understanding for the genetic basis of familial prostate cancer with identification of rare but high-risk mutations (eg, BRCA2, HOXB13) and low-risk but common alleles (77 identified so far by genome-wide association studies) that could lead to targeted screening of patients at risk. This is especially important because screening for prostate cancer based on prostate-specific antigen remains controversial due to the high rate of overdiagnosis and unnecessary prostate biopsies, despite evidence that it reduces mortality. Classification of prostate cancer into distinct molecular subtypes, including mutually exclusive ETS-gene-fusion-positive and SPINK1-overexpressing, CHD1-loss cancers, could allow stratification of patients for different management strategies. Presently, men with localised disease can have very different prognoses and treatment options, ranging from observation alone through to radical surgery, with few good-quality randomised trials to inform on the best approach for an individual patient. The survival of patients with metastatic prostate cancer progressing on androgen-deprivation therapy (castration-resistant prostate cancer) has improved substantially. In addition to docetaxel, which has been used for more than a decade, in the past 4 years five new drugs have shown efficacy with improvements in overall survival leading to licensing for the treatment of metastatic castration-resistant prostate cancer. Because of this rapid change in the therapeutic landscape, no robust data exist to inform on the selection of patients for a specific treatment for castration-resistant prostate cancer or the best sequence of administration. Moreover, the high cost of the newer drugs limits their widespread use in several countries. Data from continuing clinical and translational research are urgently needed to improve, and, crucially, to personalise management.

Introduction
Prostate cancer is the most common malignancy in men and a major cause of cancer deaths. Its incidence differs between countries due to coverage of prostate-specific antigen (PSA) screening,1 but in both populations with and without PSA screening, prostate cancer is the cause of 1–2% of deaths in men. Its greater prevalence in the west2 and migrant population data implicate lifestyle and environmental risk factors.3 Large advances have been made in the treatment and understanding of the underlying biology. These include the approval of several novel effective drugs that improve survival in men with advanced prostate cancer and the recognition that the terms hormone refractory and androgen independent have become more confusing than enlightening.4–10 Nonetheless, several areas of urgent unmet need remain—for example, we cannot yet predict in whom hormone therapy works and who will progress on hormone therapy.11

This familial risk is more than four times higher than that for the general population for first-degree relatives of men with prostate cancer diagnosed younger than 60 years.11 A 50% higher risk in monozygotic twins than in dizygotic twins12–14 and the higher incidence in African Americans (and lower rate in Americans of Asian ancestry) supports genetic factors as an important determinant of the variation in risk at the population level.15

Genetic predisposition can result from rare highly penetrant mutations, from genetic variants conferring lower risk, or from a combination of these two (figure 2). Studies of prostate cancer pedigrees suggest dominant, recessive, and X-linked models.16–21 Genetic linkage studies in multiple-case families have suggested co-segregation of multiple genetic regions; from these genetic regions, only one definite prostate cancer predisposition gene, the homeobox gene HOXB13, has been identified.21

Search strategy and selection criteria
We searched Medline, PubMed, and the Cochrane Library database for papers published in English between January, 2002 and January, 2014. We used the search terms “prostate cancer”, “aetiology”, “carcinogenesis”, “screening”, “diagnosis”, “adjuvant treatment”, “molecular prognostic and predictive markers”, “castration-resistance”, and “cost implications”. We cross-checked reference lists from our results, and asked other colleagues to recommend references. We prioritised references that we considered to have had a significant impact or introduced new ways of thinking. We cited review articles to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.
More than 20 genome-wide association studies (GWAS) of prostate cancer have been published, reporting 77 SNPs to be associated with prostate cancer. The first region identified was 8q24, which (similar to most identified SNPs) is in a non-coding region in the vicinity of the oncogene c-MYC. Chromatin conformation assays report that this affects c-MYC expression.

Rare germline BRCA2 mutations occur in families with high rates of breast and ovarian cancer and confer a five to seven times higher risk of prostate cancer, whereas NBS1 mutations, common only in Slavic populations, are the cause of Nijmegen breakage syndrome. In each case, some evidence of an association has been shown with prostate cancer.

Increased testing has led to the identification of more BRCA2 carriers with prostate cancer; men with this genetic aberration have a higher Gleason score and worse prognosis than non-BRCA2 carriers. Targeted screening in this group is being studied in the IMPACT study. The development of drugs (poly ADP ribose polymerase [PARP] inhibitors) for tumours with BRCA loss of function provides a new therapeutic option for these patients and encourages broader BRCA testing.

Profiling of a European population for the described 77 prostate cancer risk SNPs (from blood or saliva) could identify the population at highest risk (4.7-times risk compared with the general population) to allow targeted screening. However, more data are needed to confirm the clinical significance of these strategies.

**Screening and diagnosis**

PSA concentrations in blood at mid-life (50–70 years) have been shown to powerfully predict lifelong risk of patients developing prostate cancer metastases and dying of the disease. These findings could translate into a reduction in prostate cancer mortality from PSA-based screening. Discussions on early diagnosis must differentiate between population screening and screening upon request. The agreed endpoint of
screening studies is prostate cancer mortality; the evaluation of overall mortality serves quality control purposes. Although the prolongation of life on a population basis is an important endpoint, it cannot be reached by any screening trial because of insufficient power. The effect of prostate cancer screening on mortality is controversial because of divergent opinion on the level of evidence provided by different trials, and inability to match harms and benefits appropriately. This controversy has resulted in worldwide agreement that population-based screening should not be implemented despite evidence that screening reduces prostate cancer mortality. Nevertheless, men wishing early detection should arguably not be refused PSA testing. Professional advice is best based on decision aids that use open questions, available on the websites of the Society International d’Urology and the Movember website.

Meta-analyses on randomised screening trials, including an updated Cochrane review, have been limited by variable study quality. For example, criteria required in the European Randomised study of Screening for Prostate Cancer (ERSPC) were not required in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, in which only 40% of participants were compliant with biopsy indications. 44% were PSA-tested before randomisation, and there was more than 70% contamination by PSA testing in the control group. The ERSPC study has shown significant reductions in prostate cancer mortality and the numbers of men required to be invited for screening and treated to prevent one prostate cancer death have decreased from the 2009 (1410 and 48, respectively) to the 2012 publication (936 and 33, respectively). Nonetheless these results remain preliminary since less than 30% of participants have died and these might decrease further with longer follow-up.

A report to address the balance of harms and benefits by modelling quality-of-life adjusted life-years for the total expected lifetime of participants in screening studies was published in 2012. Based on the 11 year follow-up data of ERSPC, the model predicted that with yearly screening in men aged 55–69 years, 73 life-years would be gained, of which, after deduction of 23% for quality of life, 56 adjusted life-years remained. The researchers identified overdiagnosis as the most relevant harm that limits the acceptability of population screening of men at risk. Assuming no overdiagnosis, the quality-of-life adjusted life-years in this setting would increase from 56 to 79 years. Obviously, testing for PSA alone cannot resolve this issue and the application of risk stratification is necessary.

The likelihood of identification of prostate cancer on biopsy based on the commonly used PSA threshold of 4 ng/mL is about 21%. This represents overtesting (in about 75% of people) and overdiagnosis (in 30–50%, depending mainly on age) of cancers that may have remained undetected. An available risk stratification instrument, the SWOP risk calculator (appendix), could reduce this; when digital rectal examination and ultrasound studies for prostate volume and suspicious lesions are also used, the risk of a positive biopsy is reduced to 8% with a chance of aggressive disease of only 1% if these are normal with a prostate volume of more than 50 mL. A recent update of the website shows that prostate volume estimation by rectal examination can replace volume measurement by transrectal ultrasonography. Application of this strategy with a probability cutoff of 12.5% would decrease biopsy rate by 33%, although some potentially deadly cancers could be missed. Other instruments supporting risk stratification are available and include those of the Foundation for Informed Medical Decision Making, the American Cancer Society, the American College of Physicians, the pending National Institute for Health and Care Excellence update, the Canadian Task Force, Draft Statement, and US Preventive Services Task Force. In consideration of any decision method, the level of external validation should be taken into account.

Because of space restrictions, the only novel diagnostic marker that we will discuss is urinary PCA3. mRNA of the prostate cancer antigen 3 (PCA3) gene, formerly known as DD3, was identified in 1999 and was strongly overexpressed in more than 95% of tissue specimens of primary prostate cancer and prostate cancer metastases. PCA3-containing cells are detected in urine after prostatic massage and a PCA3 score obtained by normalising of urinary PCA3 mRNA concentrations with PSA. PCA3 testing improves the positive predictive value and sensitivity of detection of cancer on biopsy compared with PSA in a prescreened population. Several studies have so far proven inconclusive as to whether PCA3 is useful to selectively detect aggressive prostate cancers. One strategy to improve the performance characteristics of PCA3 could be to combine this with analysis of the TMPRSS2-ERG fusion gene.

MRI could also decrease overdiagnosis and unnecessary biopsies; level one evidence to support MRI use is not available, although several small studies have used MRI-guided biopsies, template-based biopsies based on MRI data, or MRI-transrectal ultrasonography fusion-guided biopsies. These strategies might also be used to detect more aggressive lesions and ventrally located transition-zone prostate cancers.

Carcinogenesis and molecular subclassification

Next-generation sequencing has allowed characterisation of the clonal hierarchy of genomic lesions in prostate tumours, providing information about carcinogenesis and identification of genomic rearrangements that result in androgen-driven ETS gene expression. These rearrangements are clonal, suggesting that they occur early and might result from activated androgen receptors generating DNA damage through transcription at androgen-receptor binding sites. Occurrence of
concomitant genotoxic insults that result in DNA double-strand breaks (eg, inflammation, infection) might accelerate this process by impairing high-fidelity DNA repair. However, ETS gene fusions alone are not sufficient to result in cancer; other genomic events, such as activation of the PI3K/AKT pathway by PTEN loss, are needed.

More than 50 complete prostate cancer genomes have been reported, along with hundreds of exomes. The prostate cancer genome is characterised by relatively few focal chromosomal gains or losses (most commonly focal loss of PTEN) and overall low mutation rate (roughly one per megabase). SPON, which encodes a substrate binding unit of a Cullin-based E3 ubiquitin ligase, TP53 and PTEN are among the most frequently mutated genes across several studies of localised prostate cancers. About 50–60% of PSA-screened prostate cancers in white patients have recurrent gene fusions, typically fusing the 5′ untranslated region of androgen-regulated genes (eg, TMPRSS2) to nearly the entire coding sequence of an androgen-regulated gene (eg, ERG). Many fusion partners, some of which are constitutively expressed and not androgen regulated (eg, HNRPA2B1), and other ETS family members are also less frequently involved (figure 3A). ETS gene fusions are highly clonal within a given cancer focus (although foci with different ETS status can occur in the same prostate tissue), and can be detected by both fluorescence in-situ hybridisation and immunohistochemistry. Whole-genome sequencing shows that some prostate cancers have relatively large numbers of chromosomal rearrangements, particularly in early onset cases, many involving known cancer-associated genes (commonly including ETS genes) in a distinctive closed chain pattern of rearrangement.

The cell of origin for prostate cancer is controversial, with reports of prostate cancer deriving from both luminal and basal epithelial cells, as well as evolution of basal-cell-initiation cancer evolving to adenocarcinoma maintained by luminal-like cells. Of note, overt basal-cell differentiation in prostate cancer is extremely rare (absence of basal cells is a diagnostic feature of typical prostatic adenocarcinoma), and gene-expression profiling studies of prostate cancer do not support intrinsic molecular subtypes based on luminal versus basal differentiation, as in breast and bladder cancer.

However, genomic, epigenetic, and expression profiling studies support the premise that tumours with ETS fusions (ETS-positive) are distinct from those without (ETS-negative); driving changes in several genes have been identified that occur exclusively in ETS-negative prostate cancers (figure 3B). For example, SPINK1, which encodes a serine protease inhibitor, is markedly overexpressed in about 5–10% of prostate cancers, and SPINK1-positive cancers are exclusively ETS-negative. Rare gene fusions or known activating mutations in RAF, RAS, and FGFR family members have also been identified in prostate cancer (about 1–2%); RAF-RAF-FGFR-mutant tumours are exclusively ETS-negative. Similarly, mutations in SPO, which cluster in the encoded protein’s substrate binding cleft, occur in about 5–10% of prostate cancers, and SPO negative cancers are exclusively ETS-negative. Mutations and homozygous deletions in CHD1 have been identified in 5–15% of prostate cancers, with CHD1-negative cancers also being exclusively ETS-negative. Although nearly always occurring in ETS-negative tumours, SPO negative, CHD1-negative, and SPINK-negative frequently co-occur, with these tumours being commonly PTEN and p53 wild-type. Loss or mutation of the tumour-suppressor genes PTEN and TP53 are among the most frequent events in prostate cancer, and occur in both ETS-positive and ETS-negative cancers, but occur more
frequently in ETS-positive cancers.\textsuperscript{79,80} These data represent approximate frequencies in white individuals; differing frequencies of such events have been reported in men of other ethnic origins.\textsuperscript{81} Robust, reproducible, assays for several subset-defining lesions are available including multiplexed immunohistochemistry,\textsuperscript{82} suggesting that a simple molecular barcode (ie, ETS/SPINK1/SPOP/CHD1/RAS-RAF/PTEN/TP53 status) can be used to define molecular prostate cancer subtypes (figure 3B). Immunohistochemistry for ERG, which detects the TMPRSS2-ERG gene fusion, is more than 99\%-99\% specific for prostate cancer,\textsuperscript{78,79} supporting its diagnostic use in atypical cases of prostate cancer.\textsuperscript{83,84} Research into other changes commonly seen in prostate cancer, such as PTEN and CHD1 loss or SPOP mutations, might also have clinical use.

Multiple histologically distinct foci of prostate cancer are common in one prostate; these can be genetically heterogeneous, suggesting independent clonal origins.\textsuperscript{85,86} Identification of the focus that will affect prognosis (index focus) is crucial; the main focus is usually selected based on being the largest or highest grade, but the index focus might be less easily identified. Molecular studies suggest that lethal metastatic disease is clonal\textsuperscript{87,88} and the role of subclonal evolution in prostate cancer, particularly in progression and response to treatment, is under investigation. Although interpatient heterogeneity is well recognised, lower-grade cancers are relatively homogeneous unlike aggressive prostate cancers.\textsuperscript{89,90} Frequent reactivation of androgen-receptor signalling secondary to several mechanisms (figure 1) has been reported in studies of castration-resistant prostate cancer as well as frequent disruption of chromatin and histone modellers and tumour suppressors including PTEN, TP53, and RB1. Given the many therapies directed at the androgen receptor signalling axis, real-time evaluation of androgen receptor signalling status could affect future clinical management.\textsuperscript{91,92,93}

Apart from the androgen receptor, several commonly disrupted genes and pathways are under active investigation, such as the PI3K/AKT/TOR pathway. Additionally, rare potentially targetable lesions, such as RAF fusions, focal high-level CDK4 amplification, PIK3CA mutation, FGFR1 amplification, and focal somatic loss of BRCA2 and other genes involved in DNA repair have been identified in advanced cancers.\textsuperscript{94,95} These findings suggest that therapy for advanced prostate cancer needs to be increasingly individualised. Furthermore, neuroendocrine prostate cancer can evolve after endocrine therapy, although this disease is uncommon at diagnosis. Neuroendocrine prostate cancer might suggest resistance to antiandrogen therapies and needs different treatment, even after evolving from a previously androgen-sensitive cell. Specific molecular changes, such as AURKA and MYCN amplification, have been reported in neuroendocrine prostate cancer that might be amenable to therapeutic targeting.\textsuperscript{96,97}

**Treatment of localised disease**

Men with localised disease can have very different prognoses and face a wide array of treatment options. Men are advised on treatment based on risk assessments that often combine patient age, clinical tumour stage, serum PSA, PSA density, Gleason score, number of positive prostate biopsies, and amount of malignant tissue per core to select patients for treatment ranging from active surveillance alone through to multimodality treatment. Mostly, this choice is not guided by robust randomised trials.

Many low-grade (Gleason score of 6 or less) localised prostate cancers are harmless. Active surveillance offers patients the hope of avoiding unnecessary, potentially harmful, treatment.\textsuperscript{98} Surveillance policies vary, but typically patients with assumed low-risk tumours are monitored with measurements of serum PSA, repeat prostate biopsies, and MRI. Changes on these assessments that suggest initial undersampling or disease progression should lead to radical treatment. Large studies indicate that most men with low-risk disease can safely avoid treatment with a risk of death from prostate cancer of 1% at 10 years,\textsuperscript{99,100} although the longer-term outcomes of active surveillance are not known.

Radical prostatectomy, external-beam radiotherapy, and brachytherapy are all standard local treatments for prostate cancer but have never been compared in robust randomised trials (table 1).\textsuperscript{96–101} Newer modalities such as cryotherapy, high-intensity focal ultrasound, and photodynamic therapy are also used. The best data for the efficacy and safety of local treatment are from two randomised trials that compared radical prostatectomy against watchful waiting.\textsuperscript{97,102} The Scandinavian Prostate Cancer Group 4 trial\textsuperscript{102} randomly assigned 695 men with localised prostate cancer between 1989 and 1999. Importantly, the men in this trial had clinically detected cancers—88\% had palpable disease on rectal examination. The results should therefore not be extrapolated to men with impalpable, PSA-detected cancers. Overall, mortality at 18 years was 56\% for radical prostatectomy and 69\% for watchful waiting (hazard ratio [HR] 0.71, 95\% CI 0.59–0.86, p<0.001).\textsuperscript{102} The Prostate Cancer Intervention Versus Observation Trial (PIVOT) randomly assigned 731 men with localised prostate cancer from 1994 to 2002, in the early era of PSA testing, resulting in mainly low-risk cases. Mortality at 12 years was 41\% for radical prostatectomy versus 44\% for observation (HR 0.88, 95\% CI 0.71–1.08). Radical prostatectomy was, however, associated with a trend towards decreased overall mortality in men with intermediate risk (HR 0.69; 95\% CI 0.49–0.98). In the low-risk subgroup of 296 men, the risk of death from prostate cancer was less than 3\% at 12 years, with no significant benefit from surgery. The HR for overall mortality favoured watchful waiting rather than surgery but this was not significant (HR 1.15; 95\% CI 0.80–1.66). At 2 years, surgery was also associated with greater urinary incontinence (17\% vs 6\%, p<0.001).
Table 1: Trials of radical prostatectomy versus observation

<table>
<thead>
<tr>
<th>Patients</th>
<th>Comparison</th>
<th>Overall survival outcome</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>695</td>
<td>Radical prostatectomy vs watchful waiting</td>
<td>67% vs 60% at 12 years</td>
<td>0.82 (0.65–1.03)</td>
<td>0.09</td>
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<tr>
<td>731</td>
<td>Radical prostatectomy vs watchful waiting</td>
<td>52% vs 50% at 10 years</td>
<td>0.88 (0.71–1.08)</td>
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Table 1: Trials of hormone therapy with or without radical radiotherapy

<table>
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<th>Comparison</th>
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<th>p value</th>
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<tbody>
<tr>
<td>875</td>
<td>Hormone therapy plus EBRT vs hormone therapy</td>
<td>70% vs 61% at 10 years</td>
<td>-</td>
<td>0.004</td>
</tr>
<tr>
<td>1205</td>
<td>Hormone therapy plus EBRT vs hormone therapy</td>
<td>74% vs 66% at 7 years</td>
<td>0.77 (0.61–0.98)</td>
<td>0.033</td>
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</table>

Trials of radical radiotherapy with or without adjuvant hormone therapy

<table>
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<tr>
<th>Patients</th>
<th>Comparison</th>
<th>Overall survival outcome</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>415</td>
<td>EBRT plus 3 years of hormone therapy vs EBRT</td>
<td>58% vs 40% at 10 years</td>
<td>0.60 (0.45–0.80)</td>
<td>0.0004</td>
</tr>
<tr>
<td>977</td>
<td>EBRT plus lifelong hormone therapy vs EBRT</td>
<td>43% vs 33% at 10 years</td>
<td>-</td>
<td>0.002</td>
</tr>
<tr>
<td>537</td>
<td>EBRT plus 6 months of hormone therapy vs EBRT</td>
<td>70% vs 57% at 10 years</td>
<td>0.63 (0.48–0.83)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

EBRT=external-beam radiation therapy.

Table 1: Influential phase 3 trials for localised prostate cancer

and erectile dysfunction (81% vs 44%, p<0.001). Taken together, these two trials provide support for a conservative approach in men with low-risk disease and a curative approach for some men with higher-risk disease.

The role of external-beam radiotherapy to the prostate for men with prostate cancer has been established by two randomised controlled trials done mainly in men with high-risk or locally advanced disease. The SPCG-7 trial included 875 patients between 1996 and 2002 who were randomly assigned to hormonal treatment alone (3 months of total androgen blockade followed by flutamide alone) or to the same hormonal treatment combined with radiotherapy.58 Radiotherapy significantly improved 10 year overall mortality (30% vs 39%, p=0.004). The National Cancer Institute of Canada-PR3 trial59 randomly assigned 1205 patients between 1995 and 2005 to lifelong androgen deprivation (bilateral orchiectomy or luteinising-hormone-releasing hormone agonist) with or without radiotherapy. The addition of radiotherapy significantly reduced 7-year overall mortality from 34% to 26% (HR 0.77 [95% CI 0.61–0.98], p=0.033). Toxic effects associated with radiotherapy were slight in both trials; rectal bleeding was reported in 13% of patients after radiotherapy versus 6% on androgen deprivation alone in the PR3 trial. Long-term androgen deprivation plus radical radiotherapy are now a standard of care for high-risk and locally advanced prostate cancer. Because of these two trials, hormone therapy as the sole modality of treatment is not recommended for men with localised or locally advanced disease.

Androgen deprivation is of proven value as an adjuvant to external-beam radiotherapy for higher-risk disease (table 1).60 For example, in a randomised trial of 415 patients with locally advanced disease, the addition of 3 years of androgen deprivation improved 10 year overall survival after radiotherapy from 40% to 58% (HR 0.60, 95% CI 0.45–0.80; p=0.0004).61 Adjuvant androgen deprivation has not been shown to improve survival in low-risk disease,62 which is unsurprising given its excellent prognosis even without treatment. The optimum duration of adjuvant androgen deprivation is uncertain. TROG 96.01 compared none versus 3 months versus 6 months of neoadjuvant androgen deprivation in 818 men undergoing radiotherapy for localised and locally advanced disease.63 The use of 6 months, not 3 months, neoadjuvant androgen-deprivation significantly improved overall mortality (from 43% to 29% at 10 years, HR 0.63, 0.48–0.83; p=0.0008), and 6 months should be considered the minimum duration of adjuvant treatment. EORTC 22961 randomised 970 men between 6 months and 3 years of adjuvant treatment.64 Overall mortality at 5 years was 19% and 15% (HR 1.42, 95% CI 1.09–1.85), respectively. This survival benefit comes at the cost of a substantial prolongation of treatment-related morbidity.65

Management of metastatic disease

First-line hormone treatment

Disease in many patients recurs after local therapy with a rising PSA; the optimum timing to start systemic treatment initiation is not clear. The best treatment of the prostatic primary in patients with metastatic disease at diagnosis is also unclear.66 Suppression of testicular androgens by castration (medical or surgical) is the mainstay of treatment for metastatic disease; single-agent antiandrogens such as bicalutamide have been used to initially minimise sexual dysfunction despite their inferior antitumour activity. Combination of cyproterone, flutamide, and nilutamide with castration results in little benefit,67 with a shorter survival for patients treated with cyproterone. Studies are now continuing to assess next-generation hormone treatments (eg, abiraterone acetate) as first-line therapy, with or without chemical castration. Docetaxel might also have a role in this setting; one study showed no survival benefit but another larger study (CHAARTED) has suggested a very significant improvement in survival.

M0 disease

Many patients develop progressive disease after castration with a rising PSA; frequently without radiological evidence of metastases. This is referred to as M0 castration-resistant prostate cancer, although these observations might be due to imaging limitations; whole-body diffusion-weighted MRI identifies bone metastases missed by bone and CT scan (appendix).68 Little evidence exists to help treatment selection for M0 castration-resistant prostate cancer with a rising PSA. Biochemical response rates to hormonal therapies range from 30% to 80% and multinational phase 3 studies continue to assess next-generation hormone therapies in M0 patients with time to metastases as a primary endpoint. However, concerns remain about the validity of this endpoint.
Treatment of metastatic castration-resistant prostate cancer

Several treatment options are available for men with progressing metastatic castration-resistant prostate cancer. Abiraterone with prednisone is approved on the basis of COU-302 study data. The similar PREVAIL trial confirmed the efficacy of enzalutamide in chemotherapy-naïve M1 castration-resistant prostate cancer. Availability of these next-generation therapies should decrease the use of the less effective ketoconazole and oestrogens. Single-drug steroids in the form of prednisolone 5 mg twice a day or dexamethasone 0·5 mg once a day (which has less mineralocorticoid receptor agonist activity, a longer half-life, and a higher biochemical response rate), remain popular treatment options but the absence of a proven survival benefit limits their use. The potential long-term detrimental effects of steroids should also detract from their continued use at progression. There is no evidence base to guide the sequence of taxanes compared with next-generation hormone therapies; until clinical trials address the optimum sequence for the administration of these drugs, for most men, treatment choice will be based on the better toxicity profiles of the newer hormone treatments.

Several cytotoxics have been assessed in patients with prostate cancer but so far the only cytotoxics to show a survival advantage are docetaxel and cabazitaxel. Mitoxantrone was approved based on improved palliation, but is no longer commonly used. In the TAX-327 phase 3 study, docetaxel 75 mg/m² given once every 3 weeks improved overall survival compared with mitoxantrone 12 mg/m² every 3 weeks or docetaxel 30 mg/m² given every week for five of every 6 weeks. The TAX327 study recruited 1006 chemotherapy-naïve patients with metastatic castration-resistant prostate cancer and led to about a 3 month improvement in median survival as compared to treatment with mitoxantrone. The SWOG 9916 study also showed a survival benefit for docetaxel (60 mg/m² every 3 weeks) and estramustine compared with mitoxantrone, but the estramustine seemed to only add toxic effects. Adverse events were more common in the groups treated with docetaxel but overall this treatment was well tolerated. Pharmacokinetic studies now report that in castrated men, docetaxel exposure might be decreased. Docetaxel retreatment for taxane-sensitive disease remains of proven benefit. Cabazitaxel is a second-generation semi-synthetic taxane generated to be active in docetaxel resistant or refractory models. The TROPIC study randomly assigned 755 patients with metastatic castration-resistant prostate cancer who had previously received docetaxel to either 12 mg/m² of mitoxantrone or 25 mg/m² of cabazitaxel intravenously every 3 weeks. The median survival was 15·1 months (95% CI 14·1–16·3) in the cabazitaxel group and 12·7 months (11·6–13·7) in the mitoxantrone group, with an HR for mortality of 0·70 (95% CI 0·59–0·83, p<0·0001). Subgroup analyses have reported that cabazitaxel is effective in patients refractory and resistant to docetaxel. Studies indicate that the taxanes inhibit tubulin-dependent androgen receptor nuclear shuttling which could contribute to cross-resistance between taxanes and endocrine treatments, although this remains unclear because cabazitaxel also retains anti-tumour activity against abiraterone-resistant and enzalutamide-resistant disease.

Ketoconazole is a non-specific, weak, CYP inhibitor, which is used to inhibit androgen synthesis with some antitumour activity. Abiraterone is a potent CYP17A1 inhibitor; when given to men receiving castration treatment, it inhibits androgenic steroid synthesis. CYP17A1 blockade results in a compensatory rise in adrenocorticotropic hormone, leading to increased weak glucocorticoids upstream of CYP17A1 that prevent adrenocortical insufficiency. Abiraterone is given with prednisone or prednisolone 5 mg twice a day to suppress adrenocorticotropic-hormone-generated mineralocorticoid excess. Findings of two large randomised trials (COU-AA-301 and COU-AA-302) confirmed that abiraterone was efficacious in docetaxel-treated and chemotherapy-naïve patients, leading to regulatory approval in 2011. Investigators for COU-AA-301 treated 1195 patients who had received up to two lines of chemotherapy including docetaxel; median overall survival in the abiraterone group was 15·8 months compared with 11·2 months in the placebo group. Abiraterone and prednisone significantly delayed pain progression and skeletal-related events, improving fatigue, quality of life, and pain control when compared with prednisone alone, which also had antitumour activity. A second randomised trial (COU-AA-302) enrolled 1088 chemotherapy-naïve men with metastatic castration-resistant prostate cancer and a rising PSA but minimal symptoms. At a pre-planned interim analysis after 433 deaths and a median follow-up of 22·2 months, radiological progression-free survival for abiraterone and prednisone was significantly improved compared with placebo and prednisone. At the final analysis, overall survival was also confirmed to be significantly increased (HR 0·81 [95% CI 0·70–0·93]; p=0·0033). Abiraterone improved all the secondary endpoints of the study. The mechanisms underlying resistance to abiraterone remain unclear. Researchers have reported residual ligands might reactivate androgen receptor signalling and in-vivo xenografts have shown increased CYP17A1 expression at progression on abiraterone.

Enzalutamide is a potent next-generation antiandrogen drug, selected for clinical development after showing activity in bicalutamide-resistant mice overexpressing androgen receptor or with a mutant androgen receptor. Shown to be highly active in early clinical trials, a phase 3 study randomly assigned men with metastatic castration-resistant prostate cancer who had previously received docetaxel chemotherapy to either enzalutamide 160 mg
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Significant cross-resistance. 140 Clinical trials that assess enzalutamide and could be one explanation for this been associated with resistance to abiraterone and splice variants without the ligand-binding domain has and no robust criteria exist clinically to select one drug signalling by other nuclear steroid receptors such as the glucocorticoid receptor.136 Preliminary data suggest that response rates to abiraterone after enzalutamide and conversely enzalutamide after abiraterone are low137–139 and no robust criteria exist clinically to select one drug rather than the other. The presence of androgen receptor splice variants without the ligand-binding domain has been associated with resistance to abiraterone and enzalutamide and could be one explanation for this significant cross-resistance.140 Clinical trials that assess the combination of CYP17A1 inhibition with androgen receptor antagonism are continuing, with drugs given both at start of castration treatment (NCT00268476) and in patients with castration-resistant prostate cancer (NCT01949337).

Bone-targeting treatment

Bone metastases develop in most men with metastatic castration-resistant prostate cancer and lead to complications (skeletal-related events) such as bone pain needing radiotherapy, pathological fracture, spinal cord compression, and the need for orthopaedic surgery. Two drugs have been approved for prevention of skeletal-related events. Zoledronic acid is a bisphosphonate that inhibits osteoclast-mediated bone resorption. In a randomised trial of 422 patients with zoledronic acid and bone metastases, zoledronic acid at 8 mg or 4 mg every 3 weeks was compared with placebo.141 The group given 8 mg did not have significantly better outcomes than those given placebo and had more renal toxic effects. In the group given 4 mg, the proportion of patients that had skeletal-related events was reduced from 44% to 33% (p=0.021), although overall survival was not improved in either group. Denosumab is a human monoclonal antibody against RANKL (TNFSF11) that inhibits osteoclast function. In a randomised trial of 1904 patients with metastatic castration-resistant prostate cancer, denosumab was superior to zoledronate with regard to time to first skeletal-related event (median 20·7 months vs 17·1 months; HR 0·82, 95% CI 0·71–0·95; p=0·008).142 Denosumab was associated with a higher rate of osteonecrosis of the jaw (2% vs 1% of patients) and hypocalcaemia (13% vs 6%) than was zoledronate, with no difference in overall survival. Moreover, zoledronate is given intravenously, denosumab subcutaneously, making denosumab more practical. However, the poor effect on survival for both of these drugs raises concerns about their cost-effectiveness (table 2); less frequent administration might improve this figure, although might generate less benefit. Moreover, their pivotal trials were accrued before the approval of abiraterone, enzalutamide, and radium-223, all of which reduce risk of skeletal-related events. The absolute benefit of zoledronic acid and denosumab might therefore now be smaller.

Radium-223 is an α-emitting bone-targeted radioisotope that prevents skeletal-related events and improves overall survival and quality of life for men with metastatic castration-resistant prostate cancer and bone metastases. After intravenous injection, radium-223 localises to bone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pivotal trial</th>
<th>Gain in median survival (months)</th>
<th>Approximate cost of treatment per month</th>
<th>Independent estimates of cost per QALY</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (first-line chemotherapy)</td>
<td>TAX-327141-145</td>
<td>2·9</td>
<td>£310†</td>
<td>Not available</td>
<td>Now available as generic drug</td>
</tr>
<tr>
<td>Cabazitaxel (second-line chemotherapy)</td>
<td>TROPIC130</td>
<td>2·4</td>
<td>£3670†</td>
<td>£82 950146</td>
<td>Rejected for funding by NICE</td>
</tr>
<tr>
<td>Sipuleucil-T</td>
<td>IMPACT144</td>
<td>4·1</td>
<td>£60 0001†</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Abiraterone (after docetaxel)</td>
<td>COU-AA-301144</td>
<td>3·9</td>
<td>£2630†</td>
<td>£46 800–50 000150</td>
<td>Accepted for funding by NICE</td>
</tr>
<tr>
<td>Enzalutamide (after docetaxel)</td>
<td>AFFIRM114</td>
<td>4·8</td>
<td>£4800†</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Radium-223 (after docetaxel)</td>
<td>ALSYMPCA114</td>
<td>2·8</td>
<td>Price not yet available</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Saad et al (2002)146</td>
<td>0</td>
<td>£450†</td>
<td>£100 000148</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Fizazi et al (2011)140</td>
<td>0</td>
<td>£350†</td>
<td>£650 000149</td>
<td></td>
</tr>
</tbody>
</table>

QALY=quality-adjusted life-years. NICE=National Institute for Health and Care Excellence. *Cost to the pharmacy at Princess Margaret Cancer Centre (PMCC, for available drugs, August, 2013), for a man of 1·75 m², using the dose and schedule evaluated in the pivotal trials, with cost converted to British pounds. †Based on US prices (not available at PMCC). §Price is for a course of sipuleucil-T (three infusions given at 2 week intervals). ‡This estimate was based in geographic regions (no longer true at PMCC) where the price of denosumab exceeded that of zoledronic acid.

Table 2: Cost of treatments for advanced castration-resistant prostate cancer
metastases by virtue of its chemical similarity to calcium and decays with a half-life of 11 days, emitting α particles that are highly cytotoxic with a very short penetration range (100 μm). In a randomised placebo-controlled trial of 921 men with metastatic castration-resistant prostate cancer, radium-223 improved overall survival (median 14.9 months vs 11.3 months with placebo; HR 0.70, 95% CI 0.58–0.83; p<0.001), delayed time to first skeletal-related events (median 9.8 vs 15.6 months; HR 0.66, 95% CI 0.52–0.83; p<0.001) and improved quality of life. Radium-223 was well tolerated with mild nausea and diarrhoea and a low risk of myelosuppression (eg, grade 3 or 4 thrombocytopenia in 6% vs 2% in placebo). Radium-223 has now received regulatory approval. Future trials aim to optimise the radium-223 dosing schedule and assess its use earlier in the disease and in combination with other drugs.

**Immunotherapy**

Immune-based approaches involve diverse ways to generate CD8 (killer) lymphocytes that lyse tumour cells. Sipuleucel-T is an active cellular immunotherapy composed of autologous peripheral-blood mononuclear cells including antigen-presenting cells that have been activated ex vivo with a recombinant fusion prostate cancer antigen (PSA). Three infusions are given over 6 weeks. Manufacture is done separately for each patient, and is costly, needing leukaapheresis and personalised generation of each infusion product. Sipuleucel-T is well tolerated but can cause flu-like syndromes and myalgia; it has little effect on PSA or disease progression rate. Nonetheless, a phase 3 trial of 512 patients reported a 4.1 month survival advantage for sipuleucel-T versus placebo in men with metastatic castration-resistant prostate cancer. A critical appraisal of these data has raised concerns that they could potentially be explained by a worse outcome in placebo group patients due to the control leukaapheresis product being stored at a lower temperature than the drug. ProstVac-VF is an engineered poxvirus-based vaccine targeting PSA using vaccinia-virus based priming followed by a series of fowl-pox-virus-based vaccine targeting PSA using vaccinia-virus based priming followed by a series of fowl-pox-based boosts. It is well tolerated and has shown promise in a randomised phase 2 study. Results of a randomised phase 3 trial (NCT01322490) are awaited. The CTLA4 immune checkpoint targeting antibody ipilimumab was not shown to be of significant clinical benefit in patients with late-stage metastatic castration-resistant prostate cancer in a phase 3 trial (NCT00861614), but trials are awaited for patients with earlier stage disease who have lower volume disease and are less immunocompromised (NCT01057810).

**Conclusions**

Understanding of prostate cancer genetics and molecular pathogenesis has improved substantially, with several new drugs to improve the treatment and outcome of metastatic castration-resistant prostate cancer. However, controversies about the screening of men for prostate cancer and the treatment of localised disease remain. These have been challenging to address because of contradictory results and the difficulties, including very long lead-time, of doing clinical trials in these groups. The clinical relevance of genetic testing to identify men at high risk of disease and of molecular subtyping of prostate cancer are as yet uncertain. Although the cost of docetaxel has recently decreased substantially since generic drugs became available, all the newer drugs for treatment of advanced prostate cancer are expensive and will probably remain so while under patent. Moreover, little information has been reported about the activity of newer drugs when used sequentially. Overtreatment of indolent disease, inadequate screening schedules, low cure rates, and invariable drug resistance remain crucial issues that require prioritisation. Continuing clinical and translational research will be key to improvements in and personalisation of the management of prostate cancer.

**Contributors**

RAE wrote the section about causative mechanisms. FS wrote the section on screening and diagnosis. SAT wrote the section on carcinogenesis and molecular subclassification. CP wrote the section about treatment of localised disease. JSdB, CP, GA, IT, and CGD cowrote the section on management of metastatic disease, while GA provided overall structure and editing for the Seminar. JSdB provided overall structure and the search strategy. All authors provided final review and approval for the Seminar and had input into responding to the reviewers’ comments.

**Declaration of interests**

GA and JSdB are employees of The Institute of Cancer Research (ICR) based at Sutton and Fulham, which has a commercial interest in abiraterone acetate and inhibitors of PI3K/AKT signalling. GA has received consulting fees and travel support from Janssen-Cilag, Veride, Roche-Ventana, Astellas, Novartis, and Millennium Pharmaceuticals; speaker’s fees from Janssen, Ipsen, Takeda, and Sanofi-Aventis; and grant support from AstraZeneca and Genentech. GA is on the ICR Rewards to Inventors list for abiraterone acetate. RAE has received educational grants from Vista Diagnostics, Janssen, Illumina, and GenProbe (formerly Tepnel) and honoraria from Succinct Communications. SAT is a coinventor on a patent issued to the University of Michigan on ETS fusion genes in prostate cancer. The diagnostic field of use has been licensed to Prostate-Ventana, who has sublicensed certain rights to Ventana Medical Systems, and SAT receives distributions from licensing agreements through the University of Michigan. SAT is a coinventor on a patent filed by the University of Michigan on SPINK1 in prostate cancer. The diagnostic field of use has been licensed to Prostate-Ventana, who has sublicensed certain rights to Ventana Medical Systems, and SAT receives distributions from licensing agreements through the University of Michigan. SAT is a consultant and has received honoraria from Ventana Medical Systems. CGD has interests in Medimmune and has received consulting fees from Bristol-Myers Squibb, Costimm, Dendreon, Pfizer, Roche, and Compugen. JSdB has received consulting fees from Ortho Biotech Oncology Research and Development; consulting fees and travel support from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dendreon, Enzon, Exelixis, Genentech, GlaxoSmithKline, Medication, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Supergen, and Takeda; and grant support from AstraZeneca and Genentech. CP has received honoraria from Bayer, BN Immunotherapeutics, Janssen, Sanofi-Aventis, and Takeda.

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