Gnanapragasam, V. J., Hori, S., Johnston, T., Smith, D., Muir, K., Alonzi, R., ... Koupparis, A. (2016). Clinical management and research priorities for high-risk prostate cancer in the UK: meeting report of a multidisciplinary panel in conjunction with the NCRI Prostate Cancer Clinical Studies Localised Subgroup. Journal of Clinical Urology, 9(6), 369-379. DOI: 10.1177/2051415816651362

Clinical management and research priorities for high-risk prostate cancer in the UK: Meeting report of a multi-disciplinary panel in conjunction with the NCRI Prostate Cancer Clinical Studies Localised Subgroup.

VJ Gnanapragasam*[#1], S Hori[#1], T Johnston[#1], D Smith[2], K Muir[3]: UK high-risk prostate cancer consensus group panel and NCRI Prostate Cancer Clinical Studies Localised Subgroup. R Alonzi[4], M Winkler[5], A Warren[6], J Staffurth[7], V Khoo[8], A Tree[9], A Macneill[10], R McMenemin[11], M Mason[7], P Cathcart[12], N de Souza[13], P Sooriakumaran[14], R Weston[15], J Wylie[16], E Hall[17], A Lane[18] W Cross[19], I Syndikus[20], A Koupparis[21].

[1] Academic Urology Group, University of Cambridge, Cambridge UK
[2] Patient advocate, Prostate Cancer Support Association, UK
[3] Institute of Public Health, University of Manchester, Manchester UK
[4] Department of Clinical Oncology, Royal Marsden Hospital, London, UK
[5]Department of Urology, Charing Cross Hospital, London, UK
[6]Department of Pathology, Addenbrookes Hospital, Cambridge UK
[7] Institute of Cancer and Genetics, Cardiff University, Cardiff, Wales.
[8] Academic Urology Unit, Institute of Cancer Research London
[9] Academic Uro-oncology Department London, UK
[10]Department of Urology, Western General Hospital, NHS Lothian, Edinburgh
[11]Northern Centre for Cancer Care, Newcastle upon Tyne , UK
[12]Imperial College, London, UK
[13]MRI Unit, Royal Marsden Hospital, London, UK
[14]Department of Surgery, University of Oxford, Oxford UK
[15]Department of Urology, Royal Liverpool University Hospital, Liverpool UK
[16]Department of Oncology, Christie Hospital, Manchester UK
[17]Clinical Trials and Statistics Unit, Institute of Cancer Research, London UK
[18]Department of Social Medicine, University of Bristol, Bristol UK
[19]Department of Urology, St. James's University Hospital, Leeds UK
[20]Radiotherapy Department, Clatterbridge Cancer Centre, Bebington, UK
[21]Department of Urology, Bristol Royal Infirmary, Bristol, UK

[*]**Corresponding Author:**

Mr. Vincent J Gnanapragasam, Academic Urology Group, Department of Surgery and Oncology, University of Cambridge, Box 279 [S4], Cambridge Biomedical Campus, Cambridge CB2 0QQ E-mail: vjg29@cam.ac.uk; Phone: 0044-01223-274316

#-Joint first authors

Key words

Prostate cancer

High risk

Consensus meeting

Research Priorities

Clinical priorities

Multi-disciplinary panel

Abstract

The management of high-risk prostate cancer has become increasingly sophisticated with refinements in radical therapy and the inclusion of adjuvant local and systemic therapies. Despite this, high-risk prostate cancer continues to have significant treatment failure rates with progression to metastasis, castrate resistance, and ultimately disease-specific death. In an effort to discuss the challenges in this field, the UK NCRI Prostate Cancer Clinical Studies Localised Sub-Group convened a multi-disciplinary national meeting in the autumn of 2014. The remit of the meeting was to debate and reach a consensus on the key clinical and research challenges in high-risk prostate cancer and to identify themes that the UK would be best placed to pursue to help improve outcomes. This report presents the outcome of those discussions and the key recommendations for future research in this highly heterogeneous disease entity.

Introduction

Prostate cancer is the commonest male malignancy in the western world with 41,736 new cases reported in 2011 for the UK alone (1). In men with new diagnoses the proportion of men presenting with High Risk Prostate Cancer (HR-PC) is rising year on year (2). Studies from a number of centres have shown that primary radical therapy can be very effective; however men with HR-PC have the highest incidence of disease relapse and progression. Evidence-based practice in HR-PC has been hampered by a lack of appropriate randomised controlled studies except in the field of external beam radiotherapy (EBRT). As a result, current clinical management is mainly driven by data from large case series and observational studies. To address this, the National Clinical Research Institute (NCRI) Prostate Cancer Clinical Studies Localised Sub-group held a 1-day multi-disciplinary meeting on HR-PC on the 17th November 2014 in London, UK. The remit was to evaluate current clinical pathways in the management of patients with HR-PC in the UK and to identify key research priorities in this field.

The meeting included a multi-disciplinary group of healthcare professionals that are actively involved in managing patients or researching HR-PC along with a lay expert member of the public (Table 1). The primary objective of the meeting was to 1) discuss the current clinical pathways (from definition to management) of patients with HR-PC and 2) to identify key areas that required further research. Prior to the meeting, topics for discussion were pre-selected and specific members of the group were asked to review the current state of evidence and research on the respective topics allocated to them. The findings were then presented at the meeting to the rest of group followed by a moderated discussion in order to reach a consensus view. The top priorities in each domain are listed here in the Tables relevant to each section. The meeting was chaired jointly by an epidemiologist (KM) and patient representative (DS).

Name	Place of work	Speciality
Roberto Alonzi	London	Oncology
Mathias Winkler	London	Urology
Anne Warren	Cambridge	Pathology
John Staffurth	Cardiff	Oncology
Alison Tree	London	Oncology
Alan Macneill	Edinburgh	Urology
Rhona McMenemin	Newcastle	Oncology
Malcolm Mason	Cardiff	Oncology (CSG Chair)
Vincent Khoo	London	Oncology
Paul Cathcart	London	Urology
Nandita de Souza	London	Radiology
Vincent Gnanapragasam	Cambridge	Urology
David Smith	-	Patient advocate (Chair)
Kenneth Muir	Manchester	Epidemiology (Chair)
P Sooriakumaran	Oxford	Urology
Robin Weston	Liverpool	Urology
James Wylie	Manchester	Oncology
Emma Hall	London	Statistics
Athene Lane	Bristol	Clinical Trials
William Cross	Leeds	Urology
Isabel Syndikus	Clatterbridge	Oncology
Anthony Koupparis	Bristol	Urology

Table 1 – Participants and designations of the HR-PC consensus meeting

Current perspectives on the clinical management of high-risk prostate cancer

Definitions of high-risk disease

The definition of HR-PC is contentious and varies with different guidelines. The first of the risk stratification tools that was developed for localised prostate cancer was the D'Amico classification. In this classification, high-risk patients are grouped as those with a PSA >20ng/ml, Gleason score 8-10 or patients with clinical T2c and above. This classification is the basis for the current American Urological Association (AUA) and UK National Instituite for Clinical Excellence (NICE) classifications. The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines both define high-risk cancer as Gleason score 8-10, PSA >20ng/ml or clinical stage T3a (as opposed to T2c in the D'Amico classification). The UCSF-CAPRA score (University of California, San Francisco – Cancer of the Prostate Risk Assessment) on the other hand, also takes into consideration the percentage core positivity following prostatic biopsies although its use is mainly limited parts of the US.

There is increasing recognition that prognosis can differ markedly amongst HR-PC patients and that there is significant heterogeneity within this group. Joniau *et al* demonstrated in a multi-centre, retrospective study of 1360 patients with HR-PC treated by radical prostatectomy that three distinct groups of patients could be identified with differing survival profiles (3). Lowest risk patients were those who had a single high risk factor with a 10-year prostate cancer survival (PCS) rate of 88.3%. The intermediate prognosis group were patients with a PSA >20ng/ml and stage cT3-4 while the poorest prognosis sub-group had all three high risk factors (PCS of 79.7%) (3).

The group noted that current risk stratification systems relied mainly on retrospective studies with outcomes based on high volume academic centres with particular expertise in the management of HR-PC. In the study by Joniau *et al* for example, as all patients were managed with radical prostatectomy, it is conceivable that the group defined as the 'high-risk' sub-group may in fact be more accurately classified as intermediate risk and may have had features that would favour the clinicians to recommend radical surgery (case-selection bias) (3). Furthermore, as high-volume surgeons were performing the surgery, the positive margin rates were particularly low and patients therefore had a better prognosis from the outset.

Partly because of this intergroup heterogeneity, there has been intensive research into other ways to better stratify patients, not only for HR-PC, but across the disease spectrum. The use of molecular predictive markers such as the cell cycle progression panel (CCP) and the Oncotype Dx test have all entered commercial use on this basis. The clinical role and cost-effectiveness of these panels in current clinical management remains to be elucidated particularly within the context of sub-optimal clinical risk prediction models.

The clinical utility of nomograms was also discussed. It was generally agreed that nomograms might be a useful way of presenting a non-biased, objective measure of risk to patients diagnosed with prostate cancer. However most UK oncologists and urologists do not use these predictive tools as the majority of nomograms are based on historical US data that is very different from the UK population. Thus, it was felt that there was an urgent need to develop nomograms and risk models based on UK data.

In summary, there is evidence to suggest that prognosis differs even in the context of patients with HR-PC. Future studies should therefore concentrate on better defining the different sub-categories that may exist within a HR-PC classification. Any future risk prediction tools need to be developed based on contemporary UK data in order to be applicable and also include patients from across the spectrum of treatments.

Current treatment pathways and outcomes

The optimal treatment for patients with HR-PC is currently unknown. Typically, high-risk patients are treated with EBRT with neo-adjuvant and adjuvant Androgen Deprivation Therapy (ADT) for 2-3 years. There is evidence of improved overall survival for this combined modality approach in patients with locally advanced disease from two randomised trials (4-5). In the NCIC Clinical Trials Group PR.3/Medical Research Council PR07/Intergroup T94-0110 trial patients who received EBRT and ADT had a 74% survival at 7 years compared to 66% in men who received ADT (4).

In the UK, the majority of patients are treated with EBRT to a dose of 74-78 Gy in 37-39 fractions. This typically results in a 5-year biochemical relapse free survival of approximately 75-81% in patients with localised disease, but perhaps as low as 57% in high-risk patients (6). There is some recognition, that HR-PC may behave radio-biologically in a different manner

compared to low risk prostate cancer. Dasu *et al* reported that in patients with high-risk disease 74 Gy did not achieve adequate control of the tumour with a total radiation dose of >80Gy often being required (7). Another explanation for the poorer EBRT response could also be a higher tumour burden within the prostate in men with HR-PC. An interesting question in this regard is whether the dose distribution of EBRT could be risk-adapted and in the UK, studies such as the recently completed DELINEATE trial could help answer this (ISRCTN: 04483921). In this pilot study the aim was to test the value of increasing radiation dosage to MRI-visible tumours within the prostate.

Another potential method by which the effectiveness of EBRT could be improved is by combination with other agents that are designed to block androgen receptor signalling. Current trials for example are specifically looking at the HR-PC group and whether the combination of EBRT with agents such as enzalutamide can result in a survival advantage (8).

It is currently unknown whether irradiating the prostate alone is sufficient in the management of patients with prostate cancer, or whether the whole pelvis should also be irradiated. Lepinoy *et al* recently reported that in patients who had biochemical recurrence following EBRT (primary or salvage), 45% of nodal relapses were observed to occur outside the standard EBRT field (9). The study authors therefore concluded that the upper field limit of pelvic EBRT should be extended to L2-L3 in order to cover 95% of nodal stations that are at risk of an occult relapse (9). With the lack of level 1 evidence to support pelvic nodal irradiation however, it is unknown whether further extending the field to include para-aortic nodes would result in any advantage for these patients. The additional toxicity is also of concern although the phase II PIVOTAL trial has shown low levels of toxicity with pelvic nodal IMRT in this setting (10).

The group identified that there were key areas in current management of HR-PC with EBRT that require further investigation. Firstly, it is unknown whether further escalating the dose in patients with HR-PC can improve survival outcomes in patients who are being treated with concurrent ADT. There is an increasing ability to do this with precision using image-guided and intensity modulated EBRT approaches to avoid toxicities to surrounding normal tissues. Secondly, the molecular mechanism by which ADT and EBRT together improves survival outcome is also not well understood. The perceived notion is that ADT may be

having an effect on early micro-metastatic disease and hence result in better systemic control and survival outcome in this group of patients. There is however no evidence that ADT as an adjunct treatment for radical prostatectomy confers a similar survival benefit though this question remains controversial (11). This suggests that there might be a mechanism unique to EBRT. Such mechanisms may include the effect of ADT in permitting quiescent androgen receptor negative prostate cancer stem cells to replicate thus allowing them to become susceptible to EBRT. There is also emerging data that the androgen receptor is a critical pathway in the regulation of DNA damage repair pathways (12-13). Here, the hypothesis is that androgen deprivation results in the suppression of the androgen receptor, which in turn suppresses DNA repair and enhances the effect of EBRT.

Historically, radical prostatectomy was a treatment modality reserved for patients with low to intermediate risk prostate cancer. It was generally thought that patients with high-risk disease treated with radical prostatectomy developed biochemical recurrence and systemic progression more readily compared to those patients who were treated with radical EBRT as the primary treatment modality (14). Recently however, studies have challenged this notion and radical prostatectomy has slowly become an established alternative to patients with HR-PC (15). A number of retrospective observational studies have suggested that radical prostatectomy may confer improved survival outcomes compared to EBRT (16). With the advancement of technology (laparoscopic and more recently, robotic-assisted surgery) and improvements in morbidity and functional outcomes, the uptake of radical prostatectomy in the UK has increased considerably in the last decade. Increasingly, radical prostatectomy is regarded by both urologists and oncologists as an important part of a multi-modality treatment approach in the management of HR-PC (17-18). From the outset, these patients are counselled that they may require adjuvant treatment with EBRT and possibly ADT. It was noted however that there is no evidence to suggest the superiority of this treatment modality over primary radiotherapy and this concept has entered mainstream practice without a strong evidence base. Thus, the group acknowledged this to be an on-going future clinical research priority and there was a general feeling that the UK would be ideally suited to conduct a head-to-head trial on multi-modality treatment with surgery as the initial intervention versus radical EBRT with ADT alone. Until then the group recognised that

the current selection of surgery or EBRT as the primary treatment modality should be judged on an individual basis and centred on patient and practitioner joint decision-making (19).

Factors in HR-PC treatment selection

There are a number of issues that need to be considered in selection of therapy for HR-PC. These include disease aggressiveness, life expectancy, co-morbidity, functional outcomes and complications of treatment as well as the consequences of failed primary therapy. Paramount is also the patient's own choice of the best therapy for themselves based on considerations of quality of life as well as length of life (19).

Data from the literature in which the number of high-risk factors has been shown to influence outcome from radical prostatectomy have already been discussed. It is however as yet unknown if this is also the case for EBRT. Age and co-morbidity also have a major influence on the outcome of therapy. Competing risk analyses that have been published from both natural history (non-treatment) studies as well as following therapy have clearly shown that the benefits from radical treatment are mainly seen in younger men with the fewest co-morbidities (20-21). However, this will need regular review within the context of a much longer-living population in the western world and the improving general health of men.

Functional and complication outcomes between EBRT and surgery have been keenly debated over the years and there is a significant lack of comparable data from studies that have used similar outcome measures between modalities. The Prostate Cancer Outcomes Study has shed some light on this and it is clear that radical surgery and EBRT confer significant detrimental effects to urinary and sexual functions although bowel dysfunction seems to be remarkably similar between the two groups (22). This particular study which prospectively followed men over 15 years also demonstrated that after intervention there was a gradual decline in all domains over a period of time which most likely reflects the effect of age. Between the 2 modalities most studies have shown that surgery appears to have the greatest detrimental effect on urinary and sexual function. Conversely observational work by Nam *et al* from Canadaian registry data has suggested that treatment by EBRT may have an increased risk of non-urinary and erectile complications requiring

hospital admissions including rectal or anal procedures, open surgical procedures and secondary malignancies (23).

The group discussed whether treatment selective markers could be used as a method of helping patients and clinicians choose the best first radical therapy option. Biomarker research in this area is very sparse and to date there are no studies which have demonstrated that any one biomarker can help stratify patients (24). There is however emerging evidence of this being a possibility. An example is the BRCA2 mutation (about 2% of the prostate cancer population) whereby carriers of the mutation are known to have poor outcomes from EBRT and potentially may do better from surgery instead (25). Another possible approach is to consider the toxicities from different treatments. In this context, studies are currently exploring how genomic predictors (e.g. single nucleotide polymorphisms) might identify men who are most susceptible to radiation damage to normal tissue and hence be better managed by non-EBRT or reduced dose therapy methods (26). UK trials such as Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of EBRT (RAPPER) and the linking radiation dose at the VOXel level with TOXicity (VOXTOX) are currently exploring this area of study (UKCRN Trials: 1471 and 13716 respectively).

The group concluded that currently there is no level 1 evidence to suggest the benefits of one radical treatment option over another and very little research in stratified approaches to therapy. In this context the discussion centred on the patients own choice of therapy. They recognise that a patient's choice is very individual and can rely on their own experiences, the influence of family and other co-existing conditions (e.g. urinary tract symptoms) and also to a large extent on who they see in the clinics and what counselling they receive. Most attendees agreed that for the younger or fitter men with high-risk disease, surgery may be the best initial option but again this is down to a very individual decision of the consultation between the patient and the surgeon. Quality of life becomes a key factor here and going forward studies in both EBRT and surgery have to consider using standardised methods of reporting. The group agreed that patients still very much rely on clinicians for guidance and that this is unlikely to change in the near future. Discussions about salvage options, should primary therapy fail, is also a difficult area to approach when

a patient is considering first treatment. However, considering the significant morbidity from salvage treatments, it probably needs to be brought further up the agenda when discussing the treatment choices.

Despite the lack of concrete evidence, the group did feel that there might be some value in considering constructing a treatment choice algorithm. This might include the factors discussed within this topic area to help the clinician and patient make the most appropriate decision for radical treatment to manage HR-PC. All meeting participants recognised that randomised controlled trials in this area are going to be very difficult to achieve to help inform such an algorithm. One alternative option however is to consider collecting data prospectively in registration studies and to include standardised composite oncological and quality of life measures. In this regard work initiated by the International Consortium on Health Outcomes is very welcome (27). Table 2 summarises the key clinical questions highlighted by the group.

Table 2 - Summary of the key clinical uncertainties in HR-PC

1. Unmet need for better tools to risk stratify HR-PC patients to identify optimal primary treatment combinations and those who may need early therapy escalation.
2. Uncertainty on the best primary treatment combination for HR-PC and the on-going need to undertake a randomised trial in this group.
3. In the lack of prospective randomised data, how do we make equitable comparisons of the impact of different radical treatments on functional outcome and quality of life measures?

Research priorities in high-risk prostate cancer

Research in radiotherapy

Over the past decade development of new EBRT techniques such as intensity-modulated radiation therapy, 3-D conformational radiation therapy, high and low dose brachytherapy, image guided radiation therapy and proton beam therapy have made the delivery of higher doses of radiation possible with acceptable associated morbidity. Further evaluation of the role of these external techniques as well as high dose rate (HDR) brachytherapy in the management of HR-PC was identified as a key research priority. Coupled with this is the significant current research interest in the optimal dose fractionation regime and timing as well as how this is best combined with systematic therapy.

The UK has been an international lead for many recent innovations in technical radiotherapy. An example of this is the planned HEXPROP study which will be a multi-armed comparison of EBRT dose and pelvic node radiation. More recently, the radiotherapy community has been considering the role of EBRT in men with node positive and oligo-metastatic disease though studies in this area are at an early stage. The Dutch HORRAD study (Trial register.nl NTR271), which randomised men with skeletal only metastatic disease to ADT or ADT plus local EBRT is due to report in 2015 and the results will no doubt fuel further research interest on this topic. In the UK the STAMPEDE trial has already added a prostate local EBRT arm to men with metastatic disease (ClinicalTrials.gov NCT00268476). Other studies such as the recently funded CORE study (Conventional care versus radioablation for extracranial metastases) are exploring the benefits of targeted EBRT to metastatic sites in men who have progressed despite primary androgen deprivation therapy.

Radio-sensitisation using molecular targeted drugs prior to EBRT was identified as a potential way of further improving oncological responses. Radio-sensitising drugs which target apoptotic and DNA damage response pathways are due to be assessed alone or in combination in future trials. Tumour hypoxia is known to affect EBRT effectiveness and there are hypoxia modification studies; e.g. PROCON: A trial of PROstate EBRT in CONjunction with carbogen and nicotinamide (ISRCT: N08912168) being conducted in the UK to determine if reversal of hypoxia might increase the efficacy of EBRT. Radiotherapy has also been suggested to increase the efficacy of immunotherapy in animal models (28). To

date however human trials in the castrate refractory metastatic setting combining bone directed radiotherapy and immunotherapy have not so far shown clinical benefit (29).

Non-invasive imaging of the *in situ* prostate to monitor treatment response such as with Magnetic Resonance (MR) or Positron Emission Tomography (PET) was also discussed with particular emphasis on identification of treatment failure before biochemical detected relapse. In this context the use of imaging during treatment with a view to modulating or escalating doses would be of particular interest. The role and place of MR targeted biopsies and their timing in relation to EBRT to identify suspected recurrence remains unclear. The use of such biopsy data may be informative in confirming recurrence and deciding further treatment but is limited by post treatment radiation atypia that can make the diagnosis and Gleason grading of recurrent tumours very difficult (30). The group also discussed the evidence for the use of tissue biomarkers as an alternative to guide salvage treatment choices and better predict treatment response. Here the significant paucity of research in the field was acknowledged as a major limitation. Table 3 summarises the key consensus radiotherapy research questions.

Table 3 - Research priorities in radiotherapy

1. What is the best radiotherapy fractionation regimes and combinations with optimised dose delivery for the treatment of HR-PC?
2. Does pelvic nodal and prostate ERBT have better oncological and functional outcomes compared to prostate-only ERBT?
3. Can radio-sensitising drugs and/or hypoxia modification improve oncological responses to current radiotherapy regimes while reducing toxicity?
4. Can tumour molecular characteristics or functional imaging characteristics be used to help guide dose delivery/escalation and predict therapeutic response?
5. What is the role of interim or post-radical radiotherapy functional imaging and image targeted biopsies in predicting therapy response and disease recurrence?

Research in surgery

There has been a sea change in the role of surgical management of HR-PC. Robotic-assisted laparoscopic prostatectomy (RALP) has now become the most common operation for localised prostate cancer in the United States and is becoming so in the UK as well. It is also emerging as an option in the management of locally advanced and localised high-risk disease. This change in practice has happened despite the ongoing uncertainty around which available methods; open, laparoscopic or RALP is the most effective and cost-effective. Reviews of large observational studies have reported that RALP is at least comparable in efficacy to open prostatectomy with the majority of studies reporting favourable functional and oncological outcomes (31-33). However, these types of studies are inherently flawed as they are unable to control for variations in patient factors, surgical experience and caseloads, all of which can have a significant impact on the reported outcomes. The group discussed the challenges in carrying out a randomised controlled trial and questioned what other types of studies would be a reasonable alternative. The UK LOPERA trial (Laparoscopic, Open and Robot-assisted prostatectomy as treatment for organ-confined prostate cancer ISRCTN: 59410552) for instance comparing different types of radical prostatectomy failed to recruit sufficient patients. Large multi-centred collaborations with prospective and accurate databases were deemed a potential and acceptable way of assessing these techniques. However, the group recognised that the current lack of standardised reporting between centres on oncological and functional outcomes makes direct comparisons challenging.

The Royal College of Surgeons surgical trials initiative set up five surgical trial units (STU) across England to substantially increase surgical research capacity. The STUs aim to help support researchers to produce high-quality research that can benefit patients through improved clinical outcomes, better standards of care and a reduction in the regional variations in care. The units however have reported on-going problems with gaining funding, over-regulation and delays in gaining ethical approval. These UK-wide challenges must be addressed in order to ensure surgical innovation is implemented promptly and safely. The group also felt that any future surgical research should account for surgeon/centre experience as this heterogeneity has a strong influence on reported outcomes. With the

advent of high volume centres the group felt running large randomised trials may be easier with the use of more standardised technical approaches.

The role of surgery in localised and locally advanced HR-PC disease was identified as key priority areas for future research. A higher proportion of men are having surgery as part of a first step in the multi-modal management of their disease. In some patients surgery is a one-step modality with excellent oncological prognosis however most men will need a multimodal approach. A key research area is in defining clinical or biological markers to select the most appropriate HR-PC candidates for surgery with the highest likelihood of a good outcome. In addition this may also help determine the appropriate sequencing, timing and intensity of multimodal therapies. Most recently surgery has also been proposed as an option for local treatment in men with olio-metastatic disease with observational data suggesting better biochemical and survival outcomes compared to palliative treatment alone (34-35). The evidence to date however is very limited and mainly in small selected cohorts. The comparative role of EBRT or surgery in local therapy for men with metastatic disease is also unknown and needs further research. Table 4 summarises the key consensus surgery research questions.

Table 4 - Research priorities in surgery

1. How can we better share learning experiences and adopt techniques from centres reporting superior surgical oncological and functional outcomes?
2. How do we select the best patients for surgical management of HR-PC using clinical, imaging or molecular markers?
3. What is the role of local therapy in the management of oligo-metastatic disease? Should this be treated with surgery or radiotherapy or a combination of both?

Multi modal therapy

There was a broad consensus that men with HR-PC benefited most from a multi-disciplinary and multimodal approach to therapy. This included the optimal local therapy to the prostate, the best modality to treat lymph nodes and the role and timing of neo-adjuvant and adjuvant therapy. ERBT with long-term ADT has long been considered the standard of care for HR-PC over other modalities. There still remains major controversy about the appropriate duration of ADT. The majority of patients now have ADT started prior to ERBT but it is unclear how long the treatment duration should be and how this would differ in the context of different dose regimes and fractionation. The group also discussed the uncertainties around the appropriate technique and dose of EBRT and the role of prostate-only versus whole pelvic irradiation. In this context similar uncertainties exist with regards the role of extended lymph node dissections in surgery. While it is accepted that extended lymph node dissection may improve biochemical relapse rates and certainly provide good staging information, it has not yet been consistently shown to improve survival and there are no randomised trials exploring this issue (36-37). Furthermore, the place and relative benefit of extended lymph node dissections within the context of contemporary post surgical adjuvant therapy is unknown. The group noted that in this context there was an opportunity to explore complementary roles for different modalities for treatment of the prostate and lymph nodes within a trial setting.

With the emerging possibility of accurate molecular characterisation of tumours at biopsy the group discussed how this could be exploited to guide selection and use of neo-adjuvant or adjuvant therapy. There was particular interest in the possibility of prospective trials that might randomise patients to specific treatments based on an individualised understanding of molecular perturbations. Here options for targeted novel neo-adjuvant and adjuvant combinations alongside standard radical therapies should be explored. Indeed these have already begun with current studies on the NCRI CSG portfolio incorporating novel drugs and surgery (e.g. CANCAP02, NCT:02064608). The critical issue remains as to how to translate the use of molecular profiling into real time clinical practice if efficacy is shown in such trials. In the context of new agent trials, and with survival outcomes taking a long time to accrue, there is a clear need to develop and validated intermediate and/or surrogate endpoints. The

evidence for using drugs developed in the castrate refractory setting and trialled in earlier stage disease was also debated. The group noted the historical failure of these approaches to provide complete responses or to improve survival outcomes. Of note these studies have been mainly in the surgical setting and there is very little research of efficacy in EBRT treated men. One example of this is the use of neo-adjuvant docetaxel chemotherapy prior to radical prostatectomy that to date has not as yet shown survival benefit (38-40). Taxanes however are known to be radio sensitizers in the treatment of head and neck cancers and may well have therapeutic benefit in EBRT based treatment of HR-PC (41).

The group also discussed the variety of different oncological and functional outcomes used as endpoints in trials making studies harder to compare and draw firm conclusions. The group urged that future research should try and use standardised functional outcomes and also consider using oncological outcomes more suited to non-metastatic disease e.g. freedom from the need for ADT or residual disease on MRI after EBRT. Table 5 summarises the key consensus multimodal research questions.

Table 5 - Research priorities in multimodal therapy

1. What is the appropriate timing, optimal duration and type of concurrent androgen deprivation therapy in EBRT treated HR-PC?
2. What is the optimal management of lymph nodes in HR-PC? Do patients do better with surgical excision of lymph nodes or from irradiation of lymph nodes + ADT? Can the UK lead a randomised trial of lymph-node dissection versus lymph node EBRT following radical prostatectomy?
3. How can we exploit the unique molecular characteristics of tumours to help guide primary patient therapy and selection of multimodal therapy and use of neo-adjuvant or adjuvant drugs in conjunction with radical therapy?

Salvage therapy

Men with HR-PC have the highest risk of disease relapse after primary radical therapy. In post-surgical patients, salvage EBRT with or without ADT is the mainstay of management though there remains uncertainty on the optimal duration, dosage and timing of adjuvant treatment. These issues have been partly addressed by recent randomised adjuvant trials and will be further informed by the current UK RADICALS study (Randomised Controlled Trial of Radiology and Androgen deprivation in combination after local surgery) (42-45).

The issue is much more complex in radio-recurrent prostate cancer with a multitude of salvage options including radical prostatectomy, brachytherapy, cryotherapy, high-intensity focused ultrasound and other new emerging ablative technologies. To date the established modalities appear to offer similar rates of cure but also significantly high rates of functional morbidity and toxicity. There have been no randomised trials in this area and these are difficult to undertake as demonstrated by the failed CROP trial (deferred androgen deprivation therapy +/- upfront CRyOtherapy in men with localised radiation recurrent prostate cancer) (46). Nevertheless, local salvage therapy has the potential to be curative and disease control has been reported in a substantial number of selected patients. Further research is required to determine which patients should be offered local salvage therapy and whether or not the therapeutic advantage is enough to justify the associated treatment-related morbidity.

The group agreed that there was no level 1 evidence available to help guide clinician and patient decision making and the current literature is lacking on good quality data regarding treatment-associated morbidity. Indeed it is currently unknown how many men in the UK with radio-recurrent disease are offered and received salvage therapy. A further complication is the diversity of oncological outcome measures used with different salvage modalities. The timing and duration of adjuvant ADT with salvage therapy is also a key question that needs to be answered. The group agreed that a UK prospective database for all men who received salvage therapy should be developed and established. This may be the only viable alternative to a randomised controlled trial though the group recognised that other options, including cohort design trials, were also being considered (47). Table 6 summarises the key consensus salvage therapy research questions.

Table 6 - Research priorities in salvage therapy

1. How do we best identify men who would benefit most from salvage therapy following primary radical surgery or radiotherapy?
2. In the context of radio-recurrent disease how can the best salvage option be identified?
3. If a randomised trial is not feasible, can a national prospective database of men who have received salvage treatment for radio-recurrent disease be set up using standardised outcome measures for oncological, functional and toxicity outcomes?

Summary

Compared to all solid cancers, prostate cancer continues to have some of the best survival outcomes even when classified as high-risk at diagnosis. The group recognised this and the fact that outcomes in the UK from men treated radically are comparable to those from international series (48-49). However men with HR-PC continue to be at the highest risk of treatment failure and disease progression. The group therefore agreed that a critical priority was to further improve curative outcome for this group of men. Alongside this was a need to reduce the toxicity of therapy and move to a more individual method of selecting treatment for patients.

The group recognised that the UK was well placed to undertake balanced and equitable research in HR-PC and that this was best achieved using a multi-disciplinary approach involving surgeons, oncologists, pathologists, radiologists and other allied medical specialities. Indeed the UK already has nationally endorsed standards for individual case discussions within multi-disciplinary teams. Furthermore there is generally good equity of treatment options available to patients across the UK. Despite this, randomised controlled trials in all but EBRT studies have been difficult to achieve, not least, because of patient and clinician bias. In this context robust prospective recording of data in registration studies may well be able to deliver valuable outcomes particularly if this included standardised toxicity and quality of life outcome measures.

HR-PC was recognised to be a heterogeneous entity and there is a need for focused work on sub-classifying men with high-risk disease to identify those who will and will not do well from current therapies. At the moment, the inclusion of all men with high-risk disease into a

single group is untenable for future research and to achieve improvements in individual clinical outcomes. Thus better risk models need to be defined and importantly use cohorts comparable to the UK population of patients. The integration of molecular and imaging biomarkers into such optimised models may further help to refine new risk models and help clinicians and patients in therapy selection and decisions about treatment escalation.

A critical issue for both primary surgery and EBRT is how to deal with lymph node involvement as this area lacks good evidence-based clinical guidelines. New research in this field may well need to avoid the traditional separations of surgery and EBRT. One consistent research theme was whether surgery or EBRT (potentially including ADT) was the better treatment for suspected or detected lymph node disease and there is space here for a combined effort from a multi-disciplinary research team. In the same vein, neo-adjuvant and adjuvant therapy is clearly an important research theme and the group endorsed the critical need for innovative multi-disciplinary trials.

The debate on primary radical therapy in men with oligo-metastatic disease is becoming more prominent and it remains unclear what the role of radical therapy might be. A crucial issue however is to ensure that any radical therapy does not adversely impair quality of life given the fact that there is already disseminated disease and life expectancy will be reduced. In this context quality of life should as important an outcome measure of any study in this field in tandem with survival outcomes.

Finally, it was recognised that going forward it is the integration of molecular information derived at the beginning, during and after treatment that is going to define the next generation of smart treatments and improvements in outcome. This theme is being explored but perhaps but not as rapidly as necessary and the group felt that this would be an area that would be ripe for investment into research and development.

In conclusion it is hoped that the discussions and consensus from this meeting report will help the UK Prostate Cancer Research Community to focus their research in HR-PC and provide direction for charitable funders. The key thematic areas to emerge as clinical uncertainties and research priorities have been listed in the tables. It is very likely that the

next 5-10 years will bring important changes for the better in terms of HR-PC outcomes and allow clinicians to provide their patients with the holy grail of individualised optimal therapy choice with the most durable chance of cure and minimal morbidity.

References

1.http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer

2. Greenberg DC, Wright KA, Lophathanon A, et al. Changing presentation of prostate cancer in a UK population--10 year trends in prostate cancer risk profiles in the East of England. Br J Cancer. 2013 Oct 15;109(8):2115-20.

3. Joniau S, Briganti A, Gontero P, et al. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol. 2015;67(1):157-64.

4. Warde P, Mason M, Ding K, et al. NCIC CTG PR.3/MRC UKPR07 investigators. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011Dec 17;378(9809):2104-11.

5. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet. 2009;373(9660):301-8.

6. Dearnaley DP, Sydes MR, Graham JD et al. RT01 collaborators. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2007 Jun;8(6):475-87.

7. Dasu A, Toma-Dasu I. Prostate alpha/beta revisited -- an analysis of clinical results from 14 168 patients. Acta Oncol. 2012 Nov;51(8):963-74.

8. S. Williams, I.D. Davis, C. Sweeney, M.R. Stockler, et al. Randomised phase 3 trial of Enzalutamide in androgen deprivation therapy with radiation therapy for high risk, clinically localised, prostate cancer: Enzarad (Anzup 1303) Ann Oncol (2014) 25 (suppl 4): iv278-iv279

9. Lepinoy A, Cochet A, Cueff A, et al. Pattern of occult nodal relapse diagnosed with (18)F-fluoro-choline PET/CT in prostate cancer patients with biochemical failure after prostate-only radiotherapy. Radiother Oncol. 2014;111(1):120-5.

10. Dearnaley D, Griffin C, Harris V, et al. First toxicity results of a phase II randomised trial of prostate and pelvis versus prostate alone radiotherapy. *Radiother Oncol 111(Suppl 1):31 #OC-0155*

11. Dorff TB, Glode LM. Current role of neoadjuvant and adjuvant systemic therapy for high-risk localized prostate cancer. Curr Opin Urol. 2013;23(4):366-71.

12. Polkinghorn WR, Parker JS, Lee MX, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov. 2013;3(11):1245-53.

13. Goodwin JF, Schiewer MJ, Dean JL, et al. A hormone-DNA repair circuit governs the response to genotoxic insult. Cancer Discov. 2013;3(11):1254-71.

14. Gerber GS, Thisted RA, Chodak GW, et al. Results of radical prostatectomy in men with locally advanced prostate cancer: multi-institutional pooled analysis. Eur Urol. 1997;32(4):385-90.

15. Gnanapragasam VJ, Mason MD, Shaw GL, Neal DE. The role of surgery in high-risk localised prostate cancer. BJU Int. 2012;109(5):648-58.

16. Sooriakumaran P, Nyberg T, Akre O, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. BMJ. 2014;348:g1502.

17. Gnanapragasam VJ, Persad R, Payne HA. Radiotherapy and surgery for high-risk localized prostate cancer: a UK questionnaire survey of urologists and clinical oncologists. BJU Int. 2012 Sep;110(5):608-12.

18. Surcel CI, Sooriakumaran P, Briganti A, et al. Preferences in the management of high-risk prostate cancer among urologists in Europe: results of a web-based survey. BJU Int. 2015;115(4):571-9.

19. Gnanapragasam VJ, Payne H, Syndikus I, Kynaston H, Johnstone T. Primary radical therapy selection in high-risk non-metastatic prostate cancer. Clin Oncol 2015 Mar;27(3):136-44.

20. Briganti A, Spahn M, Joniau S, et al. European Multicenter Prostate Cancer Clinical and Translational Research Group (EMPaCT). Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. Eur Urol. 2013 Apr;63(4):693-701.

21. Rider JR, Sandin F, Andrén O, et al. Long-termoutcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. Eur Urol. 2013 Jan;63(1):88-96

22. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368(5):436-45.

23. Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. Lancet Oncol. 2014;15(2):223-31.

24. Kachroo N, Gnanapragasam VJ. The role of treatment modality on the utility of predictive tissue biomarkers in clinical prostate cancer: a systematic review. J Cancer Res Clin Oncol. 2013 Jan;139(1):1-24.

25. Elena Castro, David Olmos, Chee Leng Goh, et al. EMBRACE and UKGPCS Collaborators (2013) Effect of germ-line *BRCA* mutations in biochemical relapse and survival after treatment for localized prostate cancer. J Clin Oncol 31, (suppl 6; abstr 29)

26. Kerns SL, Ostrer H, Rosenstein BS. Radiogenomics: using genetics to identify cancer patients at risk for development of adverse effects following radiotherapy. Cancer Discov. 2014;4(2):155-65.

27. Martin NE, Massey L, Stowell C, et al. Defining a standard set of patient-centered outcomes for men with localized prostate cancer. Eur Urol. 2015;67(3):460-7.

28. Ward-Kavanagh LK, Zhu J, Cooper TK, et al. Whole-body irradiation increases the magnitude and persistence of adoptively transferred T cells associated with tumor regression in a mouse model of prostate cancer. Cancer Immunol Res. 2014 Aug;2(8):777-88.

29. Kwon ED, Drake CG, Scher HI, et al. CA184-043 Investigators. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014 Jun;15(7):700-12.

30. Crook J, Malone S, Perry G, et al. Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. Int J Radiat Oncol Biol Phys. 2000;48(2):355-67.

31. Novara G, Ficarra V, Rosen RC, et al. Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol. 2012;62(3):431-52.

32. Ficarra V, Novara G, Artibani W, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol. 2009;55(5):1037-63.

33. Tewari A, Sooriakumaran P, Bloch DA, et al. Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. Eur Urol. 2012;62(1):1-15.

34. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol. 2014 Jun;65(6):1058-66.

35. Ghadjar P, Briganti A, De Visschere PJ, et al. The oncologic role of local treatment in primary metastatic prostate cancer. World J Urol. 2015 Jun;33(6):755-61.

36. DiMarco DS, Zincke H, Sebo TJ, et al. The extent of lymphadenectomy for pTXNO prostate cancer does not affect prostate cancer outcome in the prostate specific antigen era. J Urol. 2005 Apr;173(4):1121-5.

37. Gao L, Yang L, Lv X, et al. A systematic review and meta-analysis of comparative studies on the efficacy of extended pelvic lymph node dissection in patients with clinically localized prostatic carcinoma. J Cancer Res Clin Oncol. 2014 Feb;140(2):243-56.

38. Thalgott M, Horn T, Heck MM, et al. Long-term results of a phase II study with neoadjuvant docetaxel chemotherapy and complete androgen blockade in locally advanced and high-risk prostate cancer. J Hematol Oncol. 2014 Mar 5;7:20.

39. Chi KN, Chin JL, Winquist E, et al. Multicenter phase II study of combined neoadjuvant docetaxel and hormone therapy before radical prostatectomy for patients with high risk localized prostate cancer. J Urol. 2008 Aug;180(2):565-70;

40. Sfoungaristos S, Kourmpetis V, Fokaefs E, et al. Neoadjuvant Chemotherapy prior to Radical Prostatectomy for Patients with High-Risk Prostate Cancer: A Systematic Review. Chemother Res Pract. 2013;2013:386809.

41. Blanchard P, Bourhis J, Lacas B, et al ; Meta-Analysis of Chemotherapy in Head and Neck Cancer, Induction Project, Collaborative Group.

Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. J Clin Oncol. 2013 Aug 10;31(23):2854-60.

42. Bolla M, van Poppel H, Collette L, et al. Postoperativeradiotherapy after radical prostatectomy: a randomized controlled trial (EORTC trial 22911). Lancet 2005;366(9485):572e578.

43. Wiegel BD, Steiner U, Siegmann A, et al. Phase III postoperativeadjuvant radiotherapy after radical prostatectomy comparedwith radical prostatectomy alone in pT3 prostate cancer withpostoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;20(27):2924e3011.

44. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapyfor pathological T3N0M0 prostate cancer significantlyreduces risk of metastases and improves survival:long-term followup of a randomized clinical trial. J Urol 2009;181(3):956e962.

45. Parker C, Clarke N, Logue J, et al ; RADICALSTrial Management Group. RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery). Clin Oncol (R Coll Radiol). 2007 Apr;19(3):167-71.

46. Salji M, Jones R, Paul J, et al. Cryotherapy in Prostate Cancer (CROP) study team. Feasibility study of a randomised controlled trial to compare (deferred) androgen deprivation therapy and cryotherapy in men with localised radiation-recurrent prostate cancer. Br J Cancer. 2014 Jul 29;111(3):424-9.

47. Ahmed HU, Berge V, Bottomley D, et al. Prostate Cancer RCT Consensus Group. Can we deliver randomized trials of focal therapy in prostate cancer? Nat Rev Clin Oncol. 2014 Aug;11(8):482-91.

48. Sachdeva A, van der Meulen JH, Emberton M et al. Evaluating variation in use of definitive therapy and risk-adjusted prostate cancer mortality in England and the USA. BMJ Open. 2015 Feb 24;5(2):e006805.

49. Greenberg DC, Lophatananon A, Wright KA, et al. Trends and outcome from radical therapy for primary non-metastatic prostate cancer in a UK population. PLoS One. 2015 Mar 5;10(3):e0119494.