

NCRI Prostate Clinical Studies Group

Introduction

The Prostate Clinical Studies Group completed the final year of its 3 year cycle in 2009. During this time the Group has continued to build on an established and strong portfolio, consolidating in the area of recruitment to ongoing trials, initiating new studies and at the same time, investigating new areas for study, both in relation to established treatments and to new modalities for diagnosis and therapy. It is hoped that these latter areas will result in the initiation of new protocols and collaborations addressing the spectrum of prostate cancer trials and treatment in the future. The CSG subgroups have discussed a number of proposals, producing new outline protocols for funding submission and considering collaborative studies in areas of specific interest, particularly in early localised and advanced prostate cancer, imaging/diagnosis and the use of androgen deprivation therapy and in hormone refractory disease. The Group have also participated actively in the development and initiation of collaborative studies with other international trial groups and with industry, where new phase 2 studies using “pipeline” drugs have been proposed and where initiation of trials has been undertaken using a fast track approach.

The Group’s work was reviewed successfully by an international review panel in April 2009. The strengths of the Group and issues it needs to address are summarised in Appendix 1.

Membership and structure

The membership has continued the previous ethos of combining a well balanced mix of surgical and non-surgical specialists from a wide geographical area. This formula has worked effectively in previous terms and valuable contributions have been made both at the committee meetings, within the subgroups and via e mail / teleconferences at various stages of trial consultation and development. The input of the MRC Clinical trials unit and other trial groups such as the Birmingham and Institute of Cancer Research trial groups has been critical to many of the studies.

The importance of subspecialty expertise has been recognised clearly and to this end, input from Uro-radiology, Statistics and Epidemiology has been included within the Group. Specialist pathology has been more problematic: the previous incumbent had been a poor attender and there had been no applicants to fill this shortfall. This problem was dealt with by approaching Dr Dan Berney, Consultant Pathologist, who has been closely involved with the Royal College of Pathologists and with other NCRI Urology CSGs. With his help, individuals were identified and a dedicated Uro-pathologist was appointed to the Group. Mr Vincent Gnanapragasam joined the Group in the reporting year and Professor David Dearnaley, Mr Robert Mills, Dr John Logue and Professor Richard Martin have stepped down from the Group.

The working parties initiated in the 1st year of the current CSG cycle have continued to mature. Three of the four, Castrate Resistant Prostate Cancer Working Group, Dr Steve Harland (Chair), High Risk Localised Working Group, Mr David Gillatt (Chair), Imaging Working Party, Professor David Dearnaley (Chair), have been successful in holding meetings / discussion to develop new proposals. It is recognized that the fourth working party Early Diagnosis/staging Working Group, Dr Chris Parker (Chair) will need to be re-structured.

Portfolio and accrual

There are a number of studies specifically developed by or adopted by the prostate CSG which are either recruiting actively or in advanced stages of development. A summary of studies in the portfolio can be found in Table 1.

The Familial Prostate Cancer (PI Dr R Eeles) continues to make excellent progress both nationally and internationally. A further large scale genetic study, the BiPAS study (PI Prof M Seegers), centred in Birmingham has now also begun. This trial has recruited 11 % of its target population and continues to recruit well.

The ProtecT study (PI's Prof F Hamdy, Prof D Neal, Prof J Donovan) continues to make good progress nationally and further major funding has been received for the long term follow up aspect of this trial beyond 2010 in the 9 recruiting centres.

Stampede (Multi Arm Therapy in high risk hormone naïve patients: PI Prof N James) has been highly successful. The trial has recruited well to complete the first phase of its study and it is well in to its second phase, having recruited close to 600 patients to date. There has been a significant expansion of the number of recruiting UK centres in the last year. International collaborative partners are still being sought as this will augment recruitment. Negotiations with the European Association of Urology trials office and with other major European trials organisations are continuing. There is also a good expectation that a number of individual centres in Europe will join this collaboration. Supplementary to the main trial, a full TRICC application to study translational elements of the patient study population has been obtained, broadening the scope and importance of this study. Editorial reports are in press in 2 major Urology / cancer journals highlighting the progress to date and at a recent presentation of the STAMPEDE updated recruitment and results at the European Association of Urology (the worlds largest Urology meeting), the STAMPEDE results were reported in the meeting highlights as one of the best papers at the congress.

The CHHIP trial of IMRT and hypo-fractionation in localised CaP (PI Prof D Dearnaley) has been highly successful in recruiting large numbers of patients (>900, target of 2163) through 15 UK centres. This pattern of accrual is well placed to continue over the next year. This important trial will yield valuable information about efficacy and toxicity of high dose short fractionation regimens for localised prostate which will inform practice in the future.

The PATCH study of oestrogen patches for hormone manipulation (PI Mr P Abel) aims to recruit 200 patients. 91 patients have now been recruited from 17 centres and although the rate of recruitment has been slower than anticipated but it is, nonetheless, progressive. Operational issues relating to the patch oestrogen dose have been addressed and an intermediate review of the hormone suppression data (undertaken in part to counter issues raised in an adverse article in the Urological literature) show reassuring evidence that the patches suppress testosterone levels in the vast majority of patients effectively.

The SABRE trial of decision aids in brachytherapy (PI Dr D Bottomley) is funded and has now passed its basic regulatory hurdles. A trial management committee has been established and will guide the study through its MREC process and get the study underway. There have been operational delays at the Southampton trials unit but these have now been resolved and the TMG are actively developing this study with the PI, identifying recruiting centres.

The RADICALS study of radiotherapy \pm short and long term hormones post radical surgery (PI Dr C Parker) opened to recruitment in the 3rd quarter of 2007 as a collaborative study with NCI Canada. A joint TMG meets monthly to coordinate the initiation process and continue the trial development in its first years. It is expected that this study will recruit well in an area where there is considerable uncertainty regarding the optimal form of treatment.

Two surveillance studies are in progress, both coordinated by Dr Chris Parker as PI. The prospective study of Active Surveillance has now recruited 411 patients and publications from this series are currently helping to guide international practice in this area of prostate cancer management. The START study of active surveillance vs treatment in low risk CaP (PI Dr C Parker) has been developed as an international collaboration between NCI Canada, US trial Groups and the UK NCRI. This study was approved by CTAAC for funding as a pilot and the protocol has been approved by CTEP. The study opened in 2008 and is beginning to recruit.

The TRAPEZE study of combination therapy with Docetaxel, Zoledronic Acid and Strontium in men with progressive HRPc (PI Prof N James) has continued steadily. It has now recruited >600 of its target 1240 patients. Collaborations to augment the recruitment of this study may be considered in 2008.

The HEMI-HIFU Trial, (PI M Emberton), is a phase I/ II study recruiting through a single centre (UCL). The study has been extensively reviewed by the CSG and it continues to recruit well in a limited target population. Initial results were presented at the UK BAUS Conference in 2008 showing the trial to be well structured and supervised. Recruitment is now closed.

The MAPS (Men After Prostate Surgery) study completed recruitment in 2008. A successful recruitment drive in 2007 was instrumental in boosting the recruitment numbers for this trial, which will yield important information about the role of post operative physiotherapy in minimising incontinence related problems in men undergoing prostatic surgery for benign and malignant conditions.

DA (Dex+Aspirin) vs DA + Stilboestrol (PI J Shamash). This trial has been a slow recruiter but it continued to accrue and has now virtually reached its target. An extension has been approved to recruit a further small "completion" cohort. This was required because of a protocol violation in some of the patients, necessitating their withdrawal.

Industry Collaborations

There are 2 industry trials currently in the portfolio and these are likely to be supplemented by further trial proposals in 2008 / 2009.

VENICE Study: This collaboration with Sanofi / Aventis is now recruiting in 8 UK sites, evaluating the effects of VEGF-TRAP in advance prostate cancer

Onyvax (PI Prof H Pandha) is recruiting successfully through the Guildford centre.

Table 1: Prostate CSG portfolio

Acronym	Title	PI(s)	Status
Active Surveillance	A study of active surveillance for early prostate cancer	Dr Christopher Parker	Open
BiPAS	The Birmingham prostatic neoplasms association study - A genetic and environmental case control study on prostate cancer in Birmingham	Professor Maurice Zeegers	Open
CHHIP	Conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer	Professor Dr David Emma Dearnaley Hall	Open

FOCAL - HIFU	An evaluation of focal ablation therapy using high-intensity focused ultrasound in the treatment of localized adenocarcinoma of the prostate	Mr Mark Emberton	Open
IMPACT	Identification of men with a genetic predisposition to prostate cancer: targeted screening in BRCA1/2 mutation carriers and controls - IMPACT	Dr Ros Eeles	Open
Matched pair QoL/Toxicity Study in Advanced Prostate Cancer	Matched pair study to assess the quality of life and toxicity in patients with carcinoma of the prostate undergoing external beam radiotherapy plus high dose rate brachytherapy boost compared with patients receiving conformal external beam radiotherapy alone	Dr Anna Lydon	Open
NCRN018 - INDUSTRY STUDY	A multicenter, randomized, double-blind study comparing the efficacy and safety of aflibercept versus placebo administered every 3 weeks in patients treated with docetaxel / prednisone for metastatic androgen-independent prostate cancer	Dr Matthew Cooper	Open
NCRN049	A multicenter, randomized, double-blind, phase 3 study of sunitinib plus prednisone versus prednisone in patients with progressive metastatic hormone-refractory prostate cancer after failure of a docetaxel-based chemotherapy regimen	Professor Hardev Pandha	Open
PATCH	Prostate adenocarcinoma: transCutaneous hormones. A randomised-controlled trial of transcutaneous oestrogen patches versus LHRH analogues in prostate cancer.	Mr Paul Abel	Open
Pelvic IMRT for prostate cancer	A phase 1 dose escalation study of the use of intensity modulated radiotherapy (IMRT) to treat the prostate and pelvic nodes in patients with prostate cancer	Professor David Dearnaley	Open
PRECIOUS	Improving the assessment and recording of cancer treatment effects	Dr Susan Davidson	Open
ProMPT	Molecular mechanisms of disease progression and the development of novel treatment strategies in advanced prostate cancer (Northern Prostate Cancer Collaborative (ProMPT))	Professor David E Neal	Open
ProSTART	A phase III study of active surveillance therapy against radical treatment in patients diagnosed with favourable risk prostate cancer (START)	Dr Christopher Parker	Open
RADICALS (MRC PR10)	Radiotherapy and androgen deprivation in combination after local surgery	Dr Christopher Parker	Open

RAPPER	Radiogenomics: assessment of polymorphisms for predicting the effects of radiotherapy	Dr Catharine West	Open
RIB	A multicentre randomised trial of single dose radiotherapy compared to Ibandronate for localised metastatic bone pain	Professor Peter Hoskin	Open
SABRE 1	Surgery and brachytherapy - A randomised evaluation randomised controlled trial of brachytherapy versus radical prostatectomy in good risk prostate cancer: a feasibility study	Dr David Bottomley	Open
Stampede	Systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy	Professor Nicholas James	Open
TRAPEZE	A randomised phase II/III trial of docetaxel plus prednisolone vs. docetaxel plus prednisolone plus zoledronic acid vs. docetaxel plus prednisolone plus strontium-89 vs. docetaxel plus prednisolone plus zoledronic acid plus strontium-89 in hormone refractory prostate cancer metastatic to bone.	Professor Nicholas James	Open
UK Genetic Prostate Cancer Study -	UK genetic prostate cancer study	Dr Ros Eeles	Open

3516 patients were recruited to Prostate studies in 2008-09 representing 10.7% of disease incidence. 5.1% (1677 patients) were to RCTs and 5.6% (1839 patients) to non-RCTs.

Trials in development

The Group has a number of trials in development, including:

- Multi-modality treatment in high risk prostate cancer
- Intervention treatment of radiation failure
- Early targeting high risk bone mets
- Various therapies for CRPC
- Axial MRI imaging for high risk localised CaP
- Timing of hormone manipulation

Meetings

The Prostate CSG ran a highly successful joint Urological Trials Meeting in January 2009 with the Bladder, Renal and Testis CSGs. Another joint meeting is planned for January 2010. The Group has made presentations at International meetings such as the British Association of Urology, EORTC GU group, the European Association of Urology and GU ASCO.

Collaborations

The CSG members have continued to work closely with important National groups such as the British Uro-Oncology Group (BUG) and the British Association of Urological Surgeons (BAUS), particularly through its section of Oncology Chairman, and with International groups such as those in Canada, Switzerland and the EORTC.

The Group has strengthened its links with other Urological CSGs through the joint trials meeting.

The Chairman and 2 other members of the committee are members of the DoH Advisory Group for prostate cancer and a further member (Dr Graham) is Chair of the NICE Review process for prostate cancer. There are good links with the MRC and Birmingham Clinical Trials Units and links with the Bristol Unit for high risk prostate cancer and the Manchester Clinical Trials Unit for the study of axial MR scanning. The Group has close links with industry in the development of chemotherapy related trials, such as the Stampede study and has been a successful contributor to the AZ NCRN collaboration.

3 year strategy

The strategy for the Group is to:

- Facilitate succession by appointment of a new Chair
- Maintain the current momentum for trial development and recruitment amongst the membership of the CSG committee and in the wider Uro-oncology community
- Develop international collaboration for continued trial recruitment (Stampede, radicals) and initiation of new trials (Axial MR, timing and duration of ADT, novel therapies for HRPC).
- Address key areas in prostate management including:
 - Improving diagnosis and imaging related to staging and treatment decision making
 - Develop studies to measure outcomes of novel interventions such as lap prostatectomy, novel radiotherapy and salvage therapies after treatment failure.
 - Identify bio-potential and development of surveillance strategies
 - Develop better combination treatments for high risk localized disease
 - Continue studies in advanced disease utilising combinations of new agents with or without established therapies either as UK National studies or in combination with partner trial groups. Where possible this will be as a joint protocols developed with other major trial groups and/or pharma. Where this is not possible there should be an aim to develop unified datasets, facilitating later meta-analysis of pooled results.

Priorities for next year

The appointment of a new Chair will take place following advertisement and competitive interview in August 2009.

Trial protocols for MR imaging, combination surgery/radiotherapy/Hormonal approaches, Salvage therapies and novel Phase 2 agents will be developed and submitted for funding in 2009.

Collaborative work to adopt and recruit the ELAAT study with the NCIC will begin in 2009.

Professor Noel Clarke, Chair

Appendix 1

Key strengths and issues form the Progress Review, April 2009

Prostate

The key strengths of the Group identified at the April 2009 review were:

- Leadership of the Group and bringing together a disparate group of clinicians into a coherent group
- Inclusive membership in terms of specialism, age and geography
- Enthusiastic and productive CSG which work well together
- Setting up Working Parties which are clearly work well
- Awareness of what is not going well and taking steps to address the issues
- Respected consumers who have been welcomed into the Group and empowered who participate actively and productively in the Group's work
- A group which has matured and is doing a good job
- A good portfolio of studies addressing early disease
- The roadshows held to showcase trials and stimulate recruitment

The Panel identified the following issues which the Prostate CSG needs to consider:

- Enhancing research into late stage disease without impacting negatively on what it is currently doing well
- How best to harness the science through possibly establishing a Translational Subgroup or Working Party, working closely with the ECMCs or holding open meetings
- Appointing further members with basic science expertise
- Appointing paramedics to the Group (nurse research network manager)
- How the patients voice can be used to increase recruitment
- Developing a minimum dataset
- Increasing the number of industry studies in the portfolio by using ITAC

The NCRN/I need to:

- Take up the issue of all CSGs explicitly and routinely considering whether a trial idea will impact on clinical practice

Appendix 2

2008/09 Publications and abstracts

Riches, V. A. Morgan, S. A. Sohaib, D. P N. J. Van As, N. M. de Souza, S. F. Dearnaley, C. C. Parker. A study of diffusion weighted magnetic resonance imaging in men with untreated localized prostate cancer on active surveillance. *Eur Urol* (epub ahead of print)

Ng MK, Van As N, Thomas K, Woode-Amisshah R, Horwich A, Huddart R, Khoo V, Thompson A, Dearnaley D and Parker C. Prostate-specific antigen (PSA) kinetics in untreated, localized prostate cancer: PSA velocity vs PSA doubling time. *BJU Int.* [epub ahead of print]

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Parker C, Sydes M. Adjuvant Radiotherapy After Surgery for Prostate Cancer. *JAMA* 2008; 300(18):2119-211a.

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