The Cytoreductive prostatectomy in Metastatic Prostate Cancer: What the individual trials are hoping to answer

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Conflicts of interest: None

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BJU.15055](https://doi.org/10.1111/BJU.15055)

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Article type : Review

Abstract

Objective:

To review the ongoing randomized trials of cytoreductive prostatectomy (CRP) in de novo hormone sensitive metastatic prostate cancer (HSPC) in order to identify their goals and assess their strengths and weaknesses.

Methods:

Pubmed, Medline and clinical trials websites searches were performed in order to identify currently ongoing trials of CRP in de novo HSPC.

Results:

Nine randomized clinical trials in CRP were identified and included: SWOG 1802, SIMCAP, IP2-ATLANTA, TROMBONE, g-RAMPP, LOMP II, FUSCC-OMPCa and the Testing Radical Prostatectomy in Chinese Men with Prostate Cancer and oligoMetastases to the Bone study.

Each study was different; assessing various primary outcome measures including overall survival, progression free survival and feasibility to randomize between standard therapy and CRP or between radiation therapy and CRP in the metastatic setting. In the oligometastatic setting, the trials assess OS, feasibility to randomize and time to castration. Similarly a number

of secondary endpoints ranging from cancer specific outcomes to quality of life outcomes are being investigated.

The inclusion criteria in these trials also varied in terms of volume of metastatic disease (oligo-metastatic to high volume metastatic disease), diagnosis of metastases (imaging based vs biopsy proven), imaging modalities used (conventional to newer modalities) as well as outcomes and follow-up regimes.

Conclusion

While there are differences in each protocol, each trial aims to address different aspects of CRP in de novo HSPC. Therefore the specific goals of each study and the limitations have to be taken into consideration when interpreting the results of these trials.

Introduction

Metastases are detectable at first presentation in approximately 15% of men in unscreened Western populations (1). Traditionally, systemic therapy with androgen deprivation therapy (ADT) $\pm$ chemo or second-line hormone therapy was used, but the reported outcomes in men who present with metastatic prostate cancer (mCaP) have not improved over the last two decades (2-6). As such, attention has been focused on multi-modal therapy, where addition of treatment of the primary tumor to novel systemic therapy as a means to improve the outcomes compared to systemic therapy alone.

There are a number of potential benefits of treating the primary tumour such as reduction in tumour seeding by metastasis-to-metastasis spread (7) by both metastatic and primary tumor clones (8), potentially allowing for intermittent systemic therapies with reduced exposure to side effects of systemic agents (9), and also the potential for improving local symptoms (10). In addition to supportive in vitro and in vivo data (11, 12), other cancers such as ovarian (13) and colorectal cancer (14) have shown benefit with cytoreductive therapy. The combination of radiotherapy and ADT treats the primary tumor along with micrometastatic disease, reducing the overall tumor burden (15). Although radiotherapy combined with ADT did not demonstrate

any survival benefit with in men with prostate cancer with primary bone metastases in the the HORRAD study (16), more recently, the sub-group analysis of STAMPEDE Arm-H demonstrated a survival benefit from treatment of the primary tumour in low volume mCaP with the addition of prostate radiotherapy (17).

The evidence for cytoreductive prostatectomy (CRP) in mCaP is currently based on large population database studies demonstrating an associated survival benefit (18-23), with some studies showing superiority of CRP compared to radiation (18, 21). Although radiotherapy avoids the morbidity associated with surgery, the main benefits of CRP compared to radiotherapy are the removal of the primary tumor source, reduction in the local tumor complications (24) and possibly the delayed the need for ADT, reducing its associated side effects. However, there are significant biases in these CRP studies including the retrospective nature, inherent selection bias of population based data and also the lack of data regarding systemic treatments influencing these results. Given that the safety of CRP has been validated in a number of studies (25-27), a number of prospective clinical trials are now underway to investigate the role of CRP in mCaP.

We aim to identify the questions these newer trials are attempting to answer and the differences among these current accruing studies.

Evidence acquisition and synthesis

A literature review was performed using Pubmed, Medline and trials clinicaltrials.org websites to identify currently ongoing or recently closed randomized trials of CRP in de novo hormone sensitive metastatic prostate cancer. The keywords ‘metastatic’, ‘oligometastatic’, ‘prostate cancer’, ‘surgery’, ‘cytoreductive’, and ‘prostatectomy’ were used and filtered for randomized clinical trials.. Only trials investigating newly diagnosed metastatic hormone sensitive prostate cancer patients were selected. Only studies which investigated atleast M1 disease or greater and a minimum sample size of 50 were included to ensure identification of large homogeneous

randomized trials. Nine randomized clinical trials in cytoreductive prostatectomy were finally identified and included.

On identification of the individual trials, the clinical trials.org website was further queried for individual aspects of the different trials including: trial design, number of patients, inclusion criteria, trial end points, imaging modality used, volume of metastases, outcomes, current status, estimated completion date and follow up times and regime. Further information on these trials were obtained from published abstracts and personal communication (if the required information was not available).

The Trials

There are currently nine trials investigating the effectiveness of CRP in mCaP (Table 1). Following on from the phase II trial NCT01751438(28), the SWOG 1802 trial (NCT03678025) is a phase III randomized trial comparing Standard Systemic Therapy (SST) to SST plus definitive treatment (Surgery or Radiation) of the primary tumour in mCaP. Metastasis directed therapy is allowed for up to four sites as long as it is completed prior to randomization. This trial has a primary endpoint of overall survival and several secondary endpoints. It is aiming to enroll 1273 participants (29).

The SIMCAP trial (Surgery in Metastatic Carcinoma of Prostate) (NCT03456843) is a phase 2.5 multi-institution international randomized prospective clinical trial evaluating if the addition of CRP (if possible, with extended pelvic lymphadenectomy) to the best systemic therapy (BST) has an impact on oncologic and quality of life outcomes in men with newly diagnosed mCaP (30). For the initial phase 2 portion of this study, the primary endpoint is failure-free survival (FFS). If FFS shows at least 30% improvement in the CRP + BST arm at two years after randomization, the study will be triggered to a phase 3 study and the overall survival will become the new primary endpoint. The CRP arm involves ADT for at least one month prior to either Robotic Assisted Radical Prostatectomy (RARP) or open Retropubic Radical Prostatectomy (RRP) followed by BST. Assuming that phase 3 expansion occurs, the overall maximum target accrual is 860 men.

IP2 – ATLANTA trial (ISRCTN58401737) is a three-arm unblinded randomised controlled trial using systemic therapy alone as standard of care and compared with either Minimally Invasive Ablative Therapy (MIAT) +/- pelvic lymph node dissection [PLND] (intervention arm 1) or Local Radiotherapy +/- Lymph Nodes OR Radical Prostatectomy +/- PLND (intervention arm 2)(31). This aims to recruit 80 men in the pilot phase followed by a phase 2 expansion of the study if set endpoints are reached. In the MIAT arm, the treatment modalities include cryotherapy or high intensity focused ultrasound, HIFU and in intervention arm 2, the decision between radiotherapy or radical prostatectomy is based on physician and patient preference and patient co-morbidities. In randomized patients, metastasis directed therapy is allowed to be used at the time of randomization or if recurrence or new treatments during the trial but concomitant radiotherapy to the primary tumor is not allowed with MIAT or as adjuvant therapy in the prostatectomy arm, apart for palliative reasons.

The Testing Radical prostatectomy in men with prostate cancer and oligometastases to the bone trial, TROMBONE (ISRCTN15704862), is a randomized trial of 50 men with locally resectable oligometastatic CaP (one to three skeletal lesions; no visceral lesions) assessing the feasibility of randomization to the standard care vs standard care plus radical prostatectomy with extended pelvic lymphadenectomy(32). This trial has completed recruitment and awaiting publication.

The Impact of Radical Prostatectomy as Primary Treatment in Patients With Prostate Cancer With Limited Bone Metastases (g-RAMPP) trial (NCT02454543) was a randomized controlled trial of 452 men assessing the cancer specific survival with the combination of CRP with BST versus BST alone in the oligometastatic setting (33). They included men with up to five bony metastases as well as N1 disease. As a result of STAMPEDE Arm-H showing a benefit for local therapy in oligo-metastatic patients (17), this trial has closed to accrual.

After demonstrating the safety of CRP in the phase I LOMP trial, the LOMP II trial investigates the feasibility of CRP compared to cytoreductive prostate irradiation as local treatment option for mCaP as assessed by the randomized proportion at 48 months(34). This study is a direct comparison of the feasibility to randomize between CRP and radiation therapy

in mCaP. The choice of CRP (open, laparoscopic or robot-assisted) at the discretion of the operating surgeon.

The Androgen Deprivation Therapy or Androgen Deprivation Therapy Plus Definitive Treatment (Radiation or Surgery) (FUSCC-OMPCa study) (NCT02742675) is a Phase 2 randomized controlled trial in the oligometastatic setting, which investigates the overall survival in 200 men randomized to androgen deprivation (ADT) or ADT + definitive therapy (CRP or radiotherapy)(35).

The Testing Radical Prostatectomy in Chinese Men with Prostate Cancer and oligoMetastases to the Bone (NCT03988686) is the second randomized trial being conducted in the oligometastatic setting by the Fudan University in China, where 120 men will be randomized to CRP + standard care or standard care alone. The primary end point in this study is time to castrate resistance(36).

The Definition of metastatic disease

Volume of metastases

‘Oligometastatic disease’ is defined as solitary or few detectable metastatic lesions (typically defined as less than five metastases) but several definitions exist (37). As better survival rates are demonstrated with “oligometastatic” compared with “polymetastatic” disease (38, 39), it is important to accurately differentiate between these conditions in mCaP.

Most of the CRP trials do not define the volume of metastases. SWOG 1802, ATLANTA and LOMP II trials include any T staging with any volume of nodal, skeletal or visceral distant metastases, while the SIMCAP trial defines the population as clinical T1-3M1a-b. As such, these studies do not aim to address outcomes of CRP purely in the oligometastatic setting.

However, the non-stringent criteria in these studies allow for the ease of recruitment and assessment of the overall effects of CRP in mCaP. Given that the survival benefit from treatment of the primary tumor with radiotherapy in the sub-group analysis of STAMPEDE Arm-H was seen in low volume mCaP (17), these studies will likely also need to assess outcomes in the subgroup of low volume disease. As many studies were designed or finished accrual prior to the STAMPEDE Arm-H results were released and considering the small number of patients in these

studies, it may yet be difficult to convincingly answer if there is a benefit of CRP in low volume disease in some of the trials (40).

TROMBONE is currently one of four studies investigating the role of CRP in oligometastatic CaP only. They defined the oligometastatic disease as one to three skeletal metastases and do not include men with visceral metastases. Any burden of lymph nodal disease is included. In contrast, the other oligometastatic studies, g-RAMPP includes men up to five skeletal metastases while upto three skeletal metastases are allowed in the Testing Radical Prostatectomy in Chinese Men with Prostate Cancer and oligoMetastases to the Bone trial, the FUSCC-OMPCa study includes upto five nodal or skeletal metastases. Three of these studies which have finished recruitment (TROMBONE recruited ahead of target, g-RAMPP terminated early as a result of the STAMPEDE Arm-H results and the FUSCC-OMPCa trial) and the active Testing Radical Prostatectomy in Chinese Men With Prostate Cancer and oligoMetastases to the Bone trials will allow better assessment of the role of treatment of the primary in the oligometastatic CaP setting.

Identification of metastases

Conventional imaging modalities of CT (computed tomography) and bone scan are gradually being supplemented and possibly superseded by newer imaging modalities such as MRI, Choline PET (positron emission tomography) CT, Prostate Specific Membrane Antigen PET/CT (PSMA PET/CT) and Axumin PET/CT (fluciclovine). With adoption of newer imaging modalities, it is likely that more low volume metastatic disease is detected and thus upstaging some clinical M0 disease currently defined using traditional standard imaging with bone/CT scanning to “metastatic” disease. To standardize measures in studies, it is important to define the imaging modality used, as significant variations in detection rates of metastases will occur with a substantial “Will Rogers” effect.

SWOG 1802 and FUSCC-OMPCa define metastases detected on conventional imaging or magnetic resonance imaging (MRI). While SWOG 1802 allows for metastases detected on positron emission tomography (PET) scans which are not detected on conventional imaging, these require histological or cytological confirmation. Similarly, SIMCAP requires evidence of distant lymph node or bone metastasis by magnetic resonance imaging (MRI)/computed tomography (CT), bone scan, or biopsy (N1Mx or NxM1). The ATLANTA, TROMBONE and g-RAMPP protocols allow for conventional imaging or PET imaging. While g-RAMPP allows

for MRI as well as an option, a prostate MRI is mandatory in the ATLANTA protocol and all men in TROMBONE had a preoperative prostate MRI. Further, SIMCAP and ATLANTA are accruing a separate subset of patients to assess the validity of PSMA PET scans as a pilot subgroup analysis. LOMP 2 on the other hand requires metastases detected on standard imaging by CT and bone scan.

The accurate determination of the metastatic volume currently is challenging. PET scans have higher detection rates of metastases, with PSMA PET scans having a sensitivity of 80% but with false positive rates of up to 14% (41). Therefore, in order to overcome the false positives, the SWOG and SIMCAP studies have opted to biopsy these lesions. While, most of the studies attempt to integrate PET imaging in to their study protocols in order to characterize the metastatic burden more accurately, all patients are not required to have PET scans in any of these studies owing to a number of factors. PET scans are currently not the standard of care, not readily available worldwide, and different countries utilize different tracers with different protocols. Therefore, these studies will also need to take the imaging modality into account in order to accurately determine the metastatic volume or have a predetermined subgroup such as in the ATLANTA trial in order to avoid a heterogeneous definition of metastases. Further, multicenter studies involving different countries will need to ensure standardization of these factors.

The standard of care definition and the timing of integration of CRP to systemic therapy

Until recently the standard of care of mCaP has been ADT. More recently, the use of combined chemotherapy with docetaxel and newer androgen directed therapies such as abiraterone and enzalutamide are increasingly becoming accepted as standard of care. All of these current trials investigate the effects of cytoreductive prostatectomy against the “standard of care”, acknowledging that the BST or SST is likely to change over time. Yet, such flexible design may result in significant confounders. Studies involving multiple institutions in different countries may have different standard of practices owing to availability of medications, regulations and clinicians’ preference. Thus, the SST or BST definition should be uniform between the sites. The SWOG trial defines the “standard of care” as per the current National Comprehensive Cancer Network (NCCN) guidelines for metastatic prostate cancer. This involves ADT, ADT with concomitant abiraterone, or ADT plus docetaxel therapy for 6 cycles. This may also change

as newer studies alter the SOC, which makes the trial adaptable over time. S1802 accounts for the variability in systemic therapies by stratifying by the receipt of chemotherapy, in addition to several other stratification factors. Similarly, SIMCAP trial allows both docetaxel and abiraterone as part of the BST regimen. Potential impact of these new agents has been minimized by stratifying patients on the use of docetaxel and abiraterone. The TROMBONE and g-RAMPP trials allowed for all treatments including chemotherapy as determined appropriate by the treating urologists/ oncologists. Interestingly, since STAMPEDE Arm-H has reported, most of the UK has accepted that local therapy to the primary with radiotherapy is the new standard care for oligo-metastatic patients. Despite this, ATLANTA only has best systemic therapy as its standard care, and does not differentiate standard care options based on metastatic burden. It is also the only trial that is testing focal ablation techniques in the experimental arm, despite the data from CRP studies like TROMBONE and g-RAMPP showing men with oligo-metastatic disease do not typically have focal lesions in their primary. In contrast, the oligometastatic trial FUSCC-OMPCa investigates ADT as the systemic treatment while the other study from Fudan University, Testing Radical Prostatectomy in Chinese Men With Prostate Cancer and oligoMetastases to the Bone uses ADT or other systemic therapy with CRP.

An important factor to consider when comparing these studies is the timing of integration of CRP to systemic therapy. The SWOG trial allows for 22 to 28 weeks of SST, followed by randomization to local treatment. CRP takes place within 8 weeks after randomization or patients may receive radiation therapy within 4 weeks of randomization. The LOMP 2 and ATLANTA trials allows for up to 3 months of ADT prior to treatment, while in the SIMCAP trial the participants need to receive ADT for at least one month prior to CRP followed by BST. The g-RAMPP requires patients to be within a period of 6 months from diagnosis to randomization and 3 months from randomization to surgery. TROMBONE requires a period of within 12 months from randomization to surgery to allow men to complete and recover from their docetaxel therapy.

Interpreting the outcomes of different studies

The primary endpoints of these studies also differ. The primary aim in the SWOG trial is to assess any overall survival (OS) benefit from treatment of the primary tumour over a follow-up

period of 8 years. In addition, the secondary outcome measures involve assessing difference in OS in a subset who specify the surgical intent stratification factor, rate of symptomatic local progression, progression-free survival (PFS), death due to any cause and comparison of subsets of patients with and without metastasis directed therapy (MDT) to oligometastatic sites. However, this trial will not be able to directly determine if CRP will be superior to radiotherapy, as both modalities are offered in the treatment arm and subject to selection biases.

In contrast, the SIMCAP and ATLANTA trials assess the direct outcomes of CRP against SOC measures. The SIMCAP trial assesses the rate of FFS at two years after randomization with the initial target accrual of 190 men. OS will become the primary endpoint and target accrual increased to 860 patients if FFS demonstrates at least 30% improvement at two years. Safety and quality of life are secondary objectives while genomics is the major correlative study. The pilot phase of the ATLANTA trial aims to assess the feasibility of randomization between the SST vs SST + CRP + ePLND, the safety of intervention and the proportion of patients with complete pathological response as defined by prostate biopsies at 6-9 months post SOC systemic therapy. The phase two of this study assesses progression free survival (PFS) based on PSA and imaging. The secondary outcomes of quality of life, disease progression and cost effectiveness will be measured at baseline, week 12, 26, 34 then every 12 weeks for first year and every 24 weeks for remaining years two to four.

The LOMP 2 trial aims to assess the feasibility of randomization between CRP and radiation therapy in mCaP with a follow up of 48 months, thus directly comparing the outcomes of these modalities against each other. Its secondary outcome measure is castration-resistant free survival. Thus, this trial will allow direct comparison between CRP and radiotherapy in the metastatic setting.

The TROMBONE trial assesses the feasibility to randomize between standard care vs standard care plus radical prostatectomy with extended pelvic lymphadenectomy measured at three months in the oligometastatic setting. The secondary endpoints measure quality of life and time to castrate resistance at six weeks, three months and six months then ongoing as routine NHS follow-up care schedules.

The g-RAMPP study assesses the cancer specific survival as the primary outcome, time to castrate resistance, PFS, OS and QOL as their secondary outcomes. They aimed to follow up

patients for up to 5 years. However, in light of the STAMPEDE trial results, this trial has prematurely closed.

The FUSCC-OMPCa trial assesses OS as the primary outcome with time to PSA progression and QOL as secondary outcomes in the oligometastatic setting with treatment of either CRP or radiotherapy with ADT. As such, similar to the SWOG study, they will not be able to demonstrate the superiority of definitive treatment over the other.

The Testing Radical Prostatectomy in Chinese Men With Prostate Cancer and oligoMetastases to the Bone trial assesses the time to castrate resistance as the primary outcome and QOL as the secondary outcome after CRP with standard of care.

These landmark studies aim to provide answers to some important questions in the role of treating the primary with CRP in mCaP. However, the aims of these studies are very specific and the differences between individual studies should be understood to avoid confusion. While the clinical data will provide an outcome measure that will set the standard of practice, there is also a substantial opportunity to develop biobanks with tissue, blood and urine for future translational work. This can provide an opportunity to define the biologic context wherein CRP may provide benefits to individual patients. Dichotomization between high and low volume disease and treatment allocation is a simplistic approach that likely enriches for specific tumor biology, but volume cut-offs alone do not accurately define the biology of the disease. There is an urgent need for clinico-genomic identifiers to better select patients for specific systemic and local therapies. In this regard, a number of trials including SWOG, SIMCAP and TROMBONE are collecting patient specimens for such analyses. While there is much interest in exploring the cytoreductive approach, it is important to consider the potential implications of these treatments and in the absence of a standard approach this should only be completed in a clinical trial.

And finally, it is also important to look beyond the role of primary-directed therapy and to test the use of metastasis-directed therapy. The STAMPEDE group have successfully received funding to open a new arm in their multi-arm multi-stage trial, to randomize men with oligo-metastatic prostate cancer to standard care (BST plus primary-directed therapy) versus standard care plus metastasis-directed therapy using stereotactic body radiotherapy. Surgery as well as radiotherapy are planned to be allowed as forms of therapy to the primary, but focal ablatives techniques will not be included. Standard care imaging with bone scans and CT will be used to

define eligibility (5 or fewer targetable lymph nodes +/- skeletal lesions), and a comparative sub-study on men who receive novel PET imaging at sites where the technology is available will also be undertaken.

In conclusion, the two pertinent questions that remain will be answered by a combination of the studies aforementioned: (1) does CRP also work as primary therapy for (oligo) metastatic prostate cancer? and (2) does treatment of the metastases themselves work in combination with best systemic and primary-directed therapies for these men?

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Table 1: Overview of the Randomized Controlled Trials assessing the utility of Cytoreductive prostatectomy in metastatic prostate cancer.

RCT: Randomized controlled trial; SST: Standard systemic therapy; CT scan: Computed tomography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; OS: Overall Survival; mCaP: metastatic prostate cancer; CRP: Cytoreductive prostatectomy; BST: Best Standard treatment; PLND: Pelvic lymph node dissection; PFS: Progression free survival; PSA: Prostate Specific Antigen; QOL: Quality of life;

Trial	Type of study	Comparison	Number of participants (n)	Inclusion criteria	Imaging Modality	Volume of metastases	Outcomes	Status	Estimated completion date	Follow up
Best Systemic Therapy or Best Systemic	Phase 2 RCT	BST vs BST + CRP or	180	Histologically proven mCaP with	Bone scan, CT and/or MRI.	Any	Progression free survival	Closed	February	Initially 60 days, then

Therapy (BST) Plus Definitive Treatment (Radiation or Surgery) NCT01751438(2 8)		radiotherap y to primary tumor		castrate sensitive M1 disease with <6 months of starting BST. ECOG PS 0 or 1					20 20	follow up upto 10 years.
SWOG 1802 trial (NCT03678025) (29)	Phase 3 RCT	SST vs SST + definitive treatment (Surgery or Radiation) of the primary tumour	1273	Histologica lly proven mCaP. < 28 weeks of SST per NCCN guidelines.	CT/Bone scan or MRI. PET Scans allowed but require biopsy confirmatio n for PET only positives	Any, but without progression in first 22-28 weeks	Primary: OS Secondary : Difference in OS in a subset who specify the surgical intent stratificatio n factor,	Op en	Oc tob er 20 31	Measures at baseline at 6 months, 1, 2, and 3 years) up to 8 years

							rate of symptomatic local progression, PFS, death due to any cause and comparison of subsets of patients with and without metastasis directed therapy (MDT) to oligometastatic sites.			
SIMCAP trial	Phase 2.5	BST vs.	190/860	Histological	MRI/CT/Bo	T1-3M1a-b.	Primary:	Op	Se	2 -4 years

(NCT03456843) (30)	RCT	CRP + BST		lly proven CaP Clinical ≤T3 with M1a or M1b disease with no prior local therapy. ECOG ≤1 and fit for surgery	ne scan or biopsy. Additional subset to verify PSMA PET	No visceral disease	Failure- free survival at 2 yrs after randomizat ion for phase 2; if triggered to phase 3, OS. Secondary : Complicati on rates, QOL,	en	pte mb er 20 22	(phase 2); 7-10 years if phase 3 expansio n triggered
IP2 – ATLANTA trial (ISRCTN584017 37) (31)	Pilot three-arm unblinde d randomis	SST Vs Minimally Invasive Ablative	Pilot phase: 80 with total of 918	Histologica lly proven hormone sensitive mCaP.	CT/Bone scan or PET scan PLUS MRI prostate.	Any	Pilot phase: To assess the feasibility	Op en	Au gu st 20 18	Measures at baseline, week 12, 26, 34

ed controlle d trial	Therapy (MIAT) (Cryotherap y or HIFU) +/- PLND (interventio n arm 1) Vs. Local Radiothera py +/- Lymph Nodes OR Radical Prostatecto my +/- PLND (interventio n arm 2)		<3months of starting ADT. ECOG 0-2.	Additional subset to verify PSMA PET		of randomizat ion between the SST vs SST + CRP + ePLND. Safety of interventio n Proportion of patients with complete pathologic al response Phase 2: PFS. Secondary :			then every 12 weeks for first year and every 24 weeks for remainin g years 2 to 4.
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							QOL, disease progression (PSA and imaging) and cost effectiveness			
TROMBONE (ISRCTN15704862)(32)	RCT feasibility study	SST vs SST + CRP + ePLND	50	Histologically proven CaP with stage M1b (one to three skeletal metastases) . age < 75. ECOG PS 0–1. Locally resectable	CT/Bone scan or PET scan	Oligometastatic disease. M1b (1-3 skeletal metastases)	Primary: Feasibility to randomize between SST vs SST + CRP + ePLND within 12 months. Secondary :	Cl	Au	Measures at baseline then 6 weeks, 3 months, 6 months, and then ongoing as routine NHS follow-up care

				disease			QOL and time to castrate resistance			schedules
g-RAMPP (NCT02454543) (33)	RCT	CRP + BST Vs. BST	452	Histologically proven mCaP stage N0/1 and M1b (1-5 bone metastases) ECOG 0-1	CT, Bone scan, MRI or PET	Oligometastatic disease. M1b (1-5 skeletal metastases)	Primary: Cancer specific survival Secondary: Development of castrate resistance, PFS, OS QOL	Cl ose d	Cl ose d ear ly du e to ST A M PE DE res ult s	5 years
LOMP II	Phase 2	CRP	86	Histologica	CT or bone	Any	Primary:	Op	Au	48

(NCT03655886) (34)	RCT Feasibility study	Vs. cytoreductive prostate irradiation		lly proven mCaP. ECOG 0-1 (2 if related to local PC symptoms)	scan only		Feasibility of randomization between CRP and radiation therapy in mCaP at 48 months Secondary : castration-resistant free survival.	en	gu st 20 22	months
Androgen Deprivation Therapy or Androgen Deprivation	Phase 2 RCT	Androgen deprivation therapy (ADT) Vs	200	Histologically proven mCaP. ECOG 0-1	Bone scan, CT and/or MRI	≤5 nodal or boney metastases	Primary: PFS Secondary :	closed	March 20 20	3 years

Therapy Plus Definitive Treatment (Radiation or Surgery) FUSCC-OMPCa study (NCT02742675) (35)		ADT + definitive therapy (surgery (prostatecto my or radiotherap y)					OS Time of PSA progressio n QOL			
Testing Radical Prostatectomy in Chinese Men With Prostate Cancer and oligoMetastases to the Bone (NCT03988686) (36)	Open labelled RCT	CRP + Standard care Vs Standard care	120	Oligo- metastatic prostate cancer (1-3 skeletal lesions based on bone specific imaging. No visceral metastases.	Not defined	1-3 skeletal metastases.	Primary: Time to castrate resistance Secondary : QOL	Oe pn	Ma rch 31, 20 21	Not defined

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Title:

The cytoreductive prostatectomy in metastatic prostate cancer: what the individual trials are hoping to answer

Date:

2020-04-07

Citation:

Ranasinghe, W., Chapin, B. F., Kim, I. Y., Sooriakumaran, P. & Lawrentschuk, N. (2020). The cytoreductive prostatectomy in metastatic prostate cancer: what the individual trials are hoping to answer. *BJU INTERNATIONAL*, 125 (6), pp.792-800. <https://doi.org/10.1111/bju.15055>.

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