Sooriakumaran, P. et al. (2022) Feasibility and safety of radical prostatectomy for oligo-metastatic prostate cancer: the Testing Radical prostatectomy in men with prostate cancer and oligo-Metastases to the bone (TRoMbone) trial. BJU International, 130(1), pp. 43-53.

https://eprints.gla.ac.uk/289774/

Feasibility and safety of radical prostatectomy for oligo-metastatic prostate cancer: TRoMbone trial

Journal:	*BJU International*
Manuscript ID	BJU-2021-1244.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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Keywords:	
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The main outcome measures were: ability to randomise participants, optimised by a QRI. EQ-5D-5L questionnaires to capture quality-of-life (QOL) data at baseline and three months post-randomisation; routine clinico-pathological assessment to capture adverse events and prostate-specific antigen in both arms, plus standard peri-operative parameters in the surgical arm.

Results

51 men were randomised within 14 months (one was subsequently deemed ineligible), with 60-83% accrual rate in centres that recruited at least two participants. All participants completed the trial follow-up; one participant in the intervention arm subsequently did not undergo the surgical intervention and one in the SOC arm refused all therapies. The QRI positively impacted recruitment. QOL data showed similarly high functioning in both study arms. Surgery for men with oligo-metastatic prostate cancer was found to be safe and had similar impact on early functional outcomes as surgery for standard indication.

Discussion

It is feasible to randomise men with synchronous oligo-metastatic prostate cancer to a surgical intervention in addition to standard systemic therapies. While surgery appeared safe with no substantial impact on QOL in this feasibility study, a large randomised controlled trial is now warranted to examine treatment effectiveness of this additional component in the multi-modality management of oligo-metastatic prostate cancer.

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BJU International – Manuscript Information

Article word count: 3989
Number of characters in article title: CUST_TITLE_CHARACTER_COUNT :No data available.
Number of words in abstract: 285
Tables: 3
Figures: 2

"Clinical Trial" questions
Is this a clinical trial? - Yes
If yes, trial registration details are: International Standard Randomised Controlled Trial Number (ISRCTN) 15704862

Funding information: Prostate Cancer Foundation, (Grant / Award Number:)
Urology Foundation, (Grant / Award Number:)

Tick here to confirm that you have included a full Disclosure of Interest statement in your submission: Checked

Is this article for the USANZ supplement? No
Is this article for the Trainees' Corner section? No

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Feasibility and safety of radical prostatectomy for oligo-metastatic prostate cancer: TRoMbone trial

(_T_esting _R_adical pr_o_statectomy in men with prostate cancer and oligo-_M_etastases to the _bone_)

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Declaration of interests:

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Abstract

Objectives

To test feasibility of randomisation to radical prostatectomy plus pelvic lymphadenectomy (RP) in addition to standard-of-care (SOC) systemic therapy in men with newly diagnosed oligo-metastatic prostate cancer.

Patients and methods

A prospective, randomised, non-blinded, feasibility clinical trial with an embedded QuinteT Recruitment Intervention (QRI) to optimise recruitment was conducted in nine tertiary-care nationwide centres undertaking high-volume robotic surgery. We aimed to randomise 50 men with synchronous oligo-metastatic prostate cancer within an 18-month recruitment period to SOC systemic therapy versus SOC plus RP (intervention arm).

The main outcome measures were: ability to randomise participants, optimised by a QRI. EQ-5D-5L questionnaires to capture quality-of-life (QOL) data at baseline and three months post-randomisation; routine clinico-pathological assessment to capture adverse events and prostate-specific antigen in both arms, plus standard peri-operative parameters in the surgical arm.

Results

51 men were randomised within 14 months (one was subsequently deemed ineligible), with 60-83% accrual rate in centres that recruited at least two participants. All participants completed the trial follow-up; one participant in the intervention arm subsequently did not undergo the surgical intervention and one in the SOC arm refused all therapies. The QRI positively impacted recruitment. QOL data showed similarly high functioning in both study arms. Surgery for men with oligo-metastatic prostate cancer was found to be safe and had similar impact on early functional outcomes as surgery for standard indication.

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It is feasible to randomise men with synchronous oligo-metastatic prostate cancer to a surgical intervention in addition to standard systemic therapies. While surgery appeared safe with no substantial impact on QOL in this feasibility study, a large randomised controlled trial is now warranted to examine treatment effectiveness of this additional component in the multi-modality management of oligo-metastatic prostate cancer.

Word count 285

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Prostate cancer; oligo-metastatic; radical prostatectomy; robot-assisted; surgery

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Introduction

Prostate cancer is the most common cancer and the second most frequent cause of cancer death in Western men.(1) Patients presenting with metastatic disease have a median survival of 42.1 months,(2) and until recently, the standard-of-care has been initial androgen deprivation therapy (ADT) alone. Contemporary data from the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial demonstrate a survival benefit for supplementing ADT with docetaxel chemotherapy for men presenting with metastatic prostate cancer.(3) Evidence from other tumour types as well as prostate cancer supports the concept of a transitory phenotype between localised/locally advanced cancer and widely disseminated disease, otherwise called the 'oligo-metastatic' state.(4) There is continuing controversy as to whether chemotherapy should be given in men presenting with oligo-metastatic prostate cancer where the disease burden is less than widespread metastases. The AJCC TNM staging system of prostate cancer categorises all skeletal-metastatic patients as M1b,(5) and there are no official statistics of numbers presenting with newly-diagnosed oligo-metastatic disease. There is also a lack of international consensus on the definition of oligo-metastatic prostate cancer; nonetheless, 1-3 skeletal metastases without any visceral metastases is a widely-utilised definition.(6)

The 'seed and soil' hypothesis postulates that a receptive micro-environment ('soil') allows dissemination of malignant cells ('seed') to form metastases, with soil development driven by factors secreted by the primary tumour.(7) Primary tumours can seed to distant sites which can further seed the primary lesion, leading to a vicious cycle of metastasis;(8) this 'self-seeding' phenomenon is dependent on the presence of an intact primary cancer focus.(9) Furthermore, disseminated tumour cells in men with clinically localised prostate cancer before prostatectomy confer a five-fold increased risk of future metastasis, but these same cells detected after surgery do not increase such risk.(10-12) Collectively, these biological data suggest that an intact primary lesion drives metastatic progression beyond early spread of circulating tumour cells. Further, population-based data of men with likely metastatic or micro-metastatic prostate cancer showed that those who underwent initial systemic therapy without radical therapy were approximately three-fold more likely to die of prostate cancer than those that had radical therapy.(13) The STAMPEDE randomised trial investigated the role of local therapy using prostate radiotherapy rather than surgery due to safety concerns, in men presenting with metastatic prostate cancer. A sub-group analysis demonstrated a relative survival advantage of 32% at 3 years for men with oligo-metastatic disease who underwent radical radiotherapy in addition to systemic therapy. However, no survival benefit was seen in those with a high burden of metastases in the total cohort.(14) Although the sub-group analysis fulfils nine out of ten criteria for credibility of sub-group analyses,(15) it has not yet been widely adopted internationally to include prostate radiotherapy as standard-of-care for men with oligo-metastatic disease. This is partly because another similar trial, HORRAD, has not shown a benefit for local radiotherapy in men with metastatic prostate cancer, including those with lower metastatic burden.(16) Hence, the role of local therapy with radiotherapy remains controversial in the presence of oligo-metastatic disease, with conclusive evidence that it has no benefit in those with high metastatic loads.

Surgical removal of the prostate (radical prostatectomy) is an equivalent alternative to radiotherapy in men with organ-confined disease,(17) and hence represents another potential local radical therapy in the multi-modality approach to oligo-metastatic disease. There are a number of uncontrolled observational series investigating peri-operative outcomes of radical prostatectomy in men with metastatic disease, but these are limited by retrospective data collection as well as confounding indications in which only highly select men undergo surgery with poorly-defined eligibility criteria. (18, 19) Hence, there remains an urgent unmet need for randomised trials specifically examining the role of surgery in oligo-metastatic prostate cancer. However, lack of surgical experience in operating on oligo-metastatic disease mandate the need for stringent safety assessments in any such trial. Also, randomisation to surgical trials is fraught with difficulty and a number of high-profile prostate cancer trials have failed to recruit. Hence, most UK funders will not support a full surgical trial without a feasibility study confirming ability to randomise and safety of any novel intervention. One major success in recruitment terms was the Prostate Testing for Cancer and Treatment (ProtecT) study which employed a QuinteT Recruitment Intervention (QRI) that has been subsequently shown to improve recruitment in a further 13 challenging RCTs, including the recent PART prostate cancer feasibility trial.(20-23) We therefore integrated a QRI as well as robust safety assessments within this randomised controlled feasibility trial of surgery plus standard-of-care (SOC) systemic therapy versus SOC alone in men with newly-diagnosed oligo-metastatic prostate cancer (1-3 skeletal metastases from prostate cancer, no visceral metastases); the TRoMbone trial.

Our aims were: 1] to test the feasibility of recruiting and randomising men in the UK to a trial investigating radical prostatectomy (RP) in oligo-metastatic prostate cancer, with a view to launching a major trial; 2] to understand recruitment challenges and inform optimal recruitment strategies for a main trial through the QRI; and, 3] to collect quality-of-life and early oncological/safety/functional outcomes in these men.

Subjects/patients and methods

Trial design

The TRoMbone study was a prospective, randomised, controlled feasibility trial: *population*- men aged less than 75 years presenting with newly-diagnosed oligo-metastatic, locally-resectable prostate cancer and Eastern Co-operative Group performance status (ECOG PS) 0-1; *intervention*- radical prostatectomy (RP) plus standard-of-care (SOC); *comparator*- SOC, currently ADT+/-docetaxel chemotherapy; *outcome*- 50 participants recruited over 18 months after an initial three-month set-up period. Randomisation was stratified by site and allocation set in parallel on a 1:1 ratio. The randomisations were blocked within site using variable block sizes of two and four. The study was not blinded. Given that this is a feasibility study, no quantitative analysis was planned and descriptive statistics were used to inform a future possible full trial.

The study opened to recruitment initially in three centres. In QRI Phase 1, recruitment barriers were investigated in the initial three-month period through analysis of monthly screening log data and data collected through semi-structured

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interviews with surgeons, oncologists, research and specialist nurses, and audio-recorded recruitment appointments. Findings were presented and discussed with the Chief Investigator (CI) and Trial Management Group (TMG), and a plan of actions was agreed to optimise recruitment in Phase 2, including changes to the eligibility criteria, opening new centres, and feedback and 'tips' to support recruiters.

Subjects

Inclusion criteria at the start of the trial were: participant willing and able to give informed consent for participation in the study; male aged 18-74 years; diagnosed with oligo-metastatic prostate cancer (defined as 1-3 skeletal lesions on bone imaging, no visceral metastases); locally-resectable tumour (clinical/radiological stage T1-T3; ECOG PS 0-1; suitable for radical prostatectomy (RP) within three months of starting SOC. As a result of the Phase 1 QRI results (see below), the final eligibility criterion was changed to extend the maximum time from start of SOC to RP from three to 12 months. Exclusion criteria did not change during the trial and were: participants with contra-indications to RP; visceral metastases; prior radiotherapy to the abdomen/pelvis or to skeletal metastases; current involvement in other interventional research.

Three UK cancer centres were initially opened to recruitment. As a result of the Phase 1 QRI results, this was expanded to nine UK cancer centres selected based on geographical diversity. Potential participants were identified as part of routine clinical care, either from individual surgical/oncology clinics or via cancer multi-disciplinary team (MDT) meetings. Those found to have oligo-metastatic prostate cancer on staging investigations were screened for trial eligibility. Staging investigations included bone scintigram, MRI, CT, and PET depending on local practice, with some patients undergoing multiple staging tests. Recruiting sites chose the type of staging imaging they performed based on their standard clinical practice so the trial outcomes would be generalisable across the UK. Oligo-metastatic sites were not confirmed with biopsy, as this is invasive and not standard practice in the UK.

Eligible patients were approached by a specialist nurse, oncologist, or surgeon, and received a Patient Information Leaflet (PIL). Patients were given sufficient time to make a decision on whether they wanted to join the trial, and if so, were invited to give written consent. Consenting patients became subjects and completed baseline assessments (demographics, medical history, concomitant medication, vital signs, and routine bloods), and were then randomised by the Registration/Randomisation and Management of Product (RRAMP) software on the OpenClinica online platform of the Oxford Clinical Trials Research Unit (OCTRU): https://www.ndorms.ox.ac.uk/octru. Post-treatment allocation follow-up was as per routine clinical care for both groups, with patient-reported quality-of-life (QOL) collected from the EQ-5D-5L descriptive and visual analogue scale questionnaires before randomisation and 3-month post-randomisation visits. For the surgical participants, standard peri-operative and outcomes data including safety/complications/functional outcomes were also recorded until six months post-surgery.

Interventions

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All participants received SOC systemic therapy-ADT+/-docetaxel. Expected adverse effects of systemic therapy (e.g. reduced or absent libido, impotence, hot flashes) were recorded. Participants in the intervention arm underwent robot-assisted radical prostatectomy plus pelvic lymphadenectomy consistent with international guidelines for high-risk prostate cancer.(24) Excised nodal packets included obturator, external iliac, internal iliac, common iliac, and fossa of Marcille. Standard pre-operative (e.g. Gleason score, PSA, clinical stage), intra-operative (e.g. operative time, need for blood transfusion), and post-operative (e.g. Clavien-Dindo grade,(25) 21 individual complications)(26) parameters were recorded until six months post-operatively. The timing of surgery in the intervention arm was initially within three months of starting SOC but then amended via Protocol Amendment to within 12 months of starting SOC, as a result of the Phase 1 QRI results (as stated above).

Outcomes

The intervention arm in this feasibility trial received radical prostatectomy. The procedure is well established in the treatment of localised and locally-advanced prostate cancer, but here we investigated its use in oligo-metastatic disease.

The primary outcome of the feasibility study of randomisation was to recruit and randomise 50 participants, 18 months after the opening of the first site, optimised by a QRI. Secondary outcomes were quality-of-life assessment at baseline and three months post-randomisation (using EQ-5D-5L), and peri-operative outcomes including operative data (type of surgery, operative time, console time, need for blood transfusion, outcome of the procedure, return to theatre, length of hospital stay, successful catheter removal, peri-operative complications by Clavien-Dindo grade and assessment of 21 pre-specified complications), early oncological data (positive surgical margins (PSM), length of PSM, final pathological stage, lymph nodes removed, lymph nodes positive, 3-month and 6-month post-operative PSA), and early functional data (1-month, 3-month, and 6-month post-operative erectile function and continence recovery).

Sample size

A sample size of 50 participants was chosen as a result of a preliminary scoping exercise across 14 UK prostate cancer centres suggesting an average of two eligible patients per month per site for the trial. We thus estimated that 50 participants were a realistic target given we intended to open three sites with a total recruitment period of 18 months (assuming roughly one-half of eligible patients would accept randomisation, predicted from QRI results from other surgical trials).

No interim analyses were planned but a Trial Management Group (TMG) monitored safety data and had the ability to stop the trial early if the intervention was deemed unsafe. Reporting of adverse events followed standard Oxford Clinical Trials Research Unit (OCTRU) procedures.

Randomisation and masking

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Randomisation was performed using the web-based secure randomisation system provided by OCTRU. Participants were randomised on a 1:1 basis and stratified by site with block sizes of two and four. There was no blinding in the trial, and clinicians and participants were fully aware of the treatment allocation. Research/specialist nurses and surgeons at the sites were responsible for enrolling participants, and followed the web-based system with regards assigning participants to study arms.

Analytical methods

All randomised participants were included. No participant withdrew consent prior to treatment allocation. Outcomes data were summarised across the two randomised groups (Tables 1-3).

A QuinteT Recruitment Intervention (QRI) was used to understand the recruitment process and how it operates in all TRoMbone recruiting centres, so that sources of recruitment difficulties could be identified and suggestions made to improve recruitment(21). QRI findings and suggested changes were fed-back to the Chief Investigator (CI), site Principal Investigators (PI), and trial research staff. The QRI was conducted in two phases:

Phase 1- understanding recruitment: to understand the recruitment process as it occurred, and to identify and investigate sources of recruitment difficulty. Site screening logs were collected to provide data about eligibility assessment, and recruitment processes using the SEAR framework,(27) which identifies points at which patients continue or drop out of the trial. In-depth, semi-structured interviews were conducted and audio-recorded with: (i) members of the TMG, including the CI and those closely involved in trial co-ordination; (ii) clinical and recruitment staff across the three initial sites; (iii) subjects eligible for recruitment, including those who accepted or rejected randomisation; (iv) subjects after treatment allocation or receipt to discuss perceptions regarding their treatment and care while on the trial. The QRI researcher also attended investigator meetings between the CI, TMG, and clinical investigators, to gather further information about specific recruitment issues encountered. Recruiting staff audio-recorded appointments with potential subjects, such that the QRI researcher could provide feedback to recruiters in Phase 2 to optimise their recruitment technique. Study documentation (PILs and consent forms) were also reviewed and compared with the interviews and recorded appointments, to identify any disparities or improvements that could be made. All audio-recorded transcripts and notes were analysed thematically by the QRI researcher, using constant comparison and case-study approaches including targeted conversation analysis.(28)

Phase 2- feedback to CI/TMG and plan of action: after three months, the QRI researcher (CW) presented anonymised findings to the CI and TMG, identifying factors that appeared to be hindering recruitment. A plan of action was then formulated by the QRI team, CI, and TMG, in order to improve recruitment. The impact of this plan of action was evaluated by assessing the numbers of eligible patients, percentages of those approached about the trial, and numbers that consented to be randomised and accepted or rejected the treatment allocation, both before and after the first three-month period, and at regular intervals after

implementation. Ongoing interviews with recruiters also provided qualitative information about the acceptability of the plan of action and its impact.

Trial registration

International Standard Randomised Controlled Trial Number (ISRCTN) 15704862.

Results

Feasibility of randomisation and Quintet Recruitment Intervention

71/176 (40.3%) screened patients were eligible; 51/71 (71.8%) were randomised (Figure 1). Low recruitment rates were significantly improved with the QRI plan of action implemented in Phase 2 after three months (Figure 2). Phase 1 of the QRI identified the commonest causes of non-recruitment: inability to identify eligible patients; lack of clinician equipoise; and, inability to receive docetaxel chemotherapy pre-operatively.

During Phase 1, 12 potentially eligible patients were screened at MDT, of whom ten were deemed eligible. Screening data demonstrated lower than expected eligible patient numbers, most often due to systemic treatment more than three months prior to enrolment as a result of oncologists' strong preference for men with oligo-metastatic prostate cancer to be offered docetaxel chemotherapy within twelve weeks of starting ADT. Given that the chemotherapy course is six cycles administered three weeks apart, it was not possible for participants to undergo surgery within three months of starting ADT if they were to be given chemotherapy pre-operatively. As clinical practice changed from the period when the trial was set up to increasing usage of chemotherapy, this became an early barrier to recruitment. Hence, the plan of action stated that a further six geographically-diverse centres should be opened to recruitment and subject eligibility should be widened to those suitable for radical prostatectomy within 12 months of starting ADT, to allow for docetaxel chemotherapy before surgery in the intervention arm. It also became apparent that eligible patients were not being referred from outside the normal catchment areas, so it was suggested that the trial be publicised in urological and oncological forums, press outlets, and patient groups.

31 in-depth interviews were conducted with 13 surgeons, eight oncologists, and ten research/specialist nurses. 32 subjects had their consultations recorded with 11 recruiters (seven surgeons, two oncologists, and two research nurses) at five centres. 15 randomised subjects from six centres were also interviewed; eight were allocated SOC and seven intervention. 6/7 subjects in the intervention arm were interviewed after surgery. Most interviews and appointment recordings during Phase 1 demonstrated a lack of clinician equipoise. Hence, the plan of action included individual recruiter feedback to optimise recruitment consultations and share recruitment tips with all sites. Recruitment tips and feedback were individualised and, as in prior studies(21, 22), follow-up interviews with recruiters found them helpful in explaining randomisation and uncertainty, as well as fully informing patients about the potential consequences of study participation. From the outset, clinician equipoise was delicately balanced between the long-term hope of potential survival

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benefits and the more immediate known side-effects of surgery, but surgeons found it difficult to express this to patients. They became more confident about expressing equipoise as concerns about the risks and side-effects of surgery were alleviated by successful surgeries, feedback from men keen to join the study, and the growing numbers of randomisations.

From the screening logs and recruiter interviews it also became apparent that many eligible patients present to oncologists rather than urologists. Hence, individual site-specific strategies were employed, including direct booking of surgical appointments by oncologists, joint surgeon-oncologist consultations, use of nurse specialists to co-ordinate patient pathways, and pre-recruitment remote consultations for patients that would otherwise have to travel significant distances. These changes resulted in improved communication between surgeons and oncologists, with joint decision-making regarding optimal timing of chemotherapy and surgery after starting ADT for individual patients.

As a result of the plan of action implemented in Phase 2 of the study, the TRoMBone trial recruited to completion, demonstrating feasibility of randomisation. Although the recruitment rate for the TRoMBone study ranged from 60-83 percent in centres which randomised more than one patient, three centres did not recruit. These centres were open for a shorter time (median three months) compared to the six recruiting centres (median nine months) and did not manage to re-configure their pathways to implement the plan of action devised from the QRI.

Safety and early outcomes

The baseline characteristics of the subjects are shown in Table 1. 36/50 (72%) subjects had Gleason score 8-10, 45/50 (90%) had clinical T3 disease, and 6/50 (12%) had co-morbidities. Most subjects had erectile dysfunction at baseline; the median IIEF-5 score in the SOC arm was 18.5 (mild ED) and 13.0 (mild-to-moderate ED) in the intervention group. No participant had urinary incontinence at baseline. Quality-of-life (QOL) scores were high in both groups at baseline, with median EQ-5D-5L visual analogue scale (VAS) scores of 85.0 and 90.0 in the SOC and intervention cohorts, respectively. There were no clinically significant differences in any baseline characteristics between study groups.

For the intervention participants, peri-operative data are summarised in Table 2. All patients were on ADT before surgery with a median time (range) of three (1-9) months; 11/24 (45.8%) had docetaxel chemotherapy pre-operatively; all completed six cycles before surgery. All surgeries were completed successfully using robot-assisted surgery without conversion. One subject in the intervention arm felt too unwell to undergo surgery post-chemotherapy. One subject suffered a rectal injury which was diagnosed and repaired intra-operatively; this patient stayed in hospital for seven days without further complication. One subject suffered a post-operative infected lymphocoele for which he was re-admitted for percutaneous drainage; he then developed septic pericarditis and underwent a pericardiocentesis during the same re-admission, before recovering fully. One subject suffered a post-operative urinary tract infection and one had a post-operative wound infection. Erectile function was not preserved in any subject post-operatively. 4/24 (16.7%) patients remained incontinent (>1 pad/24h) six months after surgery. The positive margin rate was

10/24 (41.7%), with 19/23 (82.6%) having Gleason 8-10 on final pathology, and 21/24 (87.5%) having extra-prostatic (pT3) disease. 19/23 (82.6%) patients had a 6-month post-operative PSA<1 ng/ml.

Table 3 summarises the outcomes of the TRoMBone trial three months post-randomisation and shows that PSA levels were uniformly low due to systemic therapy. Commonly known side-effects of systemic therapy were reported in expected frequencies in both groups with no inter-group differences: reduced/absent sexual desire; shrinkage of testes and/or penis; hot flushes; breast tenderness and growth of breast tissue; osteoporosis; anaemia; decreased mental sharpness; loss of muscle mass; weight gain; fatigue; increased cholesterol; depression. Subjects were impotent with similar low IIEF-5 scores in both groups (median 5.0). SOC participants maintained their continence, while median pad use was two per day in the intervention arm. QOL scores were high and comparable between SOC and intervention groups, with no differences in EQ-5D-5L descriptive scores and clinically insignificant differences in VAS scores (median 84.0 vs. 90.0 in SOC and intervention arms, respectively).

Discussion

This trial has demonstrated feasibility to randomise men in the UK presenting with newly-diagnosed oligo-metastatic prostate cancer to standard-of-care (SOC) systemic therapy versus SOC plus radical prostatectomy with pelvic lymphadenectomy. As surgeons became more familiar with operating on metastatic patients, UK oncology and urology communities gained confidence in its safety and recruitment accelerated. The randomisation rate (randomised/eligible) was high as men with oligo-metastatic prostate cancer were supportive of research on radical local treatment and optimistic that surgery might help. However, eligible participants were fewer than expected from the preliminary scoping exercise, and careful identification and pathway optimisation for men with oligo-metastatic prostate cancer were required using the SEAR framework(27) to recruit successfully.

Robot-assisted laparoscopic surgery for randomised men in the intervention arm was technically feasible and appeared safe in those men who had been treated with ADT+/- docetaxel chemotherapy pre-operatively. Operative times, length of stay, complications, surgical margin rates, and early biochemical outcomes were all similar to radical prostatectomy series for standard indication.(26) Urinary continence outcomes were also similar to standard surgery. The surgical group did not suffer worse quality-of-life (QOL) compared to the SOC cohort.

This is the world-first randomised clinical trial examining the feasibility of radical surgery to the primary tumour in men with newly-diagnosed oligo-metastatic prostate cancer, with rigorous data collection of its primary and secondary outcomes. It represents one of few surgical trials that have recruited successfully, largely due to the embedded QuinteT Recruitment Intervention.(21) Multiple cancer centres across the UK were able to successfully recruit subjects, demonstrating generalisability of the feasibility methods. In addition, the trial has shown the safety of robot-assisted surgery for men with oligo-metastatic prostate cancer.

The lack of consistency in imaging modalities to define eligibility may have caused heterogeneity in the study cohort. This is especially so as some participants had their oligo-metastatic state defined by PSMA-PET and others by conventional imaging. While this might mean that the study population was heterogeneous in its burden of disease, this pragmatism however follows the UK current standard practice and increases the study's generalisability. Quality-of-life (QOL) impact was measured by a generic tool rather than specific prostate cancer-related QOL instruments which might have better captured urinary and sexual health domains. In our surgical feasibility study, we have also not examined the role of stereotactic body radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our main study as other investigators have shown this to be an effective approach in oligo-recurrent prostate cancer.(29)

Other studies have shown safety and technical feasibility of surgery in men with metastatic prostate cancer,(19) but none in the UK population and none to date in a randomised trial setting. Other ongoing randomised trials investigate radical surgery in metastatic disease, but do not specifically examine the role of surgery in addition to best systemic therapy in men with oligo-metastases.(18) The STAMPEDE trial has demonstrated that this is the optimal population of men with metastatic prostate cancer worth considering for local radical treatment.(14) TRoMbone now shows it is safe and feasible to investigate surgery in this setting. A future definitive trial is likely to accrue in the UK; recruitment is likely to be faster than in this feasibility study because an increasing number of surgeons will have experience and confidence in undertaking these operations as well as QRI-informed improved recruitment strategies.

Word count= 3989

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Legends to figures

Figure 1. CONSORT flow diagram

Figure 2. Recruitment

Legends to tables

Table 1. Baseline subject characterisitics. (a) categorical variables; (b) continuous variables

Table 2. Peri-operative data in intervention subjects

Table 3. PSA, functional, and quality-of-life outcomes in study groups at three months post-randomisation

Feasibility and safety of radical prostatectomy for oligo-metastatic prostate cancer: TRoMbone trial

(*T*esting *R*adical pr*o*statectomy in *m*en with prostate cancer and oligo-*M*etastases to the *bone*)

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Declaration of interests:

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Abstract

Objectives

To test feasibility of randomisation to radical prostatectomy plus pelvic lymphadenectomy (RP) in addition to standard-of-care (SOC) systemic therapy in men with newly diagnosed oligo-metastatic prostate cancer.

Patients and methods

A prospective, randomised, non-blinded, feasibility clinical trial with an embedded QuinteT Recruitment Intervention (QRI) to optimise recruitment was conducted in nine tertiary-care nationwide centres undertaking high-volume robotic surgery. We aimed to randomise 50 men with synchronous oligo-metastatic prostate cancer within an 18-month recruitment period to SOC systemic therapy versus SOC plus RP (intervention arm).

The main outcome measures were: ability to randomise participants, optimised by a QRI. EQ-5D-5L questionnaires to capture quality-of-life (QOL) data at baseline and three months post-randomisation; routine clinico-pathological assessment to capture adverse events and prostate-specific antigen in both arms, plus standard peri-operative parameters in the surgical arm.

Results

51 men were randomised within 14 months (one was subsequently deemed ineligible), with 60-83% accrual rate in centres that recruited at least two participants. All participants completed the trial follow-up; one participant in the intervention arm subsequently did not undergo the surgical intervention and one in the SOC arm refused all therapies. The QRI positively impacted recruitment. QOL data showed similarly high functioning in both study arms. Surgery for men with oligo-metastatic prostate cancer was found to be safe and had similar impact on early functional outcomes as surgery for standard indication.

Discussion

It is feasible to randomise men with synchronous oligo-metastatic prostate cancer to a surgical intervention in addition to standard systemic therapies. While surgery appeared safe with no substantial impact on QOL in this feasibility study, a large randomised controlled trial is now warranted to examine treatment effectiveness of this additional component in the multi-modality management of oligo-metastatic prostate cancer.

Word count 285

Funding

Keywords

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Prostate cancer; oligo-metastatic; radical prostatectomy; robot-assisted; surgery

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Introduction

Prostate cancer is the most common cancer and the second most frequent cause of cancer death in Western men.(1) Patients presenting with metastatic disease have a median survival of 42.1 months,(2) and until recently, the standard-of-care has been initial androgen deprivation therapy (ADT) alone. Contemporary data from the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial demonstrate a survival benefit for supplementing ADT with docetaxel chemotherapy for men presenting with metastatic prostate cancer.(3) Evidence from other tumour types as well as prostate cancer supports the concept of a transitory phenotype between localised/locally advanced cancer and widely disseminated disease, otherwise called the 'oligo-metastatic' state.(4) There is continuing controversy as to whether chemotherapy should be given in men presenting with oligo-metastatic prostate cancer where the disease burden is less than widespread metastases. The AJCC TNM staging system of prostate cancer categorises all skeletal-metastatic patients as M1b,(5) and there are no official statistics of numbers presenting with newly-diagnosed oligo-metastatic disease. There is also a lack of international consensus on the definition of oligo-metastatic prostate cancer; nonetheless, 1-3 skeletal metastases without any visceral metastases is a widely-utilised definition.(6)

The 'seed and soil' hypothesis postulates that a receptive micro-environment ('soil') allows dissemination of malignant cells ('seed') to form metastases, with soil development driven by factors secreted by the primary tumour.(7) Primary tumours can seed to distant sites which can further seed the primary lesion, leading to a vicious cycle of metastasis;(8) this 'self-seeding' phenomenon is dependent on the presence of an intact primary cancer focus.(9) Furthermore, disseminated tumour cells in men with clinically localised prostate cancer before prostatectomy confer a five-fold increased risk of future metastasis, but these same cells detected after surgery do not increase such risk.(10-12) Collectively, these biological data suggest that an intact primary lesion drives metastatic progression beyond early spread of circulating tumour cells. ~~As well as the biological rationale~~Further, population-based data of men with likely metastatic or micro-metastatic prostate cancer showed that those who underwent initial systemic therapy without radical therapy were approximately three-fold more likely to die of prostate cancer than those that had radical therapy.(13) The STAMPEDE randomised trial investigated the role of local therapy using prostate radiotherapy rather than surgery due to safety concerns, in men presenting with metastatic prostate cancer. A sub-group analysis demonstrated a relative survival advantage of 32% at 3 years for men with oligo-metastatic disease who underwent radical radiotherapy in addition to systemic therapy. However, no survival benefit was seen in those with a high burden of metastases in the total cohort.(14) Although the sub-group analysis fulfils nine out of ten criteria for credibility of sub-group analyses,(15) it has not yet been widely adopted internationally to include prostate radiotherapy as standard-of-care for men with oligo-metastatic disease. This is partly because another similar trial, HORRAD, has not shown a benefit for local radiotherapy in men with metastatic prostate cancer, including those with lower metastatic burden.(16) Hence, the role of local therapy with radiotherapy remains controversial in the presence of oligo-metastatic disease, with conclusive evidence that it has no benefit in those with high metastatic loads.

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Surgical removal of the prostate (radical prostatectomy) is an equivalent alternative to radiotherapy in men with organ-confined disease,(17) and hence represents another potential local radical therapy in the multi-modality approach to oligo-metastatic disease. There are a number of uncontrolled observational series investigating peri-operative outcomes of radical prostatectomy in men with metastatic disease, but these are limited by retrospective data collection as well as confounding indications in which only highly select men undergo surgery with poorly-defined eligibility criteria. (18, 19) Hence, there remains an urgent unmet need for randomised trials specifically examining the role of surgery in oligo-metastatic prostate cancer. However, lack of surgical experience in operating on oligo-metastatic disease mandate the need for stringent safety assessments in any such trial. Also, randomisation to surgical trials is fraught with difficulty and a number of high-profile prostate cancer trials have failed to recruit. Hence, ~~before commencing a full trial, it is imperative to assess the feasibility of such a study and the safety of the operative intervention.~~ most UK funders will not support a full surgical trial without a feasibility study confirming ability to randomise and safety of any novel intervention. One major success in recruitment terms was the Prostate Testing for Cancer and Treatment (ProtecT) study which employed a QuinteT Recruitment Intervention (QRI) that has been subsequently shown to improve recruitment in a further 13 challenging RCTs, including the recent PART prostate cancer feasibility trial.(20-23) We therefore integrated a QRI as well as robust safety assessments within this randomised controlled feasibility trial of surgery plus standard-of-care (SOC) systemic therapy versus SOC alone in men with newly-diagnosed oligo-metastatic prostate cancer (1-3 skeletal metastases from prostate cancer, no visceral metastases); the TRoMbone trial.

Our aims were: 1] to test the feasibility of recruiting and randomising men in the UK to a trial investigating radical prostatectomy (RP) in oligo-metastatic prostate cancer, with a view to launching a major trial; 2] to understand recruitment challenges and inform optimal recruitment strategies for a main trial through the QRI; and, 3] to collect quality-of-life and early oncological/safety/functional outcomes in these men.

Subjects/patients and methods

Trial design

The TRoMbone study was a prospective, randomised, controlled feasibility trial: *population*- men aged less than 75 years presenting with newly-diagnosed oligo-metastatic, locally-resectable prostate cancer and Eastern Co-operative Group performance status (ECOG PS) 0-1; *intervention*- radical prostatectomy (RP) plus standard-of-care (SOC); *comparator*- SOC, currently ADT+/-docetaxel chemotherapy; *outcome*- 50 participants recruited over 18 months after an initial three-month set-up period. Randomisation was stratified by site and allocation set in parallel on a 1:1 ratio. The randomisations were blocked within site using variable block sizes of two and four. The study was not blinded. Given that this is a feasibility study, no quantitative analysis was planned and descriptive statistics were used to inform a future possible full trial.

The study opened to recruitment initially in three centres. In QRI Phase 1, recruitment barriers were investigated in the initial three-month period through analysis of monthly screening log data and data collected through semi-structured interviews with surgeons, oncologists, research and specialist nurses, and audio-recorded recruitment appointments. Findings were presented and discussed with the Chief Investigator (CI) and Trial Management Group (TMG), and a plan of actions was agreed to optimise recruitment in Phase 2, including changes to the eligibility criteria, opening new centres, and feedback and 'tips' to support recruiters.

<u>Subjects</u>

Inclusion criteria at the start of the trial were: participant willing and able to give informed consent for participation in the study; male aged 18-74 years; diagnosed with oligo-metastatic prostate cancer (defined as 1-3 skeletal lesions on bone imaging, no visceral metastases); locally-resectable tumour (clinical/radiological stage T1-T3; ECOG PS 0-1; suitable for radical prostatectomy (RP) within three months of starting SOC. As a result of the Phase 1 QRI results (see below), the final eligibility criterion was changed to extend the maximum time from start of SOC to RP from three to 12 months. Exclusion criteria did not change during the trial and were: participants with contra-indications to RP; visceral metastases; prior radiotherapy to the abdomen/pelvis or to skeletal metastases; current involvement in other interventional research.

Three UK cancer centres were initially opened to recruitment. As a result of the Phase 1 QRI results, this was expanded to nine UK cancer centres selected based on geographical diversity. Potential participants were identified as part of routine clinical care, either from individual surgical/oncology clinics or via cancer multi-disciplinary team (MDT) meetings. Those found to have oligo-metastatic prostate cancer on staging investigations were screened for trial eligibility. <u>Staging investigations included bone scintigram, MRI, CT, and PET depending on local practice, with some patients undergoing multiple staging tests.</u> Recruiting sites chose the type of staging imaging they performed based on their standard clinical practice so the trial outcomes would be generalisable across the UK. <u>Oligo-metastatic sites were not confirmed with biopsy, as this is invasive and not standard practice in the UK.</u>

Eligible patients were approached by a specialist nurse, oncologist, or surgeon, and received a Patient Information Leaflet (PIL). Patients were given sufficient time to make a decision on whether they wanted to join the trial, and if so, were invited to give written consent. Consenting patients became subjects and completed baseline assessments (demographics, medical history, concomitant medication, vital signs, and routine bloods), and were then randomised by the Registration/Randomisation and Management of Product (RRAMP) software on the OpenClinica online platform of the Oxford Clinical Trials Research Unit (OCTRU): https://www.ndorms.ox.ac.uk/octru. Post-treatment allocation follow-up was as per routine clinical care for both groups, with patient-reported quality-of-life (QOL) collected from the EQ-5D-5L descriptive and visual analogue scale questionnaires before randomisation and 3-month post-randomisation visits. For the surgical participants, standard peri-operative and outcomes data including

safety/complications/functional outcomes were also recorded until six months post-surgery.

Interventions

All participants received SOC systemic therapy-ADT+/-docetaxel. Expected adverse effects of systemic therapy (e.g. reduced or absent libido, impotence, hot flashes) were recorded. Participants in the intervention arm underwent robot-assisted radical prostatectomy plus pelvic lymphadenectomy consistent with international guidelines for high-risk prostate cancer.(24) Excised nodal packets included obturator, external iliac, internal iliac, common iliac, and fossa of Marcille. Standard pre-operative (e.g. Gleason score, PSA, clinical stage), intra-operative (e.g. operative time, need for blood transfusion), and post-operative (e.g. Clavien-Dindo grade,(25) 21 individual complications)(26) parameters were recorded until six months post-operatively. The timing of surgery in the intervention arm was initially within three months of starting SOC but then amended via Protocol Amendment to within 12 months of starting SOC, as a result of the Phase 1 QRI results (as stated above).

Outcomes

The intervention arm in this feasibility trial received radical prostatectomy. The procedure is well established in the treatment of localised and locally-advanced prostate cancer, but here we investigated its use in oligo-metastatic disease.

The primary outcome of the feasibility study of randomisation was to recruit and randomise 50 participants, 18 months after the opening of the first site, optimised by a QRI. Secondary outcomes were quality-of-life assessment at baseline and three months post-randomisation (using EQ-5D-5L), and peri-operative outcomes including operative data (type of surgery, operative time, console time, need for blood transfusion, outcome of the procedure, return to theatre, length of hospital stay, successful catheter removal, peri-operative complications by Clavien-Dindo grade and assessment of 21 pre-specified complications), early oncological data (positive surgical margins (PSM), length of PSM, final pathological stage, lymph nodes removed, lymph nodes positive, 3-month and 6-month post-operative PSA), and early functional data (1-month, 3-month, and 6-month post-operative erectile function and continence recovery).

Sample size

A sample size of 50 participants was chosen as a result of a preliminary scoping exercise across 14 UK prostate cancer centres suggesting an average of two eligible patients per month per site for the trial. We thus estimated that 50 participants were a realistic target given we intended to open three sites with a total recruitment period of 18 months (assuming roughly one-half of eligible patients would accept randomisation, predicted from QRI results from other surgical trials).

No interim analyses were planned but a Trial Management Group (TMG) monitored safety data and had the ability to stop the trial early if the intervention was deemed unsafe. Reporting of adverse events followed standard Oxford Clinical Trials Research Unit (OCTRU) procedures.

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Randomisation and masking

Randomisation was performed using the web-based secure randomisation system provided by OCTRU. Participants were randomised on a 1:1 basis and stratified by site with block sizes of two and four. There was no blinding in the trial, and clinicians and participants were fully aware of the treatment allocation. Research/specialist nurses and surgeons at the sites were responsible for enrolling participants, and followed the web-based system with regards assigning participants to study arms.

Analytical methods

All randomised participants were included. No participant withdrew consent prior to treatment allocation. Outcomes data were summarised across the two randomised groups (Tables 1-3).

A QuinteT Recruitment Intervention (QRI) was used to understand the recruitment process and how it operates in all TRoMbone recruiting centres, so that sources of recruitment difficulties could be identified and suggestions made to improve recruitment(21). QRI findings and suggested changes were fed-back to the Chief Investigator (CI), site Principal Investigators (PI), and trial research staff. The QRI was conducted in two phases:

Phase 1- understanding recruitment: to understand the recruitment process as it occurred, and to identify and investigate sources of recruitment difficulty. Site screening logs were collected to provide data about eligibility assessment, and recruitment processes using the SEAR framework,(27) which identifies points at which patients continue or drop out of the trial. In-depth, semi-structured interviews were conducted and audio-recorded with: (i) members of the TMG, including the CI and those closely involved in trial co-ordination; (ii) clinical and recruitment staff across the three initial sites; (iii) subjects eligible for recruitment, including those who accepted or rejected randomisation; (iv) subjects after treatment allocation or receipt to discuss perceptions regarding their treatment and care while on the trial. The QRI researcher also attended investigator meetings between the CI, TMG, and clinical investigators, to gather further information about specific recruitment issues encountered. Recruiting staff audio-recorded appointments with potential subjects, such that the QRI researcher could provide feedback to recruiters in Phase 2 to optimise their recruitment technique. Study documentation (PILs and consent forms) were also reviewed and compared with the interviews and recorded appointments, to identify any disparities or improvements that could be made. All audio-recorded transcripts and notes were analysed thematically by the QRI researcher, using constant comparison and case-study approaches including targeted conversation analysis.(28)

Phase 2- feedback to CI/TMG and plan of action: after three months, the QRI researcher (CW) presented anonymised findings to the CI and TMG, identifying factors that appeared to be hindering recruitment. A plan of action was then formulated by the QRI team, CI, and TMG, in order to improve recruitment. The impact of this plan of action was evaluated by assessing the numbers of eligible patients, percentages of those approached about the trial, and numbers that

consented to be randomised and accepted or rejected the treatment allocation, both before and after the first three-month period, and at regular intervals after implementation. Ongoing interviews with recruiters also provided qualitative information about the acceptability of the plan of action and its impact.

Trial registration

International Standard Randomised Controlled Trial Number (ISRCTN) 15704862.

Results

Feasibility of randomisation and Quintet Recruitment Intervention

71/176 (40.3%) screened patients were eligible; 51/71 (71.8%) were randomised (Figure 1). Low recruitment rates were significantly improved with the QRI plan of action implemented in Phase 2 after three months (Figure 2). Phase 1 of the QRI identified the commonest causes of non-recruitment: inability to identify eligible patients; lack of clinician equipoise; and, inability to receive docetaxel chemotherapy pre-operatively.

During Phase 1, 12 potentially eligible patients were screened at MDT, of whom ten were deemed eligible. Screening data demonstrated lower than expected eligible patient numbers, most often due to systemic treatment more than three months prior to enrolment as a result of oncologists' strong preference for men with oligo-metastatic prostate cancer to be offered docetaxel chemotherapy within twelve weeks of starting ADT. Given that the chemotherapy course is six cycles administered three weeks apart, it was not possible for participants to undergo surgery within three months of starting ADT if they were to be given chemotherapy pre-operatively. As clinical practice changed from the period when the trial was set up to increasing usage of chemotherapy, this became an early barrier to recruitment. Hence, the plan of action stated that a further six geographically-diverse centres should be opened to recruitment and subject eligibility should be widened to those suitable for radical prostatectomy within 12 months of starting ADT, to allow for docetaxel chemotherapy before surgery in the intervention arm. It also became apparent that eligible patients were not being referred from outside the normal catchment areas, so it was suggested that the trial be publicised in urological and oncological forums, press outlets, and patient groups.

31 in-depth interviews were conducted with 13 surgeons, eight oncologists, and ten research/specialist nurses. 32 subjects had their consultations recorded with 11 recruiters (seven surgeons, two oncologists, and two research nurses) at five centres. 15 randomised subjects from six centres were also interviewed; eight were allocated SOC and seven intervention. 6/7 subjects in the intervention arm were interviewed after surgery. Most interviews and appointment recordings during Phase 1 demonstrated a lack of clinician equipoise. Hence, the plan of action included individual recruiter feedback to optimise recruitment consultations and share recruitment tips with all sites. Recruitment tips and feedback were individualised and, as in prior studies(21, 22), follow-up interviews with recruiters found them helpful in explaining randomisation and uncertainty, as well as fully informing patients about

the potential consequences of study participation. From the outset, clinician equipoise was delicately balanced between the long-term hope of potential survival benefits and the more immediate known side-effects of surgery, but surgeons found it difficult to express this to patients. They became more confident about expressing equipoise as concerns about the risks and side-effects of surgery were alleviated by successful surgeries, feedback from men keen to join the study, and the growing numbers of randomisations.

From the screening logs and recruiter interviews it also became apparent that many eligible patients present to oncologists rather than urologists. Hence, individual site-specific strategies were employed, including direct booking of surgical appointments by oncologists, joint surgeon-oncologist consultations, use of nurse specialists to co-ordinate patient pathways, and pre-recruitment remote consultations for patients that would otherwise have to travel significant distances. These changes resulted in improved communication between surgeons and oncologists, with joint decision-making regarding optimal timing of chemotherapy and surgery after starting ADT for individual patients.

As a result of the plan of action implemented in Phase 2 of the study, the TRoMbone trial recruited to completion, demonstrating feasibility of randomisation. Although the recruitment rate for the TRoMbone study ranged from 60-83 percent in centres which randomised more than one patient, three centres did not recruit. These centres were open for a shorter time (median three months) compared to the six recruiting centres (median nine months) and did not manage to re-configure their pathways to implement the plan of action devised from the QRI.

<u>Safety and early outcomes</u>

The baseline characteristics of the subjects are shown in Table 1. 36/50 (72%) subjects had Gleason score 8-10, 45/50 (90%) had clinical T3 disease, and 6/50 (12%) had co-morbidities. Most subjects had erectile dysfunction at baseline; the median IIEF-5 score in the SOC arm was 18.5 (mild ED) and 13.0 (mild-to-moderate ED) in the intervention group. No participant had urinary incontinence at baseline. Quality-of-life (QOL) scores were high in both groups at baseline, with median EQ-5D-5L visual analogue scale (VAS) scores of 85.0 and 90.0 in the SOC and intervention cohorts, respectively. There were no clinically significant differences in any baseline characteristics between study groups.

For the intervention participants, peri-operative data are summarised in Table 2. All patients were on ADT before surgery with a median time (range) of three (1-9) months; 11/24 (45.8%) had docetaxel chemotherapy pre-operatively; all completed six cycles before surgery. All surgeries were completed successfully using robot-assisted surgery without conversion. One subject in the intervention arm felt too unwell to undergo surgery post-chemotherapy. One subject suffered a rectal injury which was diagnosed and repaired intra-operatively; this patient stayed in hospital for seven days without further complication. One subject suffered a post-operative infected lymphocoele for which he was re-admitted for percutaneous drainage; he then developed septic pericarditis and underwent a pericardiocentesis during the same re-admission, before recovering fully. One subject suffered a post-operative urinary tract infection and one had a post-operative wound infection. Erectile function

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was not preserved in any subject post-operatively. 4/24 (16.7%) patients remained incontinent (>1 pad/24h) six months after surgery. The positive margin rate was 10/24 (41.7%), with 19/23 (82.6%) having Gleason 8-10 on final pathology, and 21/24 (87.5%) having extra-prostatic (pT3) disease. 19/23 (82.6%) patients had a 6-month post-operative PSA<1 ng/ml.

Table 3 summarises the outcomes of the TRoMBone trial three months post-randomisation and shows that PSA levels were uniformly low due to systemic therapy. Commonly known side-effects of systemic therapy were reported in expected frequencies in both groups with no inter-group differences: reduced/absent sexual desire; shrinkage of testes and/or penis; hot flushes; breast tenderness and growth of breast tissue; osteoporosis; anaemia; decreased mental sharpness; loss of muscle mass; weight gain; fatigue; increased cholesterol; depression. Subjects were impotent with similar low IIEF-5 scores in both groups (median 5.0). SOC participants maintained their continence, while median pad use was two per day in the intervention arm. QOL scores were high and comparable between SOC and intervention groups, with no differences in EQ-5D-5L descriptive scores and clinically insignificant differences in VAS scores (median 84.0 vs. 90.0 in SOC and intervention arms, respectively).

Discussion

This trial has demonstrated feasibility to randomise men in the UK presenting with newly-diagnosed oligo-metastatic prostate cancer to standard-of-care (SOC) systemic therapy versus SOC plus radical prostatectomy with pelvic lymphadenectomy. As surgeons became more familiar with operating on metastatic patients, UK oncology and urology communities gained confidence in its safety and recruitment accelerated. The randomisation rate (randomised/eligible) was high as men with oligo-metastatic prostate cancer were supportive of research on radical local treatment and optimistic that surgery might help. However, eligible participants were fewer than expected from the preliminary scoping exercise, and careful identification and pathway optimisation for men with oligo-metastatic prostate cancer were required using the SEAR framework(27) to recruit successfully.

Robot-assisted laparoscopic surgery for randomised men in the intervention arm was technically feasible and appeared safe in those men who had been treated with ADT+/- docetaxel chemotherapy pre-operatively. Operative times, length of stay, complications, surgical margin rates, and early biochemical outcomes were all similar to radical prostatectomy series for standard indication.(26) Urinary continence outcomes were also similar to standard surgery. The surgical group did not suffer worse quality-of-life (QOL) compared to the SOC cohort.

This is the world-first randomised clinical trial examining the feasibility of radical surgery to the primary tumour in men with newly-diagnosed oligo-metastatic prostate cancer, with rigorous data collection of its primary and secondary outcomes. It represents one of few surgical trials that have recruited successfully, largely due to the embedded QuinteT Recruitment Intervention.(21) Multiple cancer centres across the UK were able to successfully recruit subjects, demonstrating generalisability of

the feasibility methods. In addition, the trial has shown the safety of robot-assisted surgery for men with oligo-metastatic prostate cancer.

The lack of consistency in imaging modalities to define eligibility may have caused heterogeneity in the study cohort. This is especially so as some participants had their oligo-metastatic state defined by PSMA-PET and others by conventional imaging. While this might mean that the study population was heterogeneous in its burden of disease, tThis pragmatism however follows the UK current standard practice and increases the study's generalisability. Quality-of-life (QOL) impact was measured by a generic tool rather than specific prostate cancer-related QOL instruments which might have better captured urinary and sexual health domains. In our surgical feasibility study, we have also not examined the role of stereotactic body radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our main study as other investigators have shown this to be an effective approach in oligo-recurrent prostate cancer.(29)

Other studies have shown safety and technical feasibility of surgery in men with metastatic prostate cancer,(19) but none in the UK population and none to date in a randomised trial setting. Other ongoing randomised trials investigate radical surgery in metastatic disease, but do not specifically examine the role of surgery in addition to best systemic therapy in men with oligo-metastases.(18) The STAMPEDE trial has demonstrated that this is the optimal population of men with metastatic prostate cancer worth considering for local radical treatment.(14) TRoMbone now shows it is safe and feasible to investigate surgery in this setting. A future definitive trial is likely to accrue in the UK; recruitment is likely to be faster than in this feasibility study because an increasing number of surgeons will have experience and confidence in undertaking these operations as well as QRI-informed improved recruitment strategies.

Word count= 38773989

Acknowledgments

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Legends to figures

Figure 1. CONSORT flow diagram

Figure 2. Recruitment

Legends to tables

Table 1. Baseline subject characterisitics. (a) categorical variables; (b) continuous variables

Table 2. Peri-operative data in intervention subjects

Table 3. PSA, functional, and quality-of-life outcomes in study groups at three months post-randomisation

Response to Reviewers

Referee: 1

We thank the referee for his/her detailed review of our manuscript. We address the specific points below:

1.   The manuscript reports primarily on feasibility: will men with oligometastatic prostate cancer accept randomization to SOC or SOC + RP. The Introduction, however, focuses on what is SOC (paragraph 1), a rather convoluted discussion of the rationale for adding local to systemic therapy (paragraph 2), and then a mention of the study aims (paragraph 3). The Introduction should be devoted to the concept of the difficulty to randomize men to a SOC versus SOC + RP trial [which is the primary (I would argue the only) aim of the study]. Why was a feasibility study needed; is there prior evidence that there would be difficulty enrolling to such a trial; what were the expected obstacles and how did you plan to address these?

We feel that the Introduction sets the scene well and would refer to the positive comments of the other reviewers in this regard. We have substituted one clause in the second para with *"Further"* to reduce the word count, but feel the rest of the content is important for the reader.

The rationale for a feasibility study is well described in the third para of the Introduction and we have made this even more explicit by changing a line in that para to:

"Hence, most UK funders will not support a full surgical trial without a feasibility study confirming ability to randomise and safety of any novel intervention."

In the third para, we have stated that multiple prostate cancer surgical trials have failed to recruit in the past, that there is a lack of surgical experience in operating on oligo-metastatic disease, and that we utilized a tried-and-tested QRI as used in the ProtecT trial to inform us on the obstacles and the plan to address them. The purpose of the QRI was to independently interrogate the challenges to recruitment and then to propose solutions. We did not pre-judge what the QRI would find. Due to a limited word count, we have provided all the references the reader would require if they wish to have further details of the QRI rationale and methodology (no change to the original manuscript):

"One major success in recruitment terms was the Prostate Testing for Cancer and Treatment (ProtecT) study which employed a QuinteT Recruitment Intervention (QRI) that has been subsequently shown to improve recruitment in a further 13 challenging RCTs, including the recent PART prostate cancer feasibility trial.(20-23) We therefore integrated a QRI as well as robust safety assessments within this randomised controlled feasibility trial of surgery plus standard-of-care (SOC) systemic therapy versus SOC alone in men with newly-diagnosed oligo-metastatic prostate cancer (1-3 skeletal metastases from prostate cancer, no visceral metastases); the TRoMbone trial."

2.   While the patients had oligometastatic prostate cancer, a requirement was locally resectable disease in a surgically fit patient. It should come as no surprise that the outcome from RP was no different than in men without oligometastatic cancer. Multiple studies have shown the safety of RP in men receiving neoadjuvant ADT, neoadjuvant chemotherapy, and the combination. I'm not sure why UK men would be any different than men in other parts of Europe and America or in men randomized to RP rather than having it electively. There is nothing new in this study to add to what has already been extensively published.

We thank the reviewer with this comment but would humbly disagree. While there are studies that have examined surgery in metastatic prostate cancer (indeed our team has been involved in some of them), none of these are devoid of confounding by indication bias. These studies were retrospective and subject to selection bias, and our study examines for the first time whether it is safe to conduct surgery in this population without such selection biases. We are not claiming that UK men are different to men in other parts of Europe and America but it is true that men randomised to RP may be different to men having it "electively" as they will be subject to fewer selection biases. We therefore disagree that there is nothing new in this study or to what has been already extensively published. There has never been a randomised study published examining surgery for de novo oligo-metastatic prostate cancer, and retrospective, observational studies do not provide a high-level evidence alternative to randomisation. We have discussed the unique characteristics of our study and compared to the literature in the last para of the Discussion (no change from the original manuscript):

"Other studies have shown safety and technical feasibility of surgery in men with metastatic prostate cancer,(19) but none in the UK population and none to date in a randomised trial setting. Other ongoing randomised trials investigate radical surgery in metastatic disease, but do not specifically examine the role of surgery in addition to best systemic therapy in men with oligo-metastases.(18) The STAMPEDE trial has demonstrated that this is the optimal population of men with metastatic prostate cancer worth considering for local radical treatment.(14) TRoMbone now shows it is safe and feasible to investigate surgery in this setting. A future definitive trial is likely to accrue in the UK; recruitment is likely to be faster than in this feasibility study because an increasing number of surgeons will have experience and confidence in undertaking these operations as well as QRI-informed improved recruitment strategies."

3.   Per point 2, including information about safety and outcomes in those men randomized to RP, including Tables 2 and 3, adds nothing to this manuscript. Focus on the key aim: is it feasible to randomize men with oligometastatic prostate cancer to SOC versus SOC + RP?

As per our reply to point 1, it is important for funders to be reassured that performing surgery in this novel population is safe. Hence, our TMG were agreed that these outcomes should be recorded and these assessments are in the study protocol. It would therefore be unethical to omit these data from the publication. We feel we have shown both safety and feasibility to randomise.

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4.   Is current standard of care for men with oligometastatic prostate cancer not radiation therapy + radiation rather than systemic therapy alone? Should that not be the next trial: systemic therapy + XRT versus systemic therapy + RP?

We thank the reviewer for this incisive comment. We agree, based on STAMPEDE and others, that the standard of care for de novo oligo-metastatic prostate cancer should be systemic therapy + XRT to the primary, and thus the full trial should be a comparison of surgery to that standard of care. We have now shown that we can randomise eligible men, and as per referee 3's comments below (and our response), will plan such a study with the inclusion also of SBRT to the oligo-metastases.

As a full study is being planned and will require input from radiotherapists, patient stakeholders, imaging specialists, and others, we have not discussed the exact planned design in this manuscript. We have though added in a line in the Discussion stating that we will include SBRT to the oligo-metastases in the full trial:

"In our surgical feasibility study, we have also not examined the role of stereotactic body radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our main study as other investigators have shown this to be an effective approach in oligo-recurrent prostate cancer.(29)"

Referee: 2

We thank the referee for his/her extremely positive comments about the manuscript in its original version. We have addressed the other referee comments as best as we can and hope referee 2 agrees that manuscript has been improved even further.

Referee: 3

We thank the referee for his/her positive introductory comments. We address the specific points below:

1.   The population seems like a very low risk one given the number of mets/LN count. I would use CAPRA (and possibly CAPRA S) to better describe the population

We thank the referee for this comment. The CAPRA score includes the following variables: age, PSA, biopsy Gleason score, clinical T-stage, and percent biopsy cores involved. It does not include number of mets/ LN count. Also, for clinical T-stage, it is categorised as T1/T2 or T3a and most of our patients had T3b disease. If we were to categorise our T3 patients as T3a for the purposes of CAPRA scoring, then our median CAPRA score in both groups would be 8 and our IQR in both groups would be 7-8. Instead of a cumulative score like CAPRA we have given the summary statistics across each variable, which we feel is more informative to the reader. As pre-operative risk category defined eligibility for this trial we also feel that

adding in a post-operative cumulative scoring system like CAPRA-S might add confusion.

We have therefore not added in CAPRA (or CAPRA-S) scores to Table 1.

2. State more specifically how metastases were detected, bone scan, cross sectional imaging or both? Were such sites confirmed with biopsy? Was follow up imaging routinely done?

We thank the referee for this comment. Table 1 already contains a section titled "Distant staging modality" with numbers and percentages of participants who underwent bone scintigram, MRI, CT, and PET. We have added a line in to the Methods in the 'Subjects' sub-section to reflect the heterogeneity of staging among trial participants, reflective of current urological practice:

"Staging investigations included bone scintigram, MRI, CT, and PET depending on local practice, with some patients undergoing multiple staging tests."

We also added a line thereafter:

"Oligo-metastatic sites were not confirmed with biopsy, as this is invasive and not standard practice in the UK."

As all patients received systemic therapy, it was not deemed clinically appropriate or necessary to do follow up imaging, but rather to monitor PSA. Hence, follow-up imaging as not done routinely.

3. Given the widespread use of PSMA PET, the authors should discuss how such imaging technology would impact identification and assessment of such patients.

We thank the reviewer for this comment and fully accept that heterogeneity of imaging modalities in the study might result in heterogeneity of disease burden in the study population. However, this reflects current UK (and worldwide) clinical practice, in which there is no consistency in oligo-metastatic definitions based on defined imaging modalities. As the purpose of our feasibility study was to evaluate safety and technical feasibility to randomise men with oligo-metastatic disease, we adopted a pragmatic approach to eligibility allowing individual cancer centres to use whatever imaging modalities they routinely did. We have expanded a section in para 4 of the Discussion to reflect this:

"This is especially so as some participants had their oligo-metastatic state defined by PSMA-PET and others by conventional imaging. While this might mean that the study population was heterogeneous in its burden of disease, [this pragmatism however follows the UK current standard practice and increases the study's generalisability.]"

4. What is the role of SBRT to oligometastatic sites? How would this complement systemic therapy?

Our study was not examining the role of SBRT to oligo-metastatic sites. While there are data for this approach in oligo-recurrent prostate cancer (e.g. the STOMP trial), studies using SBRT for de novo (synchronous) oligo-metastatic prostate cancer are lacking. We plan to investigate this in our main trial and have added the below text to the penultimate para of the Discussion, along with the STOMP trial reference:

"In our surgical feasibility study, we have also not examined the role of stereotactic body radiotherapy (SBRT) to the oligo-metastatic sites; we plan to add this to our main study as other investigators have shown this to be an effective approach in oligo-recurrent prostate cancer.(29)"

The STOMP trial examined time to requiring systemic therapy as its primary endpoint. As we know that systemic therapy improves survival in de novo metastatic prostate cancer, we would include it in all arms for our main trial. We have yet to plan the details of the SBRT arm of this main trial and would require the input of our radiotherapy colleagues for this, and how SBRT would complement systemic therapy. As this is beyond the scope of this current paper, and due to a limitation on word count, we have not discussed this issue further in the text.

Figure 1. CONSORT flow diagram
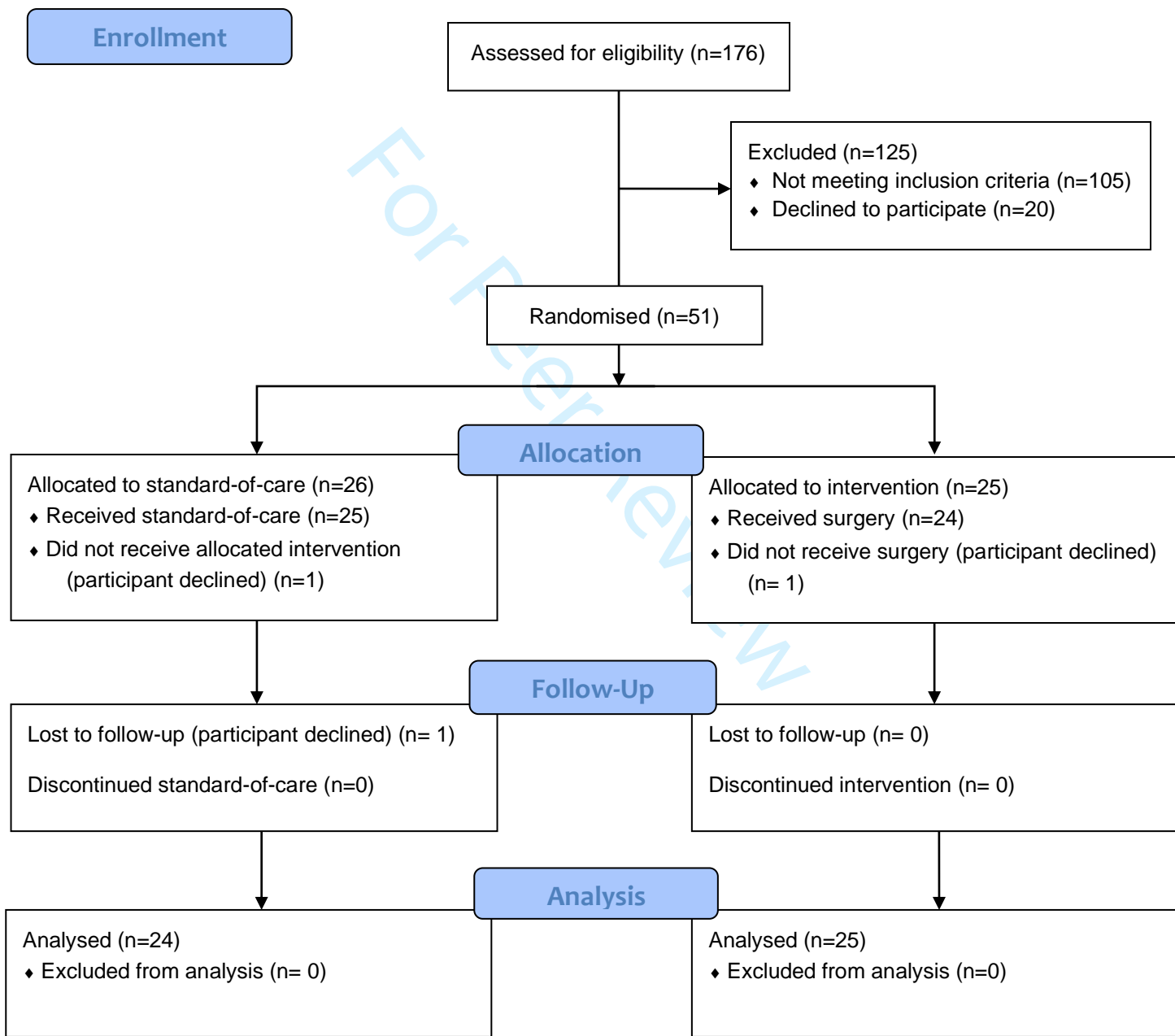
Figure 2. Recruitment
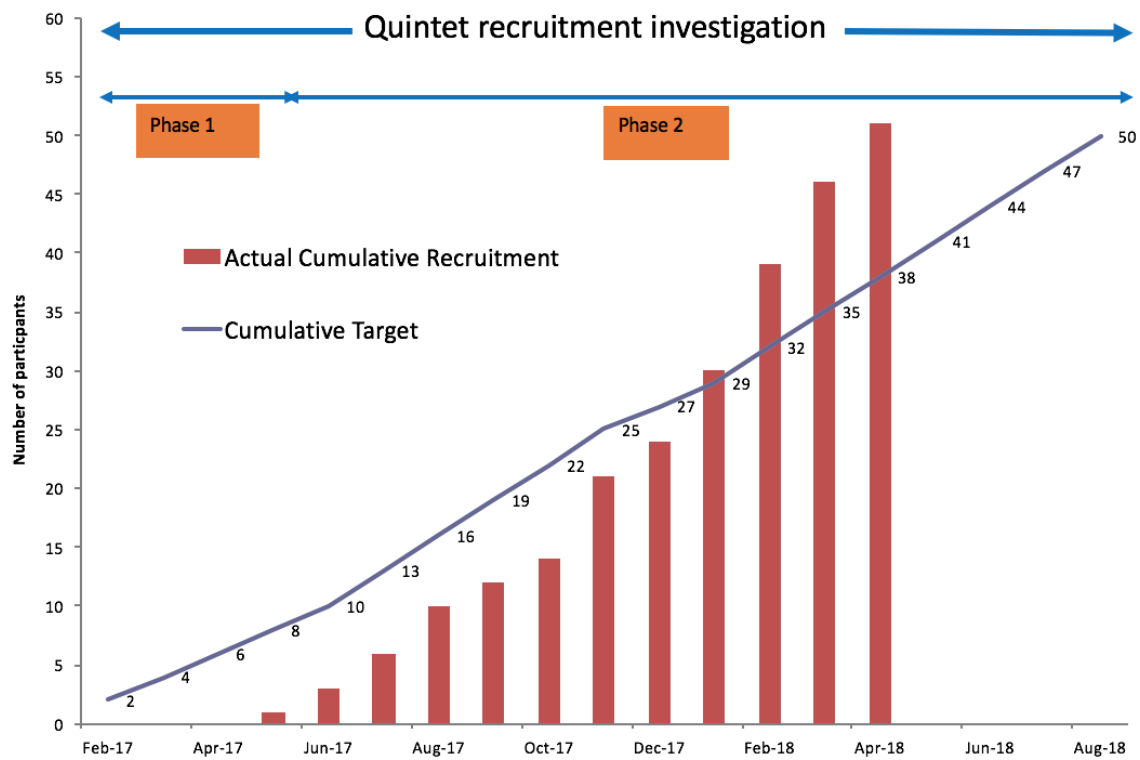
Table 1. Baseline subject characteristics

(a) Categorical variables

Variable	Full cohort	SOC arm	Intervention arm
n (%)	50 (100)	25 (50)	25 (50)
Age			
Less than 60	10 (20)	6 (24)	4 (16)
60-64	12 (24)	5 (20)	7 (28)
65-70	18 (36)	7 (28)	11 (44)
71-74	10 (20)	7 (28)	3 (12)
Ethnicity			
Caucasian	37 (74)	20 (80)	17 (68)
Black African/Caribbean	8 (16)	4 (16)	4 (16)
Asian	5 (10)	1 (5)	4 (16)
Gleason score			
7 (3+4)	3 (6)	2 (8)	1 (4)
7 (4+3)	11 (22)	5 (20)	6 (24)
8	13 (26)	6 (24)	7 (28)
9-10	23 (46)	12 (48)	11 (44)
Clinical stage (DRE)			
T2c	5 (10)	2 (8)	3 (12)
T3	45 (90)	23 (92)	22 (88)
Co-morbidities			
Myocardial infarction	0 (0)	0 (0)	0 (0)
Congestive heart failure	0 (0)	0 (0)	0 (0)
Peripheral vascular disease	0 (0)	0 (0)	0 (0)
Cerebrovascular disease	0 (0)	0 (0)	0 (0)
Dementia	0 (0)	0 (0)	0 (0)
Chronic obstructive pulmonary disease	1 (2)	1 (4)	0 (0)
Rheumatological disease	1 (2)	1 (4)	0 (0)
Connective tissue disorder	0 (0)	0 (0)	0 (0)
Peptic ulcer disease	1 (2)	0 (0)	1 (4)
Mild liver disease	0 (0)	0 (0)	0 (0)
Moderate/severe liver disease	0 (0)	0 (0)	0 (0)
Diabetes mellitus	2 (4)	0 (0)	2 (8)
Diabetes with chronic complications	0 (0)	0 (0)	0 (0)
Moderate/severe chronic kidney disease	0 (0)	0 (0)	0 (0)
Hemiplegia/paraplegia	0 (0)	0 (0)	0 (0)

Leukaemia	0 (0)	0 (0)	0 (0)
Malignant lymphoma	1 (2)	1 (4)	0 (0)
Solid tumour	1 (2)	0 (0)	1 (4)
AIDS	0 (0)	0 (0)	0 (0)
None of the above conditions	44 (88)	23 (92)	21 (84)
Distant staging modality*			
Bone scintigram	41 (82)	19 (76)	22 (88)
MRI	37 (74)	19 (76)	18 (72)
CT	23 (46)	12 (48)	11 (44)
PET	8 (16)	5 (20)	3 (12)
Radiological T-stage			
T2c	4 (8)	1 (4)	3 (12)
T3a	18 (36)	9 (36)	9 (36)
T3b	28 (56)	15 (60)	12 (48)
Missing	1 (2)	0 (0)	1 (4)
Radiological N-stage			
N0	26 (52)	10 (40)	16 (64)
N1	24 (48)	15 (60)	9 (36)
Family history of prostate cancer			
Yes	12 (24)	7 (28)	5 (20)
Missing	4 (8)	4 (16)	0 (0)
Patient on 5-alpha-reductase inhibitor			
Yes	1 (2)	1 (4)	0 (0)
Missing	1 (2)	0 (0)	1 (2)
IIEF-5 category			
7 or less (severe ED)	13 (26)	5 (20)	8 (32)
8-11 (moderate ED)	6 (12)	3 (12)	3 (12)
12-16 (mild-to-moderate ED)	7 (14)	3 (12)	4 (16)
17-21 (mild ED)	11 (22)	8 (32)	3 (12)
22-25 (no ED)	10 (20)	4 (16)	6 (24)
Missing	3 (6)	2 (8)	1 (4)
Incontinence			
No	50 (100)	25 (0)	25 (0)

*Some participants underwent multiple imaging modalities, as per routine clinical care

(b) continuous variables

Variable	SOC		Intervention	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Age	64.7 (6.6)	66.0 (60.2-71.2)	65.3 (5.1)	65.4 (62.5-69.3)
BMI*	28.2 (3.9)	28.2 (25.4-30.4)	31.5 (14.0)	26.4 (24.3-29.9)
PSA	57.0 (117.6)	16.5 (8.2-37.5)	43.3 (79.3)	14.0 (2.7-40.0)
No. of nodal metastases	3.3 (4.3)	1.0 (0.0-10.0)	1.2 (2.8)	0.0 (0.0-1.0)
No. of bone metastases	1.5 (0.7)	1.0 (1.0-2.0)	1.5 (0.8)	1.0 (1.0-2.0)
Prostate volume (cc)**	40.3 (20.3)	40.0 (26.0-50.0)	53.9 (60.7)	38.0 (23.0-60.0)
No. of biopsy cores taken***	11.4 (4.9)	12.0 (10.0-12.0)	13.2 (6.4)	12.0 (10.0-14.0)
No. of biopsy cores positive***	9.1 (4.4)	10.0 (5.0-12.0)	9.0 (3.2)	9.0 (6.0-12.0)
No. of lymph node metastases[+]	1.6 (3.0)	0.0 (0.0-2.0)	1.2 (2.8)	0.0 (0.0-1.0)
No. of bone metastases	1.5 (0.8)	1.0 (1.0-2.0)	1.4 (0.7)	1.0 (1.0-2.0)
IIEF-score[++]	15.5 (6.8)	18.5 (10.0-21.0)	13.5 (7.6)	13.0 (5.5-21.0)
No. of pads/24h	0 (0)	0 (0)	0 (0)	0 (0)
EQ-5D-5L descriptive score	0.9 (0.1)	1.0 (0.8-1.0)	0.9 (0.1)	1.0 (0.8-1.0)
EQ-5D-5L VAS score	84.7 (11.5)	85.0 (80.0-95.0)	84.7 (13.8)	90.0 (80.0-95.0)

*BMI had missing data in one SOC and four intervention arm participants

**Prostate volume had missing data in four SOC and two intervention arm participants

***No. of biopsy cores taken/positive had missing data in one SOC and one intervention arm participant

[+]No. of lymph nodes metastases had missing data in five SOC and one intervention arm participant

[++]IIEF-5 score had missing data in two SOC and one intervention arm participant

Table 2. Peri-operative data in intervention subjects*

Variable	Result
Participants, n	24
PSA at time of surgery, median (IQR)	2.0 (0.79-7.25)
ADT length before surgery (m), median (range)	3 (1-9)
Pre-operative chemotherapy, n (%)	11 (45.8)
Cycles of chemotherapy, median (range)	6 (6-6)
Time from last chemotherapy to surgery (m), median (range)	4 (3-6)
Operative time (min), median (IQR)	185 (165-217)
Console time (min), median (IQR)	150 (129-170)
Intra-operative complications**, n (%)	1 (4.2)
Intra-operative transfusions, n (%)	1 (4.2)
Procedure abandoned, n (%)	0 (0)
Length of stay, median (IQR)	1 (1-2)
Return to theatre during hospital stay, n (%)	0 (0)
Post-operative transfusions, n (%)	1 (4.2)
Failed trial without catheter, n (%)	0 (0)
Pathological Gleason score***, n (%)	
4+3	4 (16.7)
4+4	4 (16.7)
4+5	8 (33.3)
5+4	7 (29.2)
Pathological T-stage, n (%)	
pT2c	3 (12.5)
pT3a	3 (12.5)
pT3b	18 (75.0)
Lymph nodes removed, median (IQR)	11 (7-14)
Lymph node positive, n (%)	11 (45.8%)
Length of catheterisation (d), median (IQR)	14 (10-14)
Post-operative complications within 6m** of surgery, n (%)	3 (12.5)
Erections sufficient for intercourse without invasive aids within 6m of surgery, n (%)	0 (0%)
Incontinence, n (%)	
1m post-operatively	9 (37.5)
3m post-operatively	6 (25.0)
6m post-operatively	4 (16.7)
PSA 3m after surgery[+], n (%)	
<1 ng/ml	18 (78.3)
≥1 ng/nl	5 (21.7)
PSA 6m after surgery[+], n (%)	
<1 ng/ml	19 (82.6)
≥1 ng/nl	4 (17.4)
Positive surgical margins, n (%)	10 (41.7%)
Length of positive surgical margins (mm), median (IQR)	7 (2-9)

*Some of these data were collected as part of routine clinical care with follow-up to 6m after surgery

**21 individual complications were assessed as per Tewari et al.(26)

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***In one participant, Gleason grading was not possible due to treatment effect
+Missing data in one participant

Table 3. PSA, functional, and quality-of-life outcomes in study groups at three months post-randomisation

Variable	SOC (n=25)		Intervention (n=24)*	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
PSA**	2.6 (3.4)	1.2 (0.6-2.9)	1.5 (2.8)	0.4 (0.1-1.4)
IIEF-5 score**	9.0 (3.4)	5.0 (5.0-12.0)	7.7 (5.9)	5.0 (5.0-6.0)
No. of pads/24h	0 (0)	0 (0)	1.8 (0.9)	2 (1.0-2.0)
EQ-5D-5L descriptive score+	0.9 (0.2)	1.0 (0.8-1.0)	0.9 (0.2)	1.0 (0.8-1.0)
EQ-5D-5L VAS score++	82.7 (12.3	84.0 (75.0-90.0)	85.6 (13.5)	90.0 (77.5-96.5)

*At 3m post-randomisation, 17/25 (68.0%) participants had undergone surgery whereas the others in this arm had still only received SOC

**PSA had missing data in one SOC participant

***IIEF-5 score had missing data in three SOC and one intervention arm participants

+EQ5D score (UK) had missing data in four SOC and one intervention arm participant

+No. of lymph nodes metastases had missing data in five SOC and one intervention arm participant

++EQ5D VAS (visual analogue scale) score had missing data in two SOC and one intervention arm participant

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