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Combination Cytoreductive Surgery, Radiotherapy, or Ablation for De Novo Metastatic Prostate Cancer: The IP2-ATLANTA Internal Pilot, Phase 2, Randomised Controlled Trial

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Abstract

Background and objective: Cytoreduction of the primary prostate cancer, involved lymph nodes, and metastases may confer improved cancer control in de novo synchronous metastatic hormone-sensitive prostate cancer (mHSPC). Herein, we aimed to examine the safety and feasibility of novel cytoreductive therapies.

Methods: We report the internal pilot of IP2-ATLANTA, a phase 2, multicentre, three-arm, randomised controlled trial. Patients with histologically diagnosed mHSPC of performance status 0–2 were randomly allocated (1:1:1) to the standard of care control group or one of two intervention arms, and stratified by CHAARTED-defined metastatic burden, intent to treat pelvic lymph nodes, and use of docetaxel and stereotactic ablative body radiotherapy (SABR; three or fewer metastases). The minimally invasive ablative therapy (MIAT) arm included cytoreductive prostate ablation with pelvic lymph node

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Metastatic
Radiotherapy
Radical prostatectomy
Cryotherapy
Cytoreductive
Oligometastatic disease
Stereotactic ablative body radiotherapy
Metastasis-directed therapy

dissection (PLND), if involved, followed by SABR for metastases. The radical arm included treatment of the prostate with external beam radiotherapy along with pelvic lymph node radiotherapy (PLNRT), if involved, or cytoreductive radical prostatectomy with PLND, if involved, both followed by SABR for metastases. Systemic therapy was lifelong androgen deprivation therapy with docetaxel or an androgen receptor targeted agent. Repeat pretreatment prostate magnetic resonance imaging and biopsy were carried out. Pilot coprimary endpoints were complete pathological response, randomisation feasibility, and safety.

Key findings and limitations: Between April 26, 2019 and February 6, 2021, 108 patients met the eligibility criteria, of whom 81 underwent randomisation (75% [81/108, 95% confidence interval {CI} 65.7–82.8]), exceeding the target recruitment rate. The median follow-up period was 25 mo (interquartile range [IQR] 20–30), age 69.0 yr (IQR 62–74), and prostate-specific antigen 80.50 ng/ml (IQR 20.25–261.78). Metastatic burden was balanced (low 51%; high 49%). Performance status was 0 in 74/81 (91%) patients, with 69/81 (85%) receiving doublet systemic therapy. Cytoreductive interventions performed were as follows: MIAT ± PLND in 23/27 (85%), prostatectomy ± PLND in 5/26 (19%), and radiotherapy ± PLNRT in 14/26 (54%). Among patients with prostate tissue for histopathological assessment, a complete pathological response occurred in 11% (6/53 [95% CI 4.3–23.0]; 11% [3/27] MIAT; 12% [3/26] radical). Grade 3 or worse adverse events were reported in 18% (5/28) of the control group, 7% (2/26) of the MIAT group, and 15% (4/26) of the patients receiving radiotherapy or prostatectomy.

Conclusions and clinical implications: Randomisation to combination cytoreductive surgery, radiotherapy, and ablation was feasible. Cytoreductive treatment combinations were well tolerated and deserve further evaluation. The majority of patients still have viable residual prostate cancer after systemic therapy.

ADVANCING PRACTICE

What does this study add?

We assessed the feasibility, safety, and primary tumour response of sequential cytoreduction of the primary prostate cancer, involved lymph nodes, and metastases, compared with the current standard of care in patients with de novo synchronous metastatic hormone-sensitive prostate cancer. In the internal pilot of this phase 2, three-arm, randomised controlled trial, we reported that it was feasible and safe to recruit these patients and perform cytoreductive prostate ablation, radiotherapy, or surgery, in combination with metastasis-directed treatments, compared with the current standard of care. Furthermore, the majority of patients still had viable residual prostate cancer after systemic therapy alone. The presence of residual cancer in most patients following systemic therapy adds weight to the narrative that the cytoreduction of a residual viable primary tumour and established metastases may reduce the likelihood of lineage adaptation, disease progression to castrate resistance, and offer improved survival.

Clinical Relevance

The oncologic benefit of treating the primary has been demonstrated in large prospective trials in metastatic prostate cancer, mainly in low burden disease (STAMPEDE, PEACE-1). Whereas a high level of evidence exists for radiotherapy, further proofs are needed regarding surgery or other ablative options. The question of maximizing imaging-directed ablation by targeting all positive spots outside the prostate remains also open. The randomized trial aims to fuel the debate and to evaluate the safety of surgery (with or without lymph node dissection) and other ablative treatment (cryotherapy or HIFU) in addition to stereotactic body radiotherapy on metastases, in the context of intensified systemic (docetaxel or ARPI). Associate Editor: Guillaume Ploussard, MD.

Patient Summary

In this randomised controlled trial, we confirm that treatment of the prostate with ablation, surgery, or radiotherapy, with or without specialised radiotherapy to distant cancer deposits (metastases), is safe and randomising patients is feasible. The majority of patients (nine of ten) with advanced (metastatic) prostate cancer still had prostate cancer present within their prostate despite new drug therapies. This residual cancer within the prostate may be a target for additional treatments (cytoreduction). Longer-term outcomes will clarify which combination of treatments is effective for cancer control.

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1. Introduction

Overall survival in patients with de novo synchronous metastatic hormone-sensitive prostate cancer (mHSPC) has improved with the advances in systemic therapy. Consequently, there remains uncertainty about the added oncological benefit of treating the residual primary tumour, lymph nodes, and established distant metastases [1].

Studies have evaluated this approach with the STAMPEDE phase 3 trial reporting improved overall survival in a subgroup of low-burden disease patients treated using cytoreductive prostate radiotherapy (hazard ratio [HR] 0·64, 95% confidence interval [CI] 0.52–0.79, $p < 0.001$) [2]. However, in the PEACE-1 trial, overall survival was not influenced by the addition of cytoreductive prostate radiotherapy to the standard of care (SOC; androgen deprivation therapy [ADT] ± docetaxel) with abiraterone acetate (HR 0·98 [95.1% CI 0·74–1·28]; $p = 0·86$).

A single phase 2 randomised study (FUSCC-OMPCa) reported improved radiographic progression-free survival in patients with low-burden disease treated with cytoreductive radical prostatectomy (cRP) or prostate radiotherapy compared with those treated with ADT alone (not reached vs 40 mo; HR 0.43; 95% CI 0.27–0.70; $p = 0.001$) [3]. Combination approaches with distant metastasis-directed therapies (eg, stereotactic ablative body radiotherapy [SABR] or metastasectomy) or prostate ablative therapies (eg, cryotherapy or high-intensity focussed ultrasound [HIFU]) have been proposed with highly limited nonrandomised evidence [4–7].

Herein, we aimed to examine the safety and feasibility of novel sequential cytoreductive local prostate and metastasis-directed therapies. We also postulated that a viable prostate tumour for cytoreductive targeting would persist despite doublet systemic therapy escalation.

2. Methods

2.1. Study design and participants

We performed the internal pilot of a phase 2, prospective, multicentre, three-arm randomised controlled trial in 11 hospitals in the UK (Supplementary material). Research ethics committee approval was given by the Health Research Authority (Wales REC5; 19/WA0005) on January 22, 2019. Written informed consent was obtained, and the study was conducted in accordance with the International Conference on Harmonisation for Good Clinical Practice guidance and the Declaration of Helsinki. Eligible patients had histologically diagnosed de novo synchronous mHSPC confirmed on conventional imaging and of performance status 0–2. Patients were randomly allocated (1:1:1) to control group (SOC) or one of the two intervention arms and stratified by metastatic burden, intent to treat pelvic lymph nodes, use of docetaxel, or use of SABR for up to three metastases.

1. The minimally invasive ablative therapy (MIAT) arm included cytoreductive prostate ablation (cryotherapy or HIFU) with pelvic lymph node dissection (PLND), if involved, followed by SABR for metastases.
2. The radical arm included treatment of the prostate with external beam radiotherapy with pelvic lymph node radiotherapy (PLNRT), if involved, or cytoreductive robotic radical prostatectomy with PLND, if involved, both followed by SABR for metastases.

All patients had lifelong ADT with docetaxel or an androgen-receptor targeted agent (ARTA). Protocolled pretreatment prostate multiparametric magnetic resonance imaging (mpMRI) and biopsy (or whole-mount prostatectomy sample) were performed in the intervention arms at visits 3–4 (26–28 ± 12 wk) on study. Repeat biopsies were performed under general anaesthesia for MIAT patients and local anaesthesia for those undergoing radiotherapy using a standard operating procedure (Supplementary material).

All mpMRI scans of the prostate were reported by the local reporting uroradiologists, who all had at least 3 yr of reporting experience and access to prior imaging, clinical and trial treatment information, and current prostate-specific antigen (PSA) level. Baseline mpMRI was performed and reported in accordance with the technical requirements in Prostate Imaging Reporting and Data System version 2 (PI-RADSv2). A second post–systemic therapy mpMRI scan was performed in accordance with the technical requirements in PI-RADSv2, but a PI-RADS score could not be assigned due to systemic therapy effects [8]. Both mpMRI sequences included T1-weighted, T2-weighted, dynamic contrast-enhanced images, and multiple b values (for derivation of apparent diffusion coefficient maps) and a high b value of at least 1500. Magnetic resonance imaging (MRI) of the tumour, nodal stage, and prostate volume was reported descriptively.

Pathology was reported as per the local trial histopathologist, with 60% (19/32) of paired biopsy cases also undergoing a blinded central review by an expert uropathologist with more than 7 yr of experience (A.S.). A complete pathological response (independent of an MRI response) and maximum cancer core length changes were reported. Gleason grade group was not reported due to the effect of systemic therapy on accurate grade assignment [9].

All local prostate interventions were planned for week 32 on study, which permitted the completion of six cycles of docetaxel. Patients allocated to MIAT underwent cytoreductive prostate ablation with or without simultaneous robotic-assisted PLND. At the outset, the extent of total prostate volume cytoreduction following systemic therapy was unknown; thus, we permitted the use of cryotherapy or HIFU to accommodate all residual gland sizes. A dedicated MIAT quality assurance board monitored the treatments.

Patients allocated to the radical arm underwent either cRP, with or without PLND, or cytoreductive prostate radiotherapy, with or without PLNRT. The actual modality chosen in this arm was based on physician and patient preference, resectable nodal disease, as well as patient fitness. Trial surgeons were peer approved by a trial surgical quality assurance board. Predeclared, robotic-assisted PLND was performed as per local practice, and based on radiological presence of resectable nodal disease and patient fitness. Removal of the urethral catheter after cytoreductive MIAT

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or cRP occurred after a minimum period of 7 d during a hospital visit or at their GP surgery.

Cytoreductive prostate radiotherapy followed the principles of pelvic nodal treatment in the PIVOTALboost study, with variation to allow two dose and fractionation regimes (60 Gy in 20 fractions or 74–78 Gy in 37–39 fractions; Supplementary material) [10]. In patients with low-burden disease in both the intervention arms, SABR was permitted as per declaration prior to randomisation within 3 mo of local treatment. Dose and fractionation constraints were defined by the SABR UK consortium guidelines (v.6.1, 2019) or, if absent, the CORE study (v.2.0, 2018) [11,12]. Quality assurance for all radiotherapy components was performed by the independent Radiotherapy Trials Quality Assurance group.

If local prostate radiotherapy was planned at diagnosis for patients with low-burden disease, in the event they were randomised to the control group, this treatment was permitted as per the current NHS UK clinical guidelines [13]. Nodal or whole-pelvis radiotherapy and SABR were not permitted in the control group. Palliative prostate or bone radiotherapy for locoregional symptoms (eg, refractory haematuria and bone pain) was permitted.

Patient follow-up mirrored NHS standard practice; this included 12-weekly serum PSA tests in the 1st year. Clinical reviews occurred at weeks 0, 12, 26, 28, 32, 34, and 52.

2.2. Statistical analysis

The three internal pilot coprimary endpoints were the following: (1) complete pathological response, (2) feasibility, and (3) safety. Complete pathological response rate was defined as no residual cancer on prostate biopsy cores or whole-mount prostatectomy specimen (ypT0) [9,14]. Feasibility of trial design was reported by recruitment, randomisation, compliance, and withdrawal rates. Safety was defined as adverse events using the Common Terminology Criteria for Adverse Events (CTCAEv5.0) and patient-reported outcome measures.

All outcomes were analysed using all randomised patients according to the intention-to-treat principle, using a prespecified statistical analysis plan. To ascertain feasibility, we aimed to approach 80 patients over a 6-mo period to estimate a 33% (95% CI ± 10%) recruitment rate and an estimated 12.5% withdrawal rate. Data for safety, patient-reported outcome measures, symptomatic locoregional adverse events, and death were reported by the trial arm. The complete pathological response was calculated as a percentage (95% CI). All other analyses were exploratory. STATA (T, v.17.0; StataCorp LLC, College Station, TX, USA). The study was prospectively registered with ClinicalTrials.gov (NCT03763253).

3. Results

3.1. Baseline demographics and treatment exposure

Between April 26, 2019 and February 6 2021, 81 patients consented to participate in the study and were randomly allocated to the SOC (28/81; 35%), MIAT (27/81; 33%), and radical (26/81; 32%) trial arms (Fig. 1). The median follow-up period was 25 (IQR 20–30) mo. Groups were well balanced with respect to trial participants' baseline characteristics (Table 1).

The median age and PSA were 69.0 yr (IQR 62–74) and 80.5 ng/ml (IQR 20.3–261.8), respectively. World Health Organization performance status of 0 was reported in 74 of 81 (91%) patients. Participants underwent a prostate biopsy prior to randomisation and had prostate adenocarcinoma without the presence of variant pathology in all cases. Overall tumour (T) stage at randomisation was equal across all trial arms (T3 40/81 [49%]; T4 31/81 [38%]). Overall nodal (N) stage at randomisation was also well balanced across all trial arms, with a predominance towards pelvic lymph node metastases in the majority of patients (N0 24/81 [30%]; N1 47/81 [58%]). Predominantly bone metastases (M1b 46/81 [57%]) with CHAARTED-defined metastatic burden well balanced (low 41/81 [51%] vs high 40/81 [49%]). All patients received lifelong ADT, and 69 of 81 (85%) received doublet systemic therapy.

3.2. Primary tumour response

Overall, 49 of 53 (92%) intervention arm participants underwent the protocol repeat mpMRI following systemic therapy but prior to local prostate treatment. MRI prostate volume reduced from a mean of 48 cc (standard deviation [SD] 20.16) to 26 cc (SD 13.86) after systemic therapy ($p < 0.0001$ [95% CI −15.04 to −30.1]). There was a reduction in MRI T4 (45% vs 23%; $p < 0.01$) and N1 (72% vs 40%; $p < 0.05$) stages before and after systemic therapy.

Overall, 32 of 53 (60% [95% CI 46.0–73.6]) second prostate biopsies were performed following systemic therapy (Table 2). In the MIAT arm, 19 of 27 (70% [95% CI 49.8–86.3]) participants underwent a second prostate biopsy. Reasons for not performing a second biopsy were as follows: of 27 patients, one (4%) died from prostate cancer prior to biopsy, one (4%) withdrew consent for second biopsy, three (11%) withdrew from the study, and one (4%) had protocol deviation. In the radical arm, 13 of 26 (50% [95% CI 29.9–70.0]) participants underwent a second biopsy. Reasons for not performing a second biopsy were as follows: of 26 patients, three (12%) withdrew consent for a second biopsy, eight (30%) withdrew consent for trial intervention, and two (8%) were unfit for repeat biopsy/trial treatment.

The median durations of systemic therapy prior to the second biopsy in the MIAT and radical arms were 234 d (IQR 205–336) and 259 days (IQR 189–286), respectively. The median PSA levels prior to the second biopsy were 0.19 ng/ml (IQR 0.05–0.74) and 0.16 ng/ml (IQR 0.03–3.88), respectively.

The complete pathological response rate was reported as 11% (6/53 [95% CI 4.3–23.0]). This was equal in both trial arms (11% MIAT vs 12% radical) and remained unchanged on central blinded review (Supplementary material). Thus, 26 of 32 (81%) trial participants had evidence of residual prostate adenocarcinoma. In all six patients with a complete pathological response, a gonadotrophin-releasing hormone agonist was commenced in conjunction with either docetaxel chemotherapy (2/6; 33%) or enzalutamide (4/6; 67%).

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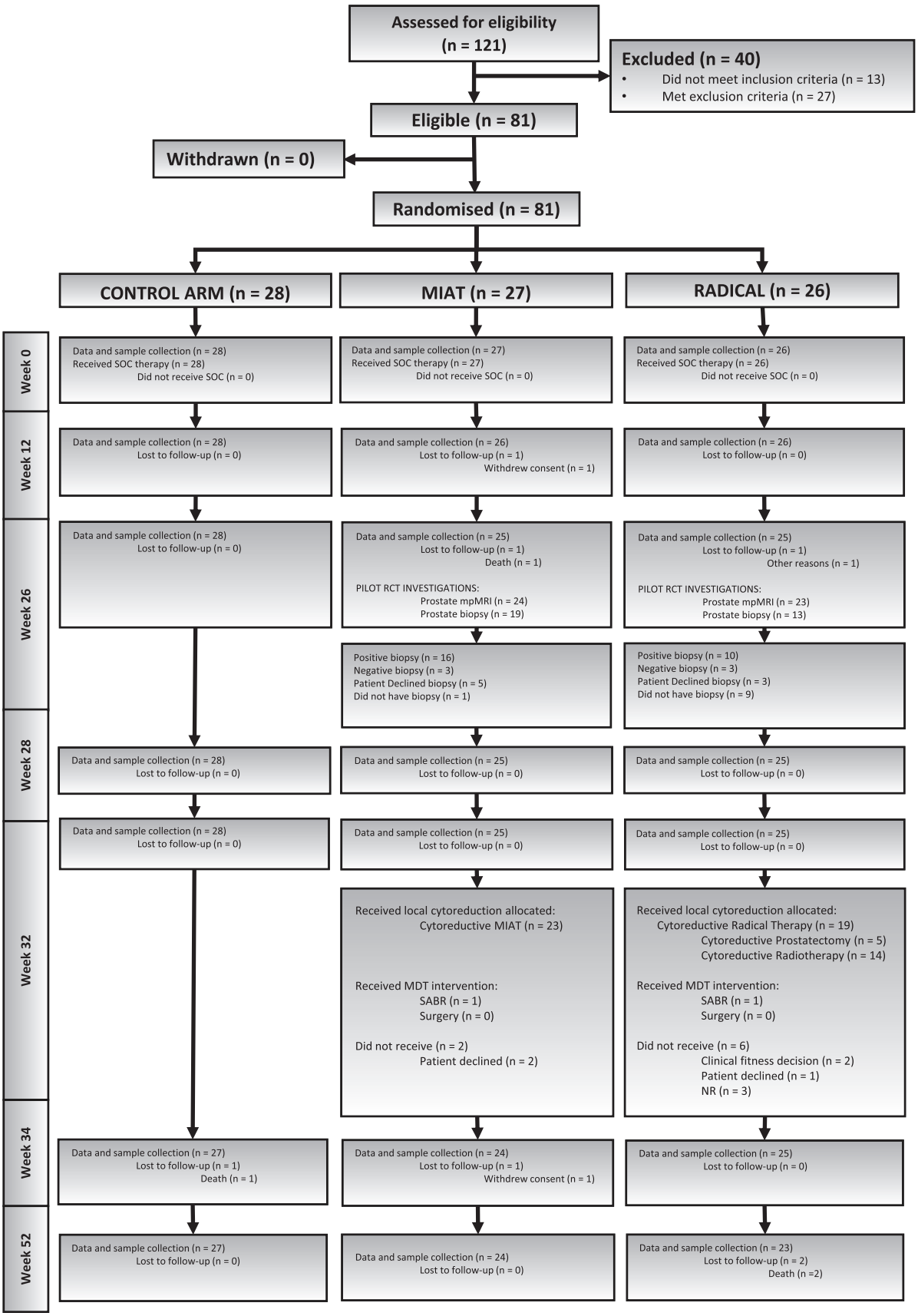

Fig. 1 – Trial profile. CONSORT diagram for the IP2-ATLANTA internal pilot RCT patients. Week 32 = local cytoreductive treatment; Week 34 = MDT. cRP = cytoreductive radical prostatectomy; MDT = metastasis-directed therapy; MIAT = minimally invasive ablative therapy; mpMRI = multiparametric magnetic resonance imaging; NR = not reported; RCT = randomised controlled trial; SABR = stereotactic ablative body radiotherapy; SOC = standard of care.

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Table 1 – Baseline characteristics of participants by arm (presented as median [IQR] unless specified)

Characteristic	SOC (n = 28)	MIAT (n = 27)	Radical (n = 26)
Age	69.5 (61.0–74.0)	67.0 (61.0–75.0)	71.5 (65.0–74.0)
Ethnicity, n (%)			
White	22 (79)	15 (57)	15 (58)
Mixed	0 (0)	0 (0)	0 (0)
Asian	1 (4)	0 (0.)	0 (0)
Black	1 (4)	1 (4)	3 (12)
Index of Multiple Deprivation Decile, n (%)			
1	0 (0)	1 (4)	1 (4)
2	1 (4)	4 (15)	0 (0)
3	1 (4)	1 (4)	5 (19)
4	4 (14)	3 (11)	5 (19)
5	4 (14)	3 (11)	3 (12)
6	2 (7)	2 (7)	3 (12)
7	2 (7)	1 (4)	3 (12)
8	3 (11)	4 (15)	2 (8)
9	6 (21)	2 (7)	1 (4)
10	3 (11)	6 (22)	3 (12)
BMI	26.2 (23.9–28.0)	25.8 (24.2–28.9)	27.5 (25.3–29.4)
Performance status, n (%)			
Grade 0	26 (93)	23 (85)	25 (96)
Grade 1	2 (7)	3 (11)	1 (4)
Grade 2	0 (0)	0 (0)	0 (0)
T stage at randomisation, n (%)			
T0	0 (0)	0 (0)	0 (0)
T1	0 (0)	0 (0)	0 (0)
T2	0 (0)	0 (0)	0 (0)
T3	13 (46)	15 (56)	12 (46)
T4	10 (36)	10 (37)	11 (42)
Tx	2 (7)	0 (0)	0 (0)
N stage at randomisation, n (%)			
N0	9 (32)	7 (26)	8 (31)
N1	16 (57)	16 (59)	15 (58)
Nx	1 (4)	1 (4)	0 (0)
M stage at randomisation, n (%)			
M1a	4 (14)	3 (11)	3 (12)
M1b	18 (64)	16 (59)	12 (46)
M1c	1 (4)	0 (0)	0 (0)
M1 (any)– not specified	5 (18)	8 (30)	11 (42)
Metastatic burden, n (%)			
High	13 (46)	14 (52)	13 (50)
Low	15 (54)	13 (48)	13 (50)
Gleason grade group/ISUP, n (%)			
≤3 + 3/ISUP 1	1 (4)	0 (0)	0 (0)
3 + 4/ISUP 2	1 (4)	0 (0)	3 (12)
4 + 3/ISUP 3	1 (4)	0 (0)	3 (12)
4 + 4, 3 + 5, 5 + 3/ISUP 4	4 (14)	7 (26)	7 (27)
4 + 5, 5 + 4, 5 + 5/ISUP 5	20 (71)	20 (74)	13 (50)
Adenocarcinoma with treatment effect, n (%)	1 (4)	0 (0)	0 (0)
Maximum cancer core length (mm)	13.0 (6.0–9.0)	14.0 (10.5–15.0)	14.0 (10.5–15.6)
Median PSA at diagnosis (ng/ml)	47.4 (14.3–202.0)	110.0 (36.0–419.6)	62.0 (17.4–258.6)
Type 2 diabetes, n (%)	3 (11)	4 (15)	3 (12)
Ischaemic heart disease, n (%)	4 (14)	3 (11)	4 (15)
Stroke, n (%)	0 (0)	0 (0)	0 (0)
Peripheral vascular disease, n (%)	0 (0)	0 (0)	0 (0)
Benign prostatic enlargement, n (%)	2 (7)	1 (4)	3 (12)
COPD, n (%)	0 (0)	0 (0)	1 (4)
Androgen deprivation treatment, n (%)			
Antiandrogen	1 (4)	0 (0)	0 (0)
LHRH agonist	27 (97)	25 (93)	26 (100)
LHRH antagonist	0 (0)	1 (4)	0 (0)
Second agent, n (%)			
Docetaxel	19 (68)	8 (30)	13 (50)
Enzalutamide	6 (21)	18 (67)	8 (31)
Abiraterone acetate	1 (4)	0 (0)	2 (8)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; IMD = Index of Multiple Deprivation Decile (England and Wales); IQR = interquartile range; ISUP = International Society of Urological Pathology; LHRH = luteinising hormone-releasing hormone; M = metastasis; Metastatic burden = metastatic disease as per CHAARTED definition "high" versus "low"; MIAT = minimally invasive ablative therapy; N = nodes; PSA = prostate-specific antigen; SOC = standard of care; T = tumour.

Following data, presented as n (%) in the SOC, MIAT, and radical arms, respectively, were unavailable: ethnicity (4 [14%], 11 [41%], and 8 [31%]), IMD (2 [7%], 0 [0%], and 0 [0%]), BMI (3 [11%], 7 [26%], and 4 [15%]), performance (3 [11%], 7 [26%], and 4 [15%]), T stage (3 [11%], 2 [7%], and 3 [12%]), N stage (2 [7%], 3 [11%], and 3 [12%]), cancer core length (1 [4%], 1 [4%], and 2 [8%]), PSA (3 [11%], 0 [0%], and 4 [15%]), androgen (0 [0%], 1 [4%], and 0 [0%]), and second agent (0 [0%], 1 [4%], and 0 [0%]).

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Table 2 – Results of prostate biopsy after standard systemic therapy

	MIAT		Radical	
	n (%)	95% CI	*n* (%)	95% CI
Second prostate biopsies following systemic therapy				
Biopsy performed, *n* (%)	19 (70)	–	13 (50)	–
Patient declined biopsy, *n* (%)	1 (4)	–	3 (12)	–
Complete pathological response				
Complete pathological response, *n* (%)	3 (11)	(2.4%–29.2%)	3 (12)	(2.5%–30.2%)

CI = confidence interval; MIAT = minimally invasive ablative therapy.
The table includes patients who were randomised to the intervention arms only (MIAT and radical). The control group did not receive a second prostate biopsy at 6 mo. All histology in the MIAT arm was acquired via a transperineal prostate biopsy. In the radical arm, radical repeat biopsy histology was acquired via a transperineal prostate biopsy in 8/13 (62%) and via a review of whole mount prostatectomy samples in 5/13 (39%) patients.

3.3. *Feasibility*

The recruitment rate exceeded the target at 75% (81/108 [95 CI% 65.8–82.8). The withdrawal rate was 9% (7/81), below the predicted rate. In the MIAT arm, 23 of 27 (85%) patients received their allocated intervention. Of 27 patients, six (22%) received cryotherapy with PLND, 11 (41%) received cryotherapy alone, and six (22%) received HIFU alone. SABR was performed in a single patient (1/27; 4%) at the time of analysis. The median operating time was 110.8 min (IQR 90.5–188.5), with a median of 14.5 (IQR 8.2–22.3) retrieved nodes and pN1 being present in five of six (83%) patients.

In the radical arm, 19 of 26 (73%) patients received trial interventions. Of 26 patients, cRP was performed in five (19%), with PLND in two (8%), cytoreductive radiotherapy in 14 (54%), and simultaneous PLNRT in eight (30%). SABR was performed in a single patient at the time of analysis, in whom cRP was performed (1/26; 4%). The median operating time and blood loss were reported as 126 min (IQR 118–156) and 150 ml (IQR 87.5–250.0), respectively. A median of 15.5 (IQR 9.8–21.3) nodes were retrieved, and pN1 was present in zero of two (0%) patients.

3.4. *Safety, adverse events, and patient-reported outcome measures*

There were no intraoperative complications, abandoned surgical procedures, or blood transfusions. Death on study occurred in 12 of 81 patients (15%). Death from prostate cancer was reported in six (21%) patients in the SOC arm, two (8%) in the MIAT arm, and three (12%) in the radical arm (Table 3).

Grade 3 (CTCAE) adverse events occurred in 3/28 (11%) patients in the SOC arm, 2/26 (8%) patients in the MIAT arm, and 4/26 (15%) patients in the radical arm. Grade 4 adverse events occurred exclusively in patients in the SOC arm (2/28; 7%). No trial treatment adverse events resulted in the death of a participant.

The incidence of symptomatic locoregional adverse events and deaths is presented in Table 3. Emergency suprapubic catheter insertion and transurethral resection of the prostate occurred infrequently, and events were confined to the SOC arm: 1/28 (4%) and 1/28 (4%) of the control group participants, respectively.

When visit 7 (Week 52) was compared with baseline, "any increase in urinary pad usage" was reported in 4% of the SOC arm, 9% of the MIAT arm, and 11% of the radical arm. In both treatment arms, mean EPIC-Urinary Domain summary score improved following induction of systemic therapy (Supplementary Fig. 2). When visit 7 was compared with baseline, the maximum improvements in the mean EPIC-Urinary Domain summary scores were reported in participants in the MIAT arm (+6.9; SD 13.7). Full patient-reported outcome measures are available in the Supplementary material.

Table 3 – Incidence of symptomatic locoregional adverse events and death (presented as frequency [percentage])

Event	SOC (*n* = 28)	MIAT (*n* = 27)	Radical (*n* = 26)
Urinary retention requiring insertion of indwelling urethral catheter or CISC, *n* (%)	1 (4)	2 (7)	1 (4)
Emergency suprapubic catheter insertion, *n* (%)	1 (4)	0 (0)	0 (0)
Transurethral resection of the prostate, *n* (%)	1 (4)	0 (0)	0 (0)
Drainage of lymphocele, *n* (%)	0 (0)	0 (0)	0 (0)
Rectal injury or rectourethral fistula formation, *n* (%)	0 (0)	0 (0)	0 (0)
Genital oedema, *n* (%)	0 (0)	2 (7)	1 (4)
Nephrostomy insertion, *n* (%)	0 (0)	0 (0)	0 (0)
Haematuria requiring intervention, *n* (%)	0 (0)	1 (4)	0 (0)
Urinary tract infection, *n* (%)	0 (0)	0 (0)	3 (12)
Any (grade ≥1) lower urinary tract symptoms, *n* (%)	4 (14)	3 (11)	6 (23)
Any grade ≥3 adverse event, *n* (%)			
All follow-up	5 (18)	2 (7)	4 (15)
Visit 1 to visit 7 (week 0 to week 52)	1 (4)	0 (0)	2 (4)
Death from prostate cancer, *n* (%)			
All follow-up	6 (21)	2 [a] (7)	3 [b] (12)
Visit 1 to visit 7 (week 0 to week 52)	1 (4)	1 [a] (4)	2 [b] (8)

CISC = clean intermittent self-catheterisation; MIAT = minimally invasive ablative therapy; SOC = standard of care.
[a] In a single patient, trial intervention was not performed due to death from prostate cancer prior to planned MIAT.
[b] In two patients, trial intervention was not performed due to clinical deterioration from prostate cancer; both patients died prior to visit 7. Note that a single patient died on study due to infective exacerbation of interstitial lung disease.

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4. Discussion

To our knowledge, this is the first multicentre randomised study to demonstrate the feasibility of allocating patients with de novo synchronous mHSPC to a combination of contemporary systemic therapy, followed by cytoreductive prostate ablation or prostatectomy or radiotherapy, with metastasis-directed therapies, against the SOC alone. We reported low rates of complete pathological response of the primary tumour to ADT with docetaxel or ARTA combination therapy. We confirmed higher than expected patient acceptance rate of consent and randomisation. All trial intervention arm treatments had an acceptable safety and adverse event profile.

Baseline characteristics (eg, International Society of Urological Pathology grade group and metastatic burden) were comparable with those of the STAMPEDE Arm-H trial [2]. Our study recruitment rate (75%) is in keeping with the TRoMBone trial (72.8%) [15]. Noncompliance to radical treatment was low (4%) in the radical arm and was comparable with that reported in cytoreductive surgery trials (2.0–4.0%) [3,6,7,15]. To the authors' knowledge, the acceptability of randomisation to cytoreductive prostate ablation has not been reported previously in the literature. Two (8%) patients did not comply with cytoreductive prostate ablation.

Following the commencement of IP2-ATLANTA, the Southwest Oncology Group 1802 randomised study opened (NCT03678025), recruiting patients with all-burden disease to either systemic therapy or systemic therapy with surgery or radiotherapy [16]. Our study demonstrates the acceptable feasibility of a pragmatic trial design that integrates cytoreductive surgery alongside radiotherapy as a radical option [17].

Limited reporting of a complete pathological response in mHSPC exists [3,18,19]. The biological significance of residual intraprostatic disease following systemic therapy in mHSPC is uncertain [20]. It has been reported that highly active systemic anticancer therapies drive cancer cells to evolve to form resistant cell lineages, so primary tumour cytoreduction might restrict this lineage crisis [20]. Our response rate (11.1%) was higher than the rate of 2.3% (2/85) following ADT monotherapy for mHSPC and the rate of 4.3% (1/23) reported in a neoadjuvant study combining enzalutamide with ADT in the high-risk nonmetastatic setting [3,18]. However, it is lower than the 30% (15/50) response rate reported when triplet therapy with neoadjuvant enzalutamide, leuprolide, and abiraterone was used prior to radical prostatectomy for nonmetastatic disease [21].

These differences may be explained by our study's histological reclassification using transperineal prostate biopsy with mpMRI targeting for patients undergoing cytoreductive radiotherapy or ablation. Whilst all biopsies followed the standard operative procedures, and MRI with transperineal prostate biopsy has good concordance in high-grade disease and in those treated with neoadjuvant ADT, it is possible that residual foci of prostate cancer may have been missed when compared with whole-mount prostatectomy specimens [22,23]. Given the nature of the trial interventions (ie, radiotherapy), this was the only viable method of histological reclassification. In addition, compliance in the radical arm in patients planned for radiotherapy was low, suggesting that it may not be a feasible strategy in clinical practice.

Despite the inclusion of cT4 disease in almost half of patients at baseline, we did not report any intraoperative rectal injury or rectourethral fistula formation. In contrast, to 1.2–4.0% rectal injury was reported in prior cytoreductive surgery trials [3,6,7,15]. In these studies, the use of docetaxel or ARTAs was highly limited (0–45.8%), compared with over 90% in the intervention arms of our study [3,6,7,15]. Cytoreduction achieved from doublet systemic therapy agents, confirmed on serial MRI in this trial, may have been protective against rectal injury.

Urinary incontinence following cytoreductive interventions is an on-going key concern for patients and clinicians [17]. Reassuringly, our incontinence rates were similar to those observed in patients undergoing our trial treatments for localised prostate cancer [24–26]. At 52-wk follow-up, approximately 10% of patients reported an increase in urinary pad usage in the intervention arms compared with 4% in the control arm. The use of more than one pad per day was not reported in patients undergoing prostate ablation but occurred in 10% of patients in the radical arm. This is comparable with the incontinence rates (8.2–16.7%) reported in prior cytoreductive prostatectomy phase 2 trials [3,15].

There is limited comparable nonrandomised evidence for cytoreductive prostate ablation in mHSPC [4,27]. A single prospective study of cytoreductive whole-gland cryotherapy has been reported previously [4]. The pilot study (NCT02489357) by Ross and colleagues [4] used the combination of pembrolizumab and ADT and reported that 11 of 12 patients had benign or clinically insignificant prostate cancer (Gleason 3 + 3 = 6) on post-treatment prostate biopsies, thus confirming adequate primary tumour response in mHSPC. In this study, five of 12 (42%) patients met the primary endpoint of a PSA level of <0.6 ng/ml at 1 yr, and the median progression-free survival was 14 mo. Wang and colleagues' [27] propensity-matched analysis (n = 54) of ADT with cytoreductive whole-gland prostate cryotherapy when compared with ADT alone reported a reduction in the risk of failure-free survival by 45.8% in favour of the cytoreductive cryotherapy group (HR = 0.542 [95% CI 0.329–0.893]; p = 0.016).

The IP2-ATLANTA full study evaluates progression-free survival in 432 patients and has completed recruitment. Although we report on a multicentre randomised controlled trial, there are a number of limitations. Histological reclassification with transperineal prostate biopsy for patients undergoing radiotherapy or ablation may have overestimated the complete pathological response rate. Our study results cannot be extrapolated to patients with metastatic burdens defined by prostate-specific membrane antigen positron emission tomography/computed tomography and those with metastatic disease visible only on molecular imaging [28].

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5. Conclusions

Randomisation to combination cytoreductive surgery, radiotherapy, and ablation was feasible. Cytoreductive treatment combinations were well tolerated and deserve further evaluation. The majority of patients still have viable residual prostate cancer after doublet systemic therapy.

***Author contributions*:** Martin J. Connor had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Basak, Heath Horan, Khoo, Khoubehi, Mangar, McGrath, Rai, Sarwar, Thippu Jayaprakash, Winkler, Dudderidge.
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***Data sharing statement*:** Permission from the executive/writing committee is necessary prior to disclosing any information relative to this study outside of the trial steering committee. Any request by site investigators or other collaborators to access the study dataset must be reviewed formally by the trial management group.

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Appendix A. Supplementary data

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