Original Article

Multicentre, prospective study on local treatment of metastatic prostate cancer (LoMP study)

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Objectives

To investigate the role of cytoreductive radical prostatectomy in addition to standard of care for patients with newly diagnosed metastatic prostate cancer.

Materials and Methods

This multicentre, prospective study included asymptomatic patients from 2014 to 2018 (NCT02138721). Cytoreductive radical prostatectomy was offered to all fit patients with resectable tumours, resulting in 40 patients. Standard of care was administered to 40 patients who were ineligible or unwilling to undergo surgery. The primary endpoint was castration resistant cancer-free survival at the time point of ≥50% events. The secondary endpoint was local event-free survival. Kaplan–Meier and Cox regression analyses with propensity-score analysis were applied.

Results

After a median (quartiles) follow-up of 35 (24–47) months, 42 patients became castration-resistant or died. The median castration resistant cancer-free survival was 53 (95% confidence interval [CI] 14–92) vs 21 (95% CI 15–27) months for cytoreductive radical prostatectomy compared to standard of care ($P = 0.017$). The 3-year estimates for local event-free survival were 83% (95% CI 71–95) vs 59% (95% CI 51–67) for cytoreductive radical prostatectomy compared to standard of care ($P = 0.012$). However, treatment group showed no significance in the multivariable models for castration resistant cancer-free survival ($P = 0.5$) or local event-free survival ($P = 0.3$), adjusted for propensity-score analysis. Complications were similar to the non-metastatic setting. Patients undergoing surgery were younger, with lower baseline prostate-specific antigen levels, alkaline phosphatase levels and metastatic burden.

Conclusion

The present LoMP study was unable to show a difference between the two inclusion groups regarding castration resistant cancer-free survival for asymptomatic patients with newly diagnosed metastatic prostate cancer. These results validate previous evidence that, in well-selected and informed patients, cytoreductive radical prostatectomy is feasible and safe, with corresponding continence rates compared to the non-metastatic, high-risk setting. Whether cytoreductive radical prostatectomy could be a valuable option to achieve good local palliation needs to be further researched. Overall, the role of cytoreductive radical prostatectomy needs to be further explored in randomized studies to correct for potential bias.

Keywords

cytoreduction, hormone-naïve, metastasis, newly diagnosed, progression-free survival, prostatic neoplasms, prostatectomy, #PCSM, #ProstateCancer

Introduction

Treatment of patients with metastatic hormone-naive prostate cancer (mHNPC) has changed noticeably in recent years. Since 1941, androgen deprivation therapy (ADT) had been the cornerstone of metastatic prostate cancer treatment [1,2]. However, given the rather disappointing outcomes observed with ADT only (median overall survival [OS] of 42 months) [3], interest emerged in alternative treatments options, setting a new era in motion. The CHAARTED [4] and STAMPEDE trials [5] led the way after proving benefit with regard to both castration resistant cancer-free survival and OS in patients treated by combining docetaxel and ADT. Subsequently, the LATITUDE [6] and STAMPEDE trials [7] demonstrated similar oncological advantages when concomitantly administering abiraterone acetate plus prednisone to ADT.

Currently, the impact of local therapy is a much discussed topic in this setting. Treatment of the primary tumour in patients with metastatic disease has already been established for numerous types of tumours. Kaplan et al. [8] introduced the 'premetastatic niche' theory, implying that the primary tumour can act as the predominant source of metastasis development and growth through circulating tumour cells, cytokines and neoantigens. Reducing the overall tumour burden and re-seeding of the primary tumour is plausibly linked to lower risk of local complications, improved response to systemic therapies, and even prolonged survival [9–11].

In 2018, prostate radiotherapy was implemented in the European Association of Urology (EAU) guidelines after the STAMPEDE trial showed a survival benefit for patients with low- volume mHNPC (low-volume disease [LVD]) [12]. Recently published meta-analyses, although currently comprising only retrospective studies, suggest a potential clinical benefit for cytoreductive radical prostatectomy [13,14]. To date, however, surgery has been reserved for patients with non-metastatic disease [15].

The present multicentre, prospective local treatment of metastatic prostate cancer (LoMP) study aimed to investigate the role of cytoreductive radical prostatectomy in addition to standard of care for patients with newly diagnosed mHNPC. We provide an analysis at the time point of ≥50% of castration resistant prostate cancer-free survival events.

Materials and Methods

From May 2014 to January 2018, 80 adult males with newly diagnosed mHNPC were included in the LoMP study after signing written informed consent (ClinicalTrials.gov NCT02138721 and Belgian registration No. B670201420709). Metastatic prostate cancer was defined as histologically confirmed prostate cancer with ≥1 metastasis after staging by thoraco-abdominopelvic CT and bone scintigraphy at diagnosis. Further investigations were performed in case of equivocal findings, i.e. full-spine multiparametric MRI, choline/prostate-specific membrane antigen positron emission tomography-CT and/or biopsy, if technically feasible. Exclusion criteria were metastatic symptoms, metastatic recurrence after local curative treatment, previous systemic or local prostate cancer treatment and N1M0 stage.

To determine clinical or iconographical T-stage, DRE, TRUS and/or multiparametric MRI of the prostate were used. Tumour grade group was assessed using the 2014 International Society of Urological Pathology grading system [16]. Patient follow-up occurred at 3-month intervals with history taking, physical examination and PSA assessment. In case of clinical deterioration, symptom development, and/or PSA progression, restaging was performed.

Cytoreductive radical prostatectomy was offered in case of: no symptoms related to metastatic lesions; patient fit to undergo cytoreductive radical prostatectomy (assessed by treating physician and/or anaesthesiologist); and a resectable tumour. Operability was assessed using DRE and multiparametric MRI. In case of clinical or iconographic T4 stage disease, the patient was deemed inoperable. Cytoreductive radical prostatectomy was performed using a non-nerve-sparing approach, with extended pelvic lymph node dissection. The first postoperative PSA was measured after 4–6 weeks (before ADT initiation). At 3 months, postoperative complications were assessed using Clavien–Dindo classification and, at 1 year, urinary continence (≤1 safety pad) was assessed as a patient-reported outcome measure.

Patients who were ineligible or unwilling to undergo cytoreductive radical prostatectomy received standard of care only. The cornerstone of standard of care was initiation of ADT, which could be started at the discretion of the treating physician, but was imperative in case of metastatic symptoms or substantial PSA progression (PSA >50 ng/mL and PSA doubling time <6 months). Initiation of additional standard of care treatments was at the discretion of the treating physician after multidisciplinary oncological consultation and according the contemporary EAU guidelines [17]. Docetaxel could be added to ADT from 2015 and abiraterone acetate from 2018, to eligible patients. No patients underwent prostate radiotherapy.

High-volume mHNPC (high-volume disease [HVD]) was defined as presence of visceral metastasis or ≥4 bone metastases with ≥1 beyond the vertebral bodies and pelvis [4]. Elevated alkaline phosphatase (ALP) was defined as any value exceeding the normal reference upper limit value of 120 U/L.

Our primary endpoint was castration resistant cancer-free survival, which was defined as the time between histological diagnosis and development of castration resistant prostate cancer-free survival. Castration resistant prostate cancer-free survival was defined according to the contemporary EAU guidelines [17]. Secondary endpoints were local event-free survival, describing the characteristics of patients with newly

diagnosed mHNPC and performing a final safety analysis for cytoreductive radical prostatectomy. An LE was defined as any LE related to disease progression and any local complication due to cytoreductive radical prostatectomy necessitating invasive treatment.

Statistical analysis was performed using SPSS 26.0™ with two sided *P* values <0.05 indicating statistical significance. Continuous and categorical variables were compared using the independent sample *t*- or Mann–Whitney *U*- and chi-squared or Fisher's exact tests, respectively. The Kaplan–Meier method with log-rank statistics was applied to assess survival. Patients were censored at the last date of known castration resistant prostate cancer-free survival-free status. Cox regression analyses were performed to identify prognostic risk factors adjusting for the baseline patient and tumour characteristics. First, all relevant variables (treatment group, age, performance status, baseline PSA level, clinical T and N stage, ALP level and metastatic volume) were separately analysed. Next, only the significant variables were included in the multivariable regression model. Since metastatic volume comprises M-stage and number of bone metastases, the latter two variables were not separately included in the model. To minimize the risk of model overfitting and to adjust the treatment effect for baseline imbalances, a propensity-score analysis was added to create a more robust Cox regression model.

Ethical Approval

This study was approved by the local ethical committee of Ghent (Belgian registration number B670201420709). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results

In total, 40 patients underwent cytoreductive radical prostatectomy and 40 patients standard of care only, of whom nine (23%) were unwilling and 31 (78%) ineligible to undergo cytoreductive radical prostatectomy. Ineligibility for cytoreductive radical prostatectomy comprised 16 patients who were unfit for surgery and 15 patients with non-resectable tumours.

Compared to standard of care, patients undergoing cytoreductive radical prostatectomy were younger (median 66 vs 76 years; *P* < 0.001), had a lower baseline PSA level (median 19.6 vs 166.0 ng/mL; *P* = 0.001), were less likely to have HVD (20% vs 65%; *P* < 0.001) and elevated ALP (0% vs 35%; *P* < 0.001), and had a higher number of bone metastases (2 vs 8; *P* = 0.001). However, tumour grade group (WHO ≥4 in 85% vs 83%; *P* = 0.8), T stage (≥T3–4 in 70% vs 83%; *P* = 0.2), N stage

(N1 in 70% vs 75%; *P* = 0.6) and Eastern Cooperative Oncology Group performance status (≥2 in 2.5% vs 18%; *P* = 0.057) were not significantly different. Patient and tumour characteristics are summarized in Table 1.

For cytoreductive radical prostatectomy, the median (quartiles) operation time was 205 (165–220) min, estimated blood loss 250 (150–325) mL and hospitalization 4 (3–5) days. There were no peri-operative complications. One year after undergoing cytoreductive radical prostatectomy, 31 patients (79%) were continent. Up to 3 months after cytoreductive radical prostatectomy, 14 (35%) and four (10%) patients, respectively, experienced a grade 1 and 2 complication, and two patients (5.0%) experienced a grade 3 complication. No grade 4 or 5 complications were observed. All surgical characteristics and morbidities are presented in Table 2.

After a median (quartiles) follow-up of 35 (24–47) months, 42 patients reached castration resistant prostate cancer-free survival stage or died (25 out of 80 patients died). As illustrated in Fig. 1A, the median castration resistant cancer-free survival was 53 (95% CI 14–92) vs 21 months (95% CI 15–27), with 3-year survival estimates of 59% (95% CI 43–74) vs 40% (95% CI 25–55) for cytoreductive radical prostatectomy compared to standard of care (*P* = 0.017), respectively. However, in the multivariable model, inclusion group (cytoreductive radical prostatectomy vs standard of care) showed no significance (*P* = 0.9). This was confirmed when adjusting for the propensity-score analysis (hazard ratio [HR] 0.73 [95% CI 0.29–1.83]; *P* = 0.5), Performance status (*P* = 0.006), HVD (*P* = 0.050) and elevated ALP (*P* = 0.024) were identified as independent risk factors for castration resistant cancer-free survival after adjusting for the baseline patient and tumour characteristics (Table 3).

Only nine LEs occurred in seven patients (18%) who received cytoreductive radical prostatectomy compared to 16 LEs in 15 patients (38%) in the standard of care group (*P* = 0.045). The 3-year survival estimates for local event-free survival were 83% (95% CI 71–95) vs 59% (95% CI 51–67; *P* = 0.012), respectively (Fig. 1B). However, in the multivariable model, inclusion group (cytoreductive radical prostatectomy vs standard of care) showed no significance (*P* = 0.7). This was confirmed when adjusting for the propensity-score analysis (HR 0.47 [95% CI 0.10–2.13]; *P* = 0.3). Baseline PSA (*P* = 0.024) and elevated ALP levels (*P* = 0.044) were identified as independent risk factors for castration resistant cancer-free survival after adjusting for the baseline patient and tumour characteristics (Table 3).

In the cytoreductive radical prostatectomy group, four patients (10%) experienced a local complication requiring surgery. Three patients (7.5%) reported BOO requiring intervention and two patients (5.0%) reported ureteric obstruction requiring JJ stenting compared to 15 patients (38%) and one patient (2.5%), respectively, in the standard of care group. All LEs are reported in Table 4.

Table 1 Patient and tumour characteristics.

	Total *n* = 80	Cytoreductive radical prostatectomy group *n* = 40	Standard of care group *n* = 40	*P*
Median (quartiles) follow-up, months	35 (24–47)	38 (32–50)	31 (15–46)	0.041
Median (quartiles) age, years	70 (63–78)	66 (59–73)	76 (69–83)	<0.001
ECOG performance status, *n* (%)				
0–1	72 (90)	39 (98)	33 (83)	0.057
2–4	8 (10)	1 (2.5)	7 (18)	
Median (quartiles) PSA, ng/mL	42.8 (19.2–230.4)	19.6 (11.2–45.2)	166.0 (37.1–592.7)	0.001
Alkaline phosphatase, *n* (%)				
Elevated*	14 (18)	0 (0)	14 (35)	<0.001
Missing	17 (21)	9 (23)	8 (20)	
Biopsy grade group, *n* (%)				
1–3	11 (14)	6 (15)	5 (13)	0.8
4–5	67 (84)	34 (85)	33 (83)	
Missing[†]	2 (2.5)	0 (0)	2 (5.0)	
T-stage, *n* (%)				
1–2	19 (24)	12 (30)	7 (18)	0.2
3–4	61 (76)	28 (70)	33 (83)	
N-stage, *n* (%)				
1	58 (73)	28 (70)	30 (75)	0.6
M-stage, *n* (%)				
1a	22 (28)	16 (40)	6 (14)	0.005
1b	45 (56)	22 (55)	23 (58)	
1c	13 (16)	2 (5)	11 (28)	
HVD, *n* (%)	34 (43)	8 (20)	26 (65)	<0.001
Median (quartiles) number of bone metastases	4 (2–14)	2 (1–6)	8 (4–18)	0.001
mHNPC systemic treatments, *n* (%)				
Upfront ADT[‡]	50 (63)	17 (43)	33 (83)	<0.001
With docetaxel	20 (25)	11 (28)	9 (23)	0.6
With abiraterone acetate	3 (3.8)	2 (5.0)	1 (2.5)	>0.9
mCRPC systemic treatments, *n* (%)				
Docetaxel	12 (15)	7 (18)	5 (13)	0.5
Cabazitaxel[§]	5 (6.5)	2 (5.0)	3 (7.5)	0.6
Abiraterone	21 (26)	11 (28)	10 (25)	0.8
Enzalutamide	13 (16)	5 (13)	8 (20)	0.4
Radium-223	6 (7.5)	3 (7.5)	3 (7.5)	>0.9

ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; HVD, high-volume disease; mHNPC, metastatic hormone-naïve prostate cancer; PSA, baseline PSA. *Defined as any value exceeding the normal reference upper limit value of 120 U/L. [†]Histological diagnosis after biopsy of metastasis. [‡]ADT was started within 3 months after prostate cancer diagnosis. [§]Only available after previous treatment with docetaxel.

Discussion

The multicentre LoMP study is the first prospective clinical trial reporting oncological results regarding the role of cytoreductive radical prostatectomy in addition to standard of care for patients with newly diagnosed mHNPC. The primary endpoint of this analysis was the difference in castration resistant cancer-free survival between our two groups. Several hypotheses have arisen over time that attempt to explain the effect of cytoreduction on oncological outcomes. As mentioned in the introduction section, the effect might be attributable to elimination of the 'premetastatic niche', diminishing tumour burden and preventing tumour seeding or otherwise because of removal of androgen-insensitive clones [8–11]. Prolonged response to ADT after cytoreductive radical prostatectomy has been previously reported in several retrospective studies [18–21].

Reviewing the available research regarding the role of cytoreductive radical prostatectomy in mHNPC, most evidence stems from small and heterogeneous studies with a high susceptibility to significant selection bias. One of the first studies published by Culp et al. [22] utilized a large cohort of patients from the Surveillance Epidemiology and End Result (SEER) database and showed significantly better 5-year OS (67% vs 21%; *P* < 0.001) and cancer-specific survival (CSS; 76% vs 49%; *P* < 0.001) for those undergoing cytoreductive radical prostatectomy compared to only standard of care. Various publications followed that also used this database, with similar results [23–27]. Another large registry database that is extensively employed is the National Cancer Database [28,29]. Parikh et al. [30] reported a significantly beneficial 5-year OS of 51% vs 17% (*P* < 0.001). Gratzke et al. [31] studied the smaller Munich Cancer Registry and showed a 5-year OS of 55% for cytoreductive radical prostatectomy vs 21% for only standard of care (*P* < 0.01). None of these

Table 2 Surgical characteristics and morbidity for cytoreductive radical prostatectomy.

	40
Median (IQR) operation time, min	205 (165–220)
Median (IQR) blood loss, mL	250 (150–325)
Median (IQR) hospital stay, days	4 (3–5)
Pathological tumour grade group, n (%)	
3	7 (18)
4	8 (20)
5	25 (63)
Pathological T-stage, n (%)	
pT2	6 (15)
pT3	32 (80)
pT4	2 (5.0)
Pathological N-stage, n (%)	31 (78)
pN1	
Median (IQR) lymph nodes resected	17 (11–21)
Median (IQR) lymph nodes positive	4 (1–10)
Surgical margins, n (%)	
R1	32 (80)
Procedure, n (%)	
Open	2 (5.0)
Robot-assisted laparoscopic	38 (95)
Clavien–Dindo 90 days, n (%)	
0	20 (50)
I	14 (35)
Urinary infection	1 (2.5)
Bladder catheter*[,†,§]	7 (18)
Neuropraxis[‡,§]	6 (15)
Incisional hernia	1 (2.5)
Lymphoedema[‡]	2 (5.0)
Paraphimosis	1 (2.5)
II	4 (10)
Anticoagulation for DVT*	2 (5.0)
Antibiotics for infection[†]	1 (2.5)
Transfusion for anemia	1 (2.5)
III	2 (5.0)
Drainage of lymphocele	1 (2.5)
Cardioversion for AF	1 (2.5)
Continent after 1 year, n (%)	
Yes	31 (79)
Continent at time of analysis, n (%)	
Yes	35 (88)

AF, atrial fibrillation; DVT, deep vein thrombosis; IQR, interquartile range. *One patient required a bladder catheter and anticoagulation for DVT. [†]One patient required a bladder catheter and antibiotics for infection. [‡]One patient suffered neuropraxis of the genitofemoral nerve and lymphedema. [§]One patient suffered neuropraxis of the genitofemoral nerve and a bladder catheter.

registry studies investigated castration resistant prostate cancer-free survival or progression-free survival. Jang et al. [32] retrospectively reviewed the records of 79 patients with oligometastatic disease treated with cytoreductive radical prostatectomy vs only ADT. Progression-free survival was 75 vs 28 months ($P = 0.008$) and CSS was not reached vs 40 months ($P = 0.002$), respectively. A few smaller-scale retrospective studies were published without a control group. In a multicentre European study encompassing 106 patients receiving cytoreductive radical prostatectomy, Sooriakumaran et al. [33] reported a 2-year survival of 89%. Another more recent multicentre European study by Heidenreich et al. [34] included 113 oligometastic patients undergoing cytoreductive radical prostatectomy. The 5-year clinical relapse-free survival

was 58%, and OS and CSS were 80% and 81%, respectively. The study with longest follow-up was by Gandaglia et al. [35], who included only 11 oligometastatic patients after cytoreductive radical prostatectomy, but demonstrated a 7-year clinical progression-free survival of 45% and CSS of 82%. The only study to date, using prospective data in the cytoreductive radical prostatectomy group and retrospective data in the standard of care group (Steuber et al. [36]), could not demonstrate this possible survival benefit in terms of castration resistant cancer-free survival or OS.

Similarly, the present study did not show a significant influence of cytoreductive radical prostatectomy on castration resistant cancer-free survival because this could not be identified as an independent risk factor using a propensity-score analysis-adjusted multivariable Cox regression model. We acknowledge that our prospective study, like most previously published retrospective studies, is limited due to selection and consequently lead-time bias. Patients receiving cytoreductive radical prostatectomy were younger, with lower baseline PSA levels, ALP levels and metastatic burden. This might be the reason for the better castration resistant cancer-free survival in the cytoreductive radical prostatectomy group. Our results underline the importance of prospective, randomized phase II and III studies with potential to reach firm conclusions regarding the role of cytoreductive radical prostatectomy for patients with newly diagnosed mHNPC.

The multivariable analysis seems to validate our published prognostic model (Buelens et al. [37]), in which HVD and elevated ALP were identified as the main prognostic risk factors for patients with mHNPC. Interestingly, age was not a predictive risk factor for castration resistant cancer-free survival.

Overall, the major limitation regarding the present study is the misbalance in metastatic burden, with patients in the intervention group predominantly having LVD (80%) and only 35% of patients in the control group having LVD. Following the results of the STAMPEDE trial [12], prostate radiotherapy was only implemented in the EAU guidelines for patients with LVD because the oncological benefit was absent in the overall cohort [12]. Subsequently, this encouraged our ethical committee to approve the expansion of our patient groups so we could perform a sub-analysis for LVD. Furthermore, we set up a prospective phase II feasibility trial investigating the randomization between cytoreductive radical prostatectomy and prostate radiotherapy, both in addition to standard of care, in which we primarily stratify for metastatic volume (NCT03655886).

With regard to functional outcomes, although complications were reported in half of our patients up to 3 months after cytoreductive radical prostatectomy, the majority experienced only grade 1 complications, with complete resolution. This percentage corresponds to previous literature reporting a

Fig. 1 Cytoreductive radical prostatectomy tended to show longer castration resistant cancer-free survival and local event-free survival. (**A**) Median castration resistant prostate cancer-free survival was 53 (95% CI 14–92) vs 21 months (95% CI 15–27), with 3-year survival estimates of 59% vs 40% for the cytoreductive radical prostatectomy group (blue line) compared to the standard of care group (red line; $P = 0.017$). (**B**) The 3-year survival estimates for LE-free survival were 83% vs 59% for the cytoreductive radical prostatectomy group (blue line) compared to the standard of care group (red line; $P = 0.012$), respectively.
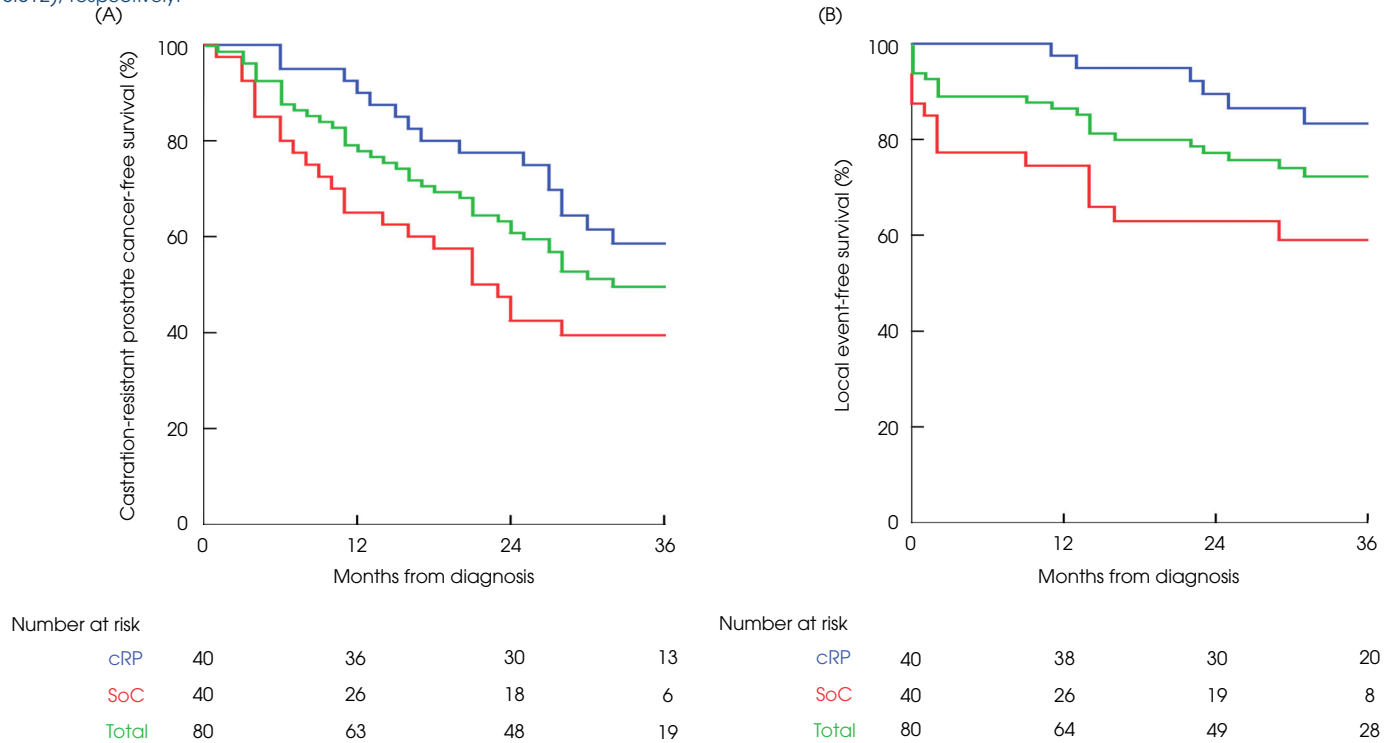

Number at risk				
cRP	40	36	30	13
SoC	40	26	18	6
Total	80	63	48	19

Number at risk				
cRP	40	38	30	20
SoC	40	26	19	8
Total	80	64	49	28

Table 3 Stepwise multivariable Cox regression analyses for castration-resistant prostate cancer-free and local event-free survival.

		Castration resistant prostate cancer-free survival		Local event-free survival	
		HR (95% CI)	P	HR (95% CI)	P
Inclusion group	Cytoreductive radical prostatectomy vs standard of care	0.93 (0.37–2.38)	0.9	0.77 (0.19–3.13)	0.7
Performance status	<2 vs ≥2	4.36 (1.54–12.3)	0.006	0.99 (0.28–3.48)	0.9
PSA (ng/mL)				1.001 (1.000–5.1.002)	0.024
Tumour grade group	<4 vs ≥4	1.33 (0.91–1.96)	0.1	1.38 (0.81–2.36)	0.2
Metastatic volume	LVD vs HVD	2.48 (1.00–6.15)	0.050	1.07 (0.30–3.87)	0.9
ALP (U/L)	≤120 vs >120	3.27 (1.17–9.16)	0.024	4.89 (1.04–23.0)	0.044

ALP, Alkaline phosphatase; HR, hazard ratio; HVD, high-volume disease; LVD, low-volume disease; PSA, baseline PSA.

complication rate of 22–50% [13,14,20,35,38]. The study with the longest available follow-up by Gandaglia et al. [35] also reported a complication rate of 50%. As in the present study, those authors showed a higher pathological T-stage and tumour grade group compared to most published reports, which might explain these higher complication rates. Additionally, we performed an extended pelvic lymph node dissection in all patients and reported the grade 1 complications extensively (Table 2). Only two patients (5%) experienced a grade 3 complication and no patient had a grade 4 or 5 complication in the present study. This corresponded with the reported percentages of 5–18%

[20,35,38], but was noticeably lower than the complication rate of 18% reported by Gandaglia et al. [35]. One year after undergoing cytoreductive radical prostatectomy, 79% of patients were continent, which corresponds to the reported continence rate of 82% in non-metastatic high-risk disease [26]. Similarly, the operation time, blood loss and length of stay were comparable to the non-metastatic setting [39]. This study validates our initial data (Poelaert et al. [40]) and previous retrospective publications [13,14,19,20] reporting that cytoreductive radical prostatectomy is a technically feasible and safe procedure for well-selected patients with comparable peri- and postoperative functional outcomes, as

Table 4 Local events.

	Cytoreductive radical prostatectomy + standard of care (n = 40)	Only standard of care (n = 40)
Local complications of cytoreductive radical prostatectomy, number of events (%)	**4 (10)**	**0 (0)**
Artificial urinary sphincter	1 (2.5)	0 (0)
Male sling	1 (2.5)	0 (0)
Erection prosthesis	1 (2.5)	0 (0)
Lymphocele drainage	1 (2.5)	0 (0)
BOO, number of events (%)	**3 (7.5)**	**15 (38)**
Transurethral catheter	0 (0)	6 (15)
Suprapubic catheter	1 (2.5)	5 (13)
Intermittent catheterization	0 (0)	3 (7.5)
Sachse urethrotomy	2 (5)	0 (0)
Transurethral bladder neck resection	0 (0)	1 (2.5)
Ureteric obstruction, number of events (%)	**2 (5)**	**1 (2.5)**
JJ stenting	2 (5)	1 (2.5)
Total, number of patients (%)	7 (18)*	15 (38)†

*One patient received a suprapubic catheter and afterwards a Sachse urethrotomy, one patient received JJ stenting and Sachse urethrotomy.
†One patient received a transurethral catheter and JJ stenting.

in the non-metastatic setting, when performed by experienced surgeons. Potential complications and side effects should be extensively discussed with the patient before performing this surgery.

Another important functional outcome we investigated was the occurrence of LEs. Patients in our cytoreductive radical prostatectomy group experienced significantly fewer LEs and lived longer without their manifestation. However, this could not be proven to be related to cytoreductive radical prostatectomy, considering the imbalance between our two research groups. The propensity-score analysis-adjusted multivariable analysis could not provide any evidence regarding the role of cytoreductive radical prostatectomy on the occurrence of LEs. Longer follow-up is needed to provide strong research data. When reviewing literature, it is shown that, in patients receiving no local therapy, up to 50% will present LEs as a result of disease progression of the primary tumour, potentially requiring hospitalization and interventions [13,20,41]. For men with mHNPC, quality of life is substantially affected not only by the development of metastases, but also by morbidity caused by local disease progression [13,41]. Interestingly, surgery showed a lower probability of LEs compared to prostate radiotherapy [12,41]. Moreover, in the STAMPEDE trial [12], one-third of patients needed to undergo local palliative therapy for locally progressing prostate cancer. Overall, the available retrospective literature presents cytoreductive radical prostatectomy as a valuable option to achieve good local palliation in men who ultimately are not cured by this treatment method [13,20,30,36,41]. As in the non-metastatic setting, radical prostatectomy is suggested to be the favourable treatment option for those patients at risk for LEs, indicated by a history of LUTS, weak peak flow rates and worse IPSSs. As for oncological outcomes, this needs to be

further explored in prospective, randomized studies to correct for potential bias in the two groups before any statements can be made regarding the role of cytoreductive radical prostatectomy.

Several limitations of this study warrant mention. Firstly, although the study was prospective, there was no randomization between eligible patients in the two arms. At the beginning of this study, data on the safety of cytoreductive radical prostatectomy were lacking. Therefore, the choice not to randomize was driven by ethical reasons. Cytoreductive radical prostatectomy with its inherent morbidity should be an informed and shared decision between patient and treating physician after discussion of all possible (dis)advantages. Secondly, as extensively mentioned before, because of the selection and lead-time bias, patients in the intervention group would be expected to develop fewer LEs and have a better life expectancy regardless of cytoreductive radical prostatectomy. Therefore, the superior castration resistant cancer-free survival and local event-free survival in the cytoreductive radical prostatectomy group of the present study, similarly to all previously published data, should be interpreted with extreme caution, as it is not adjusted for potential confounders. We therefore included Cox regression analyses adjusted for propensity-score analysis. Similar to randomization, propensity-score methods remove the effect of confounding by comparing outcomes in treated and untreated subjects who have a similar distribution of measured baseline covariates. Thirdly, there was no standardized systemic treatment protocol after surgery but the number of patients receiving each castration resistant prostate cancer-free survival treatment was comparable (Table 1) and in accordance with the contemporary EAU guidelines. Finally, different surgeons performed the intervention across several institutions. They were, however, all experienced, which

resulted in similar peri- and postoperative functional outcomes to those observed in the non-metastatic setting.

In conclusion, the LoMP study was unable to show a difference between cytoreductive radical prostatectomy and standard of care regarding castration resistant cancer-free survival for asymptomatic patients with newly diagnosed mHNPC. The potential role of cytoreductive radical prostatectomy needs to be further explored in prospective, randomized phase II and III studies to correct for potential bias. Patients in the intervention group would be expected to have a better life expectancy regardless of the intervention, due to favourable characteristics such as lower age, baseline PSA level, ALP level and metastatic burden. Until then, cytoreductive radical prostatectomy must be exclusively limited to clinical trials.

These results validate previous evidence that, in well-selected and informed patients, cytoreductive radical prostatectomy is feasible and safe, with corresponding continence rates to those obtained the non-metastatic, high-risk setting.

Whether cytoreductive radical prostatectomy could be a valuable option to achieve good local palliation in men who ultimately are not cured by this treatment method needs to be further explored.

Acknowledgements

Conflict of Interest

None declared.

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Abbreviations: ADT, androgen deprivation therapy; ALP, alkaline phosphatase; CSS, cancer-specific survival; EAU, European Association of Urology; HR, hazard ratio; HVD, high-volume disease; LE, local event; LVD, low-volume disease; mHNPC, metastatic hormone-naive prostate cancer; OS, overall survival.