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EUO Priority Article

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Combination of Androgen Deprivation Therapy with Radical Local Therapy Versus Androgen Deprivation Therapy Alone for Newly Diagnosed Oligometastatic Prostate Cancer: A Phase II Randomized Controlled Trial

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Abstract

Background: Previous studies suggested that men with metastatic prostate cancer might benefit from local treatment of the primary tumor.
Objective: To determine whether radical local therapy (RLT) improves survival for men with oligometastatic prostate cancer (OMPCa).
Design, setting, and participants: This open-label randomized controlled trial included patients with newly diagnosed OMPCa defined as five or fewer bone or extrapelvic lymph node metastases and no visceral metastases.
Intervention: Patients were randomly allocated to androgen deprivation therapy (ADT) or ADT and RLT. Men allocated RLT received either cytoreductive radical prostatectomy (RP) or prostate radiation therapy (RT) with a radical dose schedule.
Outcome measurements and statistical analysis: The primary outcome was radiographic progression-free survival (rPFS). Secondary outcomes were overall survival (OS) and prostate-specific antigen (PSA) progression-free survival.
Results and limitations: Between September 2015 and March 2019, 200 patients were randomized, with 100 men allocated to each group. The median age was 68 yr and the median PSA at diagnosis was 99 ng/ml. In the study group, 96 patients underwent RLT (85 RP and 11 RT). In the control group, 17 patients eventually received RLT (15

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survival

RP and two RT). All patients were included for an intention-to-treat analysis. After a median follow-up of ~48 mo, the median rPFS was not reached in the study group and was 40 mo in the control group (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.27–0.70; $p = 0.001$). The 3-yr OS rate was 88% for the study group and 70% for the control group (HR 0.44, 95% CI 0.24–0.81; $p = 0.008$).

Conclusions: Men with newly diagnosed OMPCa who received ADT plus RLT (mainly prostatectomy) had significantly higher rates of rPFS and OS than those who received ADT alone.

Patient summary: This study investigated the effect of radical local therapy (RLT) of the primary tumor on survival in patents with oligometastatic prostate cancer. In our group, RLT improved radiographic progression-free and overall survival.

1. Introduction

Historically, patients with metastatic prostate cancer (MPCa) typically undergo systemic treatment to alleviate symptoms, delay progression, and extend life, with local therapy reserved for symptom palliation targeted to the primary tumor and metastatic lesions [1].

Several retrospective studies employing large databases found improved overall survival (OS) among patients with MPCa treated with prostatectomy or prostate radiotherapy (RT) [1–5]. The HORRAD [6] and STAMPEDE [7] trials report controversial results. The HORRAD trial randomized 432 patients with primary bone MPCa who were administered androgen deprivation therapy (ADT) to the prostate, with or without RT [6]. There was no significant benefit to OS [6]. The STAMPEDE trial enrolled 2061 men with newly diagnosed MPCa and compared standard of care (SOC) with SOC plus external-beam RT to the prostate [7]. RT did not improve OS compared with SOC alone in all patients [7]. However, a prespecified subgroup analysis found that prostate RT improved the OS of patients with a low metastatic burden [7]. Therefore, more evidence is required to determine whether local therapy targeted to the primary tumor should be administered to men with newly diagnosed MPCa, particularly those with a low metastatic burden.

Here, we report the results of a prospective randomized controlled trial (RCT), which evaluated ADT with or without radical local therapy (RLT) of the primary tumor in men with newly diagnosed oligometastatic prostate cancer (OMPCa).

2. Patients and methods

2.1. Study design and participants

This was a single-center, open-label, phase II randomized trial to test the hypothesis that ADT with RLT of the primary tumor in men with newly diagnosed OMPCa is superior to standard ADT. The Ethics and Scientific Committee of Fudan University Shanghai Cancer Center approved the trial. All patients were recruited at our center. Eligible patients (age range, 18–80 yr) were selected according to the following criteria: newly diagnosed disease (≤6 mo before randomization), histologically proven prostate adenocarcinoma without evidence of neuroendocrine differentiation, no previous treatment of the primary tumor, and oligometastatic disease confirmed using conventional imaging modalities including scintigraphic bone scan, thoracic computed tomography (CT), abdominal CT, and pelvic magnetic resonance imaging (MRI) or CT. Oligometastases were defined as five or fewer bone or extrapelvic lymph node lesions not associated with detectable visceral metastases. Patients previously treated within ≤6 mo of traditional ADT (castration with or without first-generation antiandrogens) were eligible. Patients treated with chemotherapy, abiraterone, or second-generation antiandrogens were excluded.

All patients were required to have Eastern Cooperative Oncology Group performance status scores of 0–1, no contraindications to surgery or RT, and no serious cardiovascular or mental disorders. The trial was undertaken in accordance with the Good Clinical Practice Guidelines. All patients provided their written informed consent. This study is registered with ClinicalTrials.gov (NCT02742675).

2.2. Randomization and masking

Randomization was described in detail in the Supplementary material. Briefly, patients were randomly assigned (1:1) to undergo ADT (control group) or ADT plus RLT (prostatectomy or RT) to treat their primary lesions (study group) using a simple randomization method. The computer-generated random number table was created by an independent statistician. Patients as well as clinical and study staff members were informed of treatment allocations for practical reasons.

2.3. Procedures

All patients received lifelong ADT employing gonadotropin-releasing hormone agonists (goserelin, leuprolide, and triptorelin) or underwent orchidectomy. Combination therapy employing the first-generation antiandrogens bicalutamide or flutamide was permitted in both groups. Administration of docetaxel, cabazitaxel, abiraterone, and second-generation antiandrogens was not allowed before disease progressed to castration resistance.

To evaluate the primary lesions, the study group underwent digital rectal examination and contrast-enhanced pelvic MRI after randomization. Patients with clinical stages T2 to T3b primary tumors were considered to have resectable tumors, and those with apparent invasion of the rectum,

bladder neck, or both were considered to have unresectable tumors. Cytoreductive radical prostatectomy (RP) was recommended for all patients with resectable disease and was performed by surgeons as an open or laparoscopic approach. Regardless of whether ADT was started before randomization, patients were allowed to undergo additional ADT for $\leq$3 mo after randomization, if the primary tumor was considered unresectable, or to decrease the difficulty of RP.

Patients were evaluated monthly during ADT. RP was performed if the primary lesion was re-evaluated as resectable after a period of ADT. Prostate RT using a radical dose schedule was recommended as an alternative for patients with an unresectable primary lesion after 3 mo ADT or for those who refused surgery. RLT to the primary lesion was not administered to patients with increased prostate-specific antigen (PSA) levels after initial ADT. Pelvic lymphadenectomy was an optional component of RP, particularly for patients with multiple bulky pelvic lymph nodes combined with a suspicion of vascular invasion.

The pathology of prostatectomy specimens of patients who underwent RP was assessed using the American Joint Committee on Cancer staging system (eighth edition, 2017) and Gleason grading. Perioperative complications were evaluated according to the Clavien-Dindo classification system.

Intensity-modulated RT was administered to patients who underwent RT as follows: 74 Gy (37 fractions) for all patients and 45 Gy (18 fractions) to the draining lymph node for those with pelvic lymph node metastases. Toxicity of RT was recorded using the Radiation Therapy Oncology Group scale.

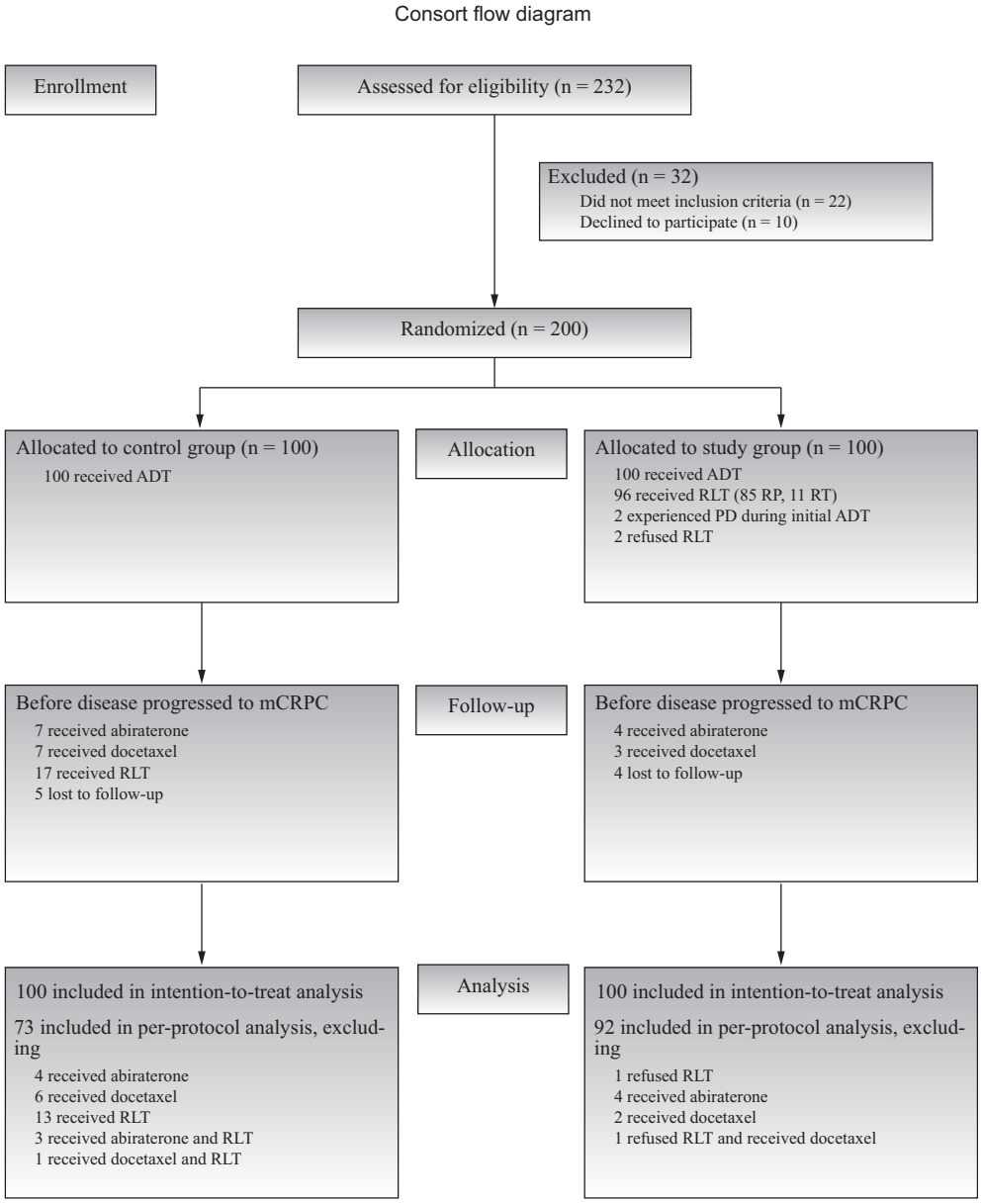

Fig. 1 – Consort flow diagram of patient enrollment. ADT = androgen deprivation therapy; mCRPC = metastatic castration-resistant prostate cancer; PD = progressive disease; RLT = radical local therapy; RP = cytoreductive radical prostatectomy; RT = prostate radiotherapy.

All patients were followed. PSA and testosterone levels were measured monthly for the first 6 mo, every 3 mo for the first 2 yr, and every 6 mo thereafter. Imaging studies including enhanced CT (chest, abdomen, and pelvis) and bone scans were performed every 6 mo, or if a patient showed symptomatic progression or an increase in PSA level. Assessment of radiographic progression was centrally reviewed by three radiologists (X.H.L., B.N.Z., and C.L.) blinding to the trail.

All patients received continuous ADT until disease progressed to castration-resistant prostate cancer (CRPC), which was defined according to the European Association of Urology guidelines. Treatment after progression to CRPC was initiated at the discretion of patients and their physicians. Salvage RT to any site of metastatic disease was allowed in both groups. Bisphosphonates were allowed for reducing skeletal-related events in both groups.

2.4. Outcomes

The primary endpoint was radiographic progression-free survival (rPFS), defined as the time from randomization to radiographic progression or death from any cause. Radiographic progression was evaluated according to Prostate Cancer Working Group (PCWG)-2 criteria for bone lesions and RECIST1.1 for soft-tissue lesions. Secondary endpoints included OS and PSA progression-free survival (PSA-PFS). OS was defined as the time from randomization to death from any cause. PSA-PFS was defined as the time from randomization to the earliest PSA progression according to the PCWG-2 criteria (confirmed relative increase in the PSA level from the nadir value by ≥25% and by ≥2 ng/ml) or death from any cause.

2.5. Statistical analysis

Determination of sufficient sample size was based on the estimated median rPFS of 18 and 30 mo for the control and study groups, respectively. To detect the hypothesized difference with a two-sided significance level (α) of 0.05 and a statistical power (β) of 0.80, 200 patients were enrolled, allowing for 15% patient loss during follow-up. The intention-to-treat population included all randomly assigned patients. Descriptive statistics were used to summarize patients' clinical and pathological characteristics. Pearson's chi-square test and the Kruskal-Wallis H test were used to compare categorical and continuous variables, respectively. A Kaplan-Meier analysis was conducted to estimate survival. The log-rank test was applied to compare survival parameters between the control and study groups. Cox proportional hazard regression was conducted to calculate hazard ratios (HRs). All p values were two sided (α = 0.05). Owing to the potential for type 1 errors associated with multiple comparisons, findings from analyses of secondary endpoints were interpreted as exploratory. Statistical analyses were performed using SPSS 24.0 software (IBM).

3. Results

Between September 1, 2015 and March 10, 2019, 232 men were screened for inclusion, and 200 men with OMPCa were randomly assigned to the control group (ADT, n = 100) or the study group (ADT + RLT, n = 100; Fig. 1). Patients' baseline

Table 1 – Baseline characteristics of 200 oligometastatic prostate cancer patients

Characteristics	Control group (n = 100)	Study group (n = 100)
Age at randomization (yr), median (IQR)	69 (64–73)	67 (62–71)
PSA at diagnosis (ng/ml), median (IQR)	102 (49–254)	90 (35–236)
Time from diagnosis to randomization (d), median (IQR)	31 (14–82)	26 (12–62)
Biopsy Gleason score, *n*		
≤7	12	14
8–10	85	86
Unknown	3	0
Clinical T stage at randomization, *n*		
≤T2c	20	14
T3a-T3b	61	72
T4	19	14
Clinical N stage at randomization, *n*		
N0	52	55
N1	42	37
Nx	6	8
Location of distant metastases, *n*		
Distant lymph node	20	10
Bone	95	97
Number of distant metastases, *n*		
1	27	32
2	19	21
3	17	16
4	18	13
5	19	18
Type of ADT, *n*		
Castration alone	6	7
Castration + bicalutamide	90	87
Castration + flutamide	4	6

ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate-specific antigen.

Table 2 – Clinicopathological characteristics of 85 patients who underwent RP

Characteristics	RP (IQR or %)
PSA at RP (ng/ml), median (IQR)	1.6 (0.3–15)
Treated by ADT prior to surgery, *n* (%)	
No	22 (26)
Yes (start before inclusion)	27 (32)
Yes (start after inclusion)	36 (42)
Open surgery approach, *n* (%)	68 (80)
Pathological T stage, *n* (%)	
≤T2c	12 (14)
T3a–T3b	57 (67)
T4	16 (19)
Pathological N stage, *n* (%)	
N0	34 (40)
N1	26 (31)
Nx (without PLND)	25 (29)
Unresectable or to avoid vascular injury	13 (15)
No palpable enlarged lymph node	12 (14)
Positive surgical margins, *n* (%)	36 (42)
Postoperative Gleason score, *n* (%)	
No residual cancer	2 (2.3)
Residual cancer cannot be graded	46 (54)
≤7	6 (7.1)
8–10	31 (37)
PSA at 6 wk after RP (ng/ml), *n* (%)	
<0.1	48 (57)
≥0.1 and <0.2	8 (9.4)
≥0.2	29 (34)

ADT = androgen deprivation therapy; IQR = interquartile range; PLND = pelvic lymphadenectomy; PSA = prostate-specific antigen; RP = cytoreductive radical prostatectomy.

Table 3 – Peri- and postoperative complications for patients underwent radical prostatectomy

		Patients, *n* (%)
Perioperative complications[a]		
Grade I	Anastomotic leakage (*n* = 5), asymptomatic lymphocele (*n* = 3)	8 (9.4)
Grade II	Blood transfusion (*n* = 3), catheter for acute urinary retention (*n* = 2), antibiotic treatment for infection (*n* = 4)	9 (11)
Grade IIIa	Percutaneous drainage of lymphorrhagia (*n* = 1), double-J stent for upper urinary tract obstruction (*n* = 1), suprapubic cystostomy or urethral dilatation for lower urinary tract obstruction (*n* = 2)	4 (4.7)
Grade IIIb	Repeat laparotomy for bleeding or hematoma (*n* = 1), transurethral incision for lower urinary tract obstruction (*n* = 1)	2 (2.4)
Grade IVa	Rectal injury (*n* = 1)	1 (1.2)
Grade IVb		0
Grade V		0
Total		24 (28)
Late postoperative (>90 d) symptomatic local events		
Urinary incontinence[b]		
	At 1st year	7 (8.2)
	At 2nd year	4 (4.7)
Urethral stricture		
	Caused by hypertrophic scar	1 (1.2)
	Caused by tumor recurrence at anastomotic stoma	1 (1.2)
Urethrorectal leakage caused by rectal injury at RP		1 (1.2)

RP = radical prostatectomy.
[a] The grade of perioperative complications was evaluated according to Clavien-Dindo grade I–V complications.
[b] Urinary incontinence was defined as one or more pads per day.

characteristics are shown in Table 1. The median age was 68 yr and the median PSA level at diagnosis was 99 ng/ml.

Ninety-six patients in the study group received RLT, including 49 who received RP immediately after randomization, 36 who received RP after 1–3 mo of initial ADT, and 11 who received a radical dose of RT (Fig. 1). Among 11 patients who underwent RT, seven refused RP and four had unresectable primary lesions after initial ADT. ADT was administered for a mean of 109 d before RP (interquartile range 35–148 d, including ADT administered before and after randomization). Four patients in the study group did not receive RLT, including two patients who experienced disease progression during initial ADT and two patients who refused RLT after randomization. Protocol deviations included four men in the study group who received abiraterone for at least 1 mo, and three men received one or more cycles of docetaxel before disease progressed to CRPC.

In the control group, seven patients received abiraterone for $\geq$1 mo, seven received one or more cycles of docetaxel, and 17 (including three and one who received abiraterone and docetaxel, respectively) received RLT targeted to their primary lesions before disease progressed to CRPC. Among 17 patients who received RLT, 15 underwent RP after 1–14 mo (median, 7 mo) after inclusion and two underwent RT for 10–11 mo (median, 10.5 mo) after inclusion.

Among 85 patients who underwent RP in the study group, 68 (80%) and 17 (20%) underwent open retropubic and laparoscopic RP, respectively (Table 2). Sixty (71%) patients underwent bilateral pelvic lymphadenectomy; the median number of resected lymph nodes was 6 (range 1–32). Among patients who underwent lymphadenectomy, 26/60 (43%) had positive pelvic lymph nodes. Twenty-four patients (28%) developed perioperative complications within 90 d after RP, among which eight, nine, and four were of Clavien-Dindo grade 1, 2, and 3a, respectively. Three men developed grade 3b or 4a complications as follows: one each with a pelvic hematoma, an anastomotic stenosis, and a rectal injury. There was no grade 4b complication and no perioperative death; 8% of patients who underwent RP suffered urinary incontinence during the 1st year after surgery, and the rate decreased to 5% during the 2nd year (Table 3). The data on quality of life are presented in Supplementary Table 1.

Four patients underwent RT to the prostate and the lymphatic drainage area, and seven underwent RT to the prostate only (Supplementary Table 2). Among these 11 patients, five suffered grade 1–2 acute bowel or bladder toxicity, without grades 3–4 toxicity, and one suffered grade 3–4 late toxicity.

For an intention-to-treat analysis, the median follow-up was 48 mo (95% confidence interval [CI] 43–50). Radiological progression occurred more slowly in the study group (HR 0.43, 95% CI 0.27–0.70, $p = 0.001$): Radiographic progression was experienced by 23 and 47 patients in the study and control groups, respectively (Fig. 2A). The median rPFS, which was not reached in the study group, was 40 mo in the control group. The 3-yr rPFS rates were 79% and 56% for the study and control groups, respectively, and 47 patients died during follow-up. Deaths in the study group included 15 associated with prostate cancer (PCa) and one caused by pneumonia. In the control group, there were 28 PCa-related deaths, one death from primary lung cancer (diagnosed 27 mo after inclusion), one death from pneumonia, and one death from aortic dissection. The 3-yr OS rates were 88% and 70% for the study and control groups, respectively. The HR for OS was 0.44 (95% CI 0.24–0.81, $p = 0.008$; Fig. 2B).

PSA progression was experienced by 33 and 58 patients in the study and control groups, respectively. The HR for PSA-PFS was 0.44 (95% CI 0.29–0.67, $p < 0.001$), and 3-yr PSA-PFS rates were 71% and 45% for the study and control groups, respectively (Fig. 2C).

The per-protocol analysis included 73 and 92 patients in the control and study groups, respectively (Supplementary Fig. 1).

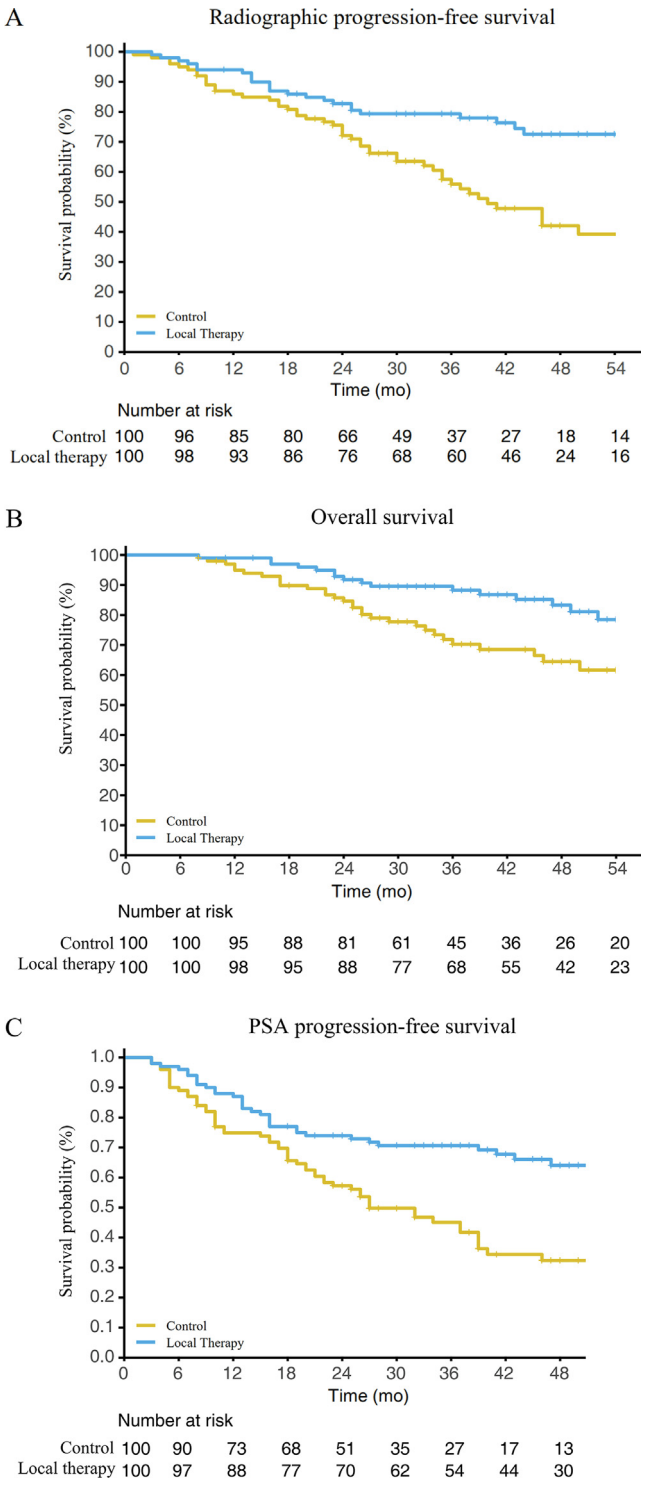

Fig. 2 – Kaplan-Meier estimates of primary and secondary endpoints for the ITT cohort: (A) radiographic progression-free survival, (B) overall survival, and (C) PSA progression-free survival. ITT = intention to treat; PSA = prostate specific antigen.

During follow-up, 16 patients underwent RT targeting all metastatic sites, including nine and seven patients from the study and control groups, respectively; 34 and 61 in the study and control groups, respectively, progressed to CRPC. Subsequent therapies were administered to 27/34 (79%) and 45/61 (74%) patients in the study and control groups, respectively (Supplementary Table 3).

4. Discussion

The RCT described here investigated the efficacy and safety of ADT combined with RLT (mainly prostatectomy) targeted to the primary tumors of patients with newly diagnosed OMPCa. The study met its primary and secondary endpoints: RLT plus ADT increased 3-yr rPFS, OS, and PSA-PFS rates significantly and was well tolerated.

The 3-yr OS rate (70%) of the control group was similar to those of the control groups in the STAMPEDE (73%) and CHAARTED trials (each approximately 70%) [7,8] for patients with a low metastatic burden allocated to receive ADT alone. This cross-trial comparison supports the conclusion that the survival benefit experienced by our patients who received ADT plus RLT is not explained by shorter survival of the control group but by longer survival in the study group.

In the present study, 85% of patients assigned to the study group underwent prostatectomy. Compared with RT, the advantages of prostatectomy include shorter treatment duration and acquisition of accurate information about pathology. Most prospective studies selected RT as local treatment because investigators believe that prostatectomy is less safe or unsuitable for many patients. In the present study, perioperative complications were experienced by 28% of patients, and grade $\geq$4b complications were not observed (Table 2). This overall complication rate is acceptable and similar to that associated with patients with locally advanced PCa who undergo RP at our center as well as reported by retrospective studies of RP for MPCa [9,10].

Here, we permitted administration of initial ADT to patients whose primary tumors were evaluated as difficult for surgery at the time of inclusion. RT served as an alternative for patients with unresectable disease after initial ADT or those who refused surgery. Moreover, to avoid severe complications, pelvic lymphadenectomy with prostatectomy was optional. These strategies helped decrease the incidence of severe complications.

In the present study, control group patients received ADT with or without first-generation antiandrogens, because the study was initiated in 2015 when ADT was the SOC for newly diagnosed MPCa. Since 2015, large RCTs found that adding docetaxel, abiraterone, enzalutamide, or apalutamide to ADT administered to men with metastatic hormone-sensitive PCa prolongs OS, and clinical guidelines were therefore modified [8,11–15]. However, the survival benefit for low-volume disease was not widely accepted until 2019, and consequently, our protocol was not adjusted.

The limitations of the present study are as follows: (1) certain patients did not follow the prescribed treatment strictly, and 17% of patients in the control group received RLT; (2) we used conventional imaging techniques to estimate metastatic burden, which have relatively low sensitivity; (3) the treatment group was heterogeneous regarding

the use of ADT and pelvic lymph node dissection, And also, second-line life-prolonging systemic therapy was administered to <70% of patients with progression; (4) the median rPFS and OS rates of patients in the study group were not reached because of encouraging therapeutic efficacy and short follow-up period; and (5) the sample size of this study was relatively small, and the results require validation through large multicenter clinical trials.

5. Conclusions

In conclusion, based on the evidence of this study, RP should be considered by experienced urologists as an alternative strategy to improve outcome for newly diagnosed OMPCa patients.

***Author contributions*:** Ding-Wei Ye 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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Statistical analysis: Mo.
Obtaining funding: Ye.
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Supervision: Ye.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2022.06.001.

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