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RESEARCH ARTICLE

Neoadjuvant radiohormonal therapy for oligo-metastatic prostate cancer: safety and efficacy outcomes from an open-label, dose-escalation, single-center, phase I/II clinical trial

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Abstract **To evaluate the safety and efficacy of neoadjuvant radiohormonal therapy for oligometastatic prostate cancer (OMPC), we conducted a 3 + 3 dose escalation, prospective, phase I/II, single-arm clinical trial (CHiCTR1900025743), in which long-term neoadjuvant androgen deprivation was adopted 1 month before radiotherapy, comprising intensity modulated radiotherapy to the pelvis, and stereotactic body radiation therapy to all extra-pelvic bone metastases for 4–7 weeks, at 39.6, 45, 50.4, and 54 Gy. Robotic-assisted radical prostatectomy was performed after 5–14 weeks. The primary outcome was treatment-related toxicities and adverse events; secondary outcomes were radiological treatment response, positive surgical margin (pSM), postoperative prostate-specific antigen (PSA), pathological down-grading and tumor regression grade, and survival parameters. Twelve patients were recruited from March 2019 to February 2020, aging 66.2 years in average (range, 52–80). Median baseline PSA was 62.0 ng/mL. All underwent RARP successfully without open conversions. Ten patients recorded pathological tumor down-staging (83.3%), and 5 (41.7%) with cN1 recorded negative regional lymph nodes on final pathology. 66.7% (8/12) recorded tumor regression grading (TRG) –I and 25% (3/12) recorded TRG-II. Median follow-up was 16.5 months. Mean radiological progression-free survival (RPFS) was 21.3 months, with 2-year RPFS of 83.3%. In all, neoadjuvant radiohormonal therapy is well tolerated for oligometastatic prostate cancer.**

Keywords neoadjuvant; radiotherapy; oligometastatic; prostate cancer; radical prostatectomy

Introduction

The first-line treatment for metastatic prostate cancer (mPCa) has been androgen deprivation therapy (ADT) over the past 50 years, but the median survival for this systematic treatment is only 42 months [1]. Radical prostatectomy (RP) or cytoreductive surgery has been regarded as contraindicated for mPCa, and is only reserved for symptom-relieving purposes in the European Association of Urology (EAU) treatment guidelines [2]. However, studies have indicated that the subpopulation of oligometastatic prostate cancer (OMPC) [3] may benefit from comprehensive therapy integrated by both systemic and local therapy [4,5], with acceptable postoperative quality of life and safety profiles [6,7], but some studies have also reported higher surgical margin and perioperative complications, with limited benefit in overall survival [8,9]. Therefore, the potential value of neoadjuvant treatment to both improve prognosis and enhance surgical safety should be further explored for OMPC.

The concept of preoperative radiotherapy has been validated on colorectal cancer and other types of advanced malignant tumors [10–13], showing better oncological and toxicity control compared with postoperative radiotherapy or systematic therapy alone, but such

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treatment modality remains under-explored for prostate cancer. Several recent clinical trials have given credit to the treatment regimen of neoadjuvant radiotherapy (naRT) followed by robotic-assisted radical prostatectomy (RARP), which is well tolerated for high-risk localized and locally advanced prostate cancer with promising short-term follow-up results [14–17], but an oligometastatic setting has not been investigated, which is believed to draw higher clinical significance.

The current study aims to further validate the value of metastasis-directed therapy with neoadjuvant radiohormonal therapy combined with robotic-assisted radical prostatectomy and adjuvant ADT, and verify its feasibility, safety and efficacy on OMPC patients.

Materials and methods

Study design, inclusion and exclusion criteria

From March 2019 to February 2020, 12 patients with treatment-naive prostate cancer were prospectively enrolled in an open-label, dose-escalation, single-center, phase I/II clinical trial (Chinese Clinical Trial Registry no#: CHiCTR1900025743), after approval by the institutional review board of Changhai Hospital, Shanghai, China (IRB grant no#: CHEC2019-110), the sample size of which was determined by a classic 3 + 3 dose-escalation protocol. The general treatment design was neoadjuvant ADT (naADT) for 1 month, followed by naRT for 4–7 weeks. After a 5- to 14-week gap, RARP plus extended pelvic lymph node dissection (ePLND) was performed. ADT was administered for at least 2 years postoperatively (Fig. S1). The patients enrolled were biopsy confirmed adenocarcinoma of the prostate, with any T/N clinical stages (AJCC cancer staging manual, 8th edition), any non-regional lymph nodes, and ⩽ 5 bone metastases, with no visceral metastases. Clinical staging, gross tumor volume (GTV), and site of metastases was evaluated by ^{68}Ga prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT) before enrollment. World Health Organization (WHO) performance status (PS) of 0–1 was required on initial assessment. All patients were fully aware of their physical condition, diagnosis of the disease, treatment protocol and potential risks and complications throughout the procedure. Written informed consent was obtained from all patients following the International Council for Harmonization/Good Clinical Practice (ICH/GCP) regulations before registration and prior to any trial-specific procedures. Patients with any previous or ongoing treatment for PCa, or endourological treatment of the prostate were excluded. Other exclusion criteria were: a history of abdominal surgery within 3 months, a history of transrectal prostatic biopsy within 2 weeks, a history of long-term anti-coagulant or anti-platelet medications with discontinuation of less than 1 week, a history of other malignancies, acute or chronic blood-borne infections, as well as any underlying medical, psychological, psychiatric, familial, or geographic conditions contraindicate to the entire treatment protocol, as well as those who had participated in other clinical trials within the last three months, and those who were unwilling to participate, had low compliance to the clinical trial, or deemed unsuitable for participation by the investigators, were excluded from the present study.

Treatment protocol

Neoadjuvant and adjuvant androgen deprivation therapy

The participants were scheduled with naADT on the day of enrollment, with bicalutamide (50 mg, daily) plus goserelin (3.6 mg, monthly or 10.8 mg, trimonthly) 14 days after treatment initiation, and carried on for at least 2 years after surgery, following the same medication and dosage.

Neoadjuvant radiotherapy

naRT started after 1 month of ADT. Intensity modulated radiation therapy (IMRT) was delivered to the pelvis, including the prostatic fossa, regional lymph nodes and bone metastases in irradiation area, and stereotactic body radiation therapy (SBRT) was performed for all extra-pelvic bone metastases. For symptomatic patients, SBRT was delivered first for oligometastatic lesions for 1–2 weeks, followed by IMRT on the prostatic fossa for 4–7 weeks. For asymptomatic patients, IMRT was offered first, following the same dose and time course. For IMRT, the surrounding organs at risk (OARs) and tumor size were contoured according to the tissue contouring guidelines of the Radiation Therapy Oncology Group (RTOG) [18], in which 50 Gy with 25 fractions was recommended for bone metastases. Dose escalation was conducted with a 3 + 3 design. Four radiation dose levels were planned: 39.6 Gy, 45 Gy, 50.4 Gy, and 54 Gy in 22 fractions, 25 fractions, 28 fractions, and 30 fractions, respectively, resulting in 3 patients in each dose group. The rationale of dose escalation and determination of maximal tolerable dose (MTD) was based on development of dose-limiting toxicity (DLT) (Fig. S2), defined as any grade III/IV toxicities. The initial two dose levels targeted the whole pelvis/retroperitoneum, whereas the following two dose levels acted as a subsequent boost for the prostate, seminal vesicles and pelvic/retroperitoneal metastatic lymph nodes, which was added after reaching 45 Gy. SBRT was delivered to bone metastases outside the IMRT irradiation area, in which 31–40 Gy with 5 fractions was recommended for dose segmentation,

depending on the surrounding OARs and tumor size. Dose determination for OARs in SBRT was based upon the AAPM Task Group 101 guidelines [19].

Radical prostatectomy

Radical prostatectomy was performed on da Vinci Si robotic platform (Intuitive Surgical Inc., Sunnyvale, CA, USA), adopting a transperitoneal multi-port access with extrafascial non-nerve-sparing procedures. Extended pelvic lymph node was performed, dissecting bilateral obturator, external iliac, internal iliac, presacral, as well as radiologically identified positive non-regional and/or retroperitoneal lymph nodes, up to the level of the renal arteries.

Study endpoints and outcome measurements

The primary endpoints of the current study were safety parameters. Treatment-related adverse events, including early and late gastrointestinal (GI), genitourinary (GU), and other morbidities, were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Intraoperative and 30-day postoperative morbidities were assessed by the Clavien-Dindo Complication system [20]. The secondary endpoints were efficacy parameters, consisting of positive surgical margin (pSM), MD Anderson tumor regression grading (TRG) classification, postoperative PSA, biochemical recurrence-free survival (BFS), and radiological progression-free survival (RPFS). Biochemical failure was defined as two consecutive postoperative PSA > 0.2 ng/mL. Radiological progression was defined as newly identified metastases, or increased volume or contrast uptake of existing lesions on subsequent PSMA-PET/CT images. Continence recovery was defined as ⩽ 1 daily pad use (pad weight increase < 50 g). Operative time, estimated blood loss (EBL), open conversion, fibrosis and adhesions at the site of radiotherapy, postoperative continence, and quality-of-life parameters, were documented as well.

Follow-up

^{68}Ga PSMA-PET/CT was conducted before registration, before radiotherapy, before surgery, and 1 year after surgery. PSA and testosterone levels of the participants were checked monthly. After patient discharge, follow-up was conducted every 3 months or when necessary in the first 2 years, every 6 months in the next 3 years, and annually thereafter. In case of disease progression, salvage treatment (e.g., second-generation anti-androgen, re-radiation, chemotherapy, targeted therapy) was advised according to the EAU guidelines [2] after being evaluated by our multi-disciplinary team.

Results

Baseline characteristics

Patients' baseline characteristics were listed in Table 1. The patients aged 52 to 80 years (mean, 66.2 yrs) with a body mass index ranging from 19.1 to 29.9 kg/m^2 (mean, 25.5 kg/m^2). Median baseline PSA was 62.0 ng/mL. Ten of 12 were International Society of Urological Pathology (ISUP) grade V (Gleason Score 9 or 10) on prostate biopsy. Nine of 12 had a clinical T4 stage, and ten presented with regional lymph node metastasis. Five

Table 1 Patient demographics, clinical stage and perioperative data in each individual patient

ID	Age	BMI (kg/m^2)	cStage	bGS	PSA0 (ng/mL)	Bonemets	OT (min)	EBL (mL)	LoS	pStage	pSM	Nodes retrieved	TRG	12mo pads
1	57	25.16	cT4N1M1a,b	4 + 4 = 8	21.23	5	100	50	5	pT3aN0Mx	+	24	1	⩽ 1
2	59	19.14	cT4N0M1b	4 + 4 = 8	40	2	95	80	7	pT2cN0Mx	–	18	1	⩽ 1
3	70	29.3	cT4N1M1a,b	4 + 5 = 9	60.987	3	90	200	5	pT3bN1Mx	+	12	2	⩽ 1
4	61	29.94	cT4N1M1a,b	5 + 4 = 9	146	1	185	50	8	pT2aN0Mx	–	17	1	⩽ 1
5	76	23.53	cT4N1M1a,b	5 + 4 = 9	14.677	1	90	50	9	pT3aN0Mx	+	8	2	3–4
6	66	23.77	cT4N1M1b	4 + 5 = 9	62	1	85	100	6	pT2aN0Mx	–	16	1	⩽ 1
7	56	28.69	cT4N1M1b	5 + 4 = 9	15.85	2	80	50	6	pT3bN1Mx	+	21	3	3–4
8	74	21.23	cT3bN0M1a,b	3 + 4 = 7	196.8	3	125	100	4	pT3bN0Mx	+	16	1	⩽ 1
9	76	21.72	cT3bN1M1b	3 + 3 = 6	66.16	1	90	40	7	pT3aN0Mx	–	5	1	⩽ 1
10	80	25.58	cT4N1M1b	5 + 4 = 9	>100	1	110	50	7	pT2cN0Mx	+	5	1	⩾ 5
11	52	29.94	cT4N1M1b	4 + 4 = 8	221.2	3	105	50	7	pT3bN1Mx	+	6	1	⩽ 1
12	67	28.52	cT2cN1M1b	4 + 5 = 9	241	1	110	200	6	pT3aN0Mx	–	12	2	⩽ 1

BMI, body mass index; cStage, clinical stage; bGS, biopsy Gleason score; OT, operative time; EBL, estimated blood loss; LoS, length of stay; pStage, pathological stage; pSM, positive surgical margin; TRG, tumor regression grade; PSA, prostate-specific antigen.

patients showed non-regional lymph node invasion. All presented oligometastatic bone lesions, in which 11 had ⩽ 3 lesions and 1 had 5 lesions. Vertebral, pelvic, femoral, sternal, clavicular and costal lesions accounted for 4, 9, 1, 1, 1, and 1, respectively.

Treatment morbidities

Acute and late toxicities, perioperative complications throughout the treatment procedure and follow-up were recorded in Tables 2 and S1. Overall, all patients were alive on their last follow-up, and no Grade III or IV morbidities were recorded. In radiotherapy, diarrhea (50.0%), myelosuppression (33.3%), urinary frequency (33.3%), decreased appetite (25.0%) and proctitis (25.0%) were the most frequently encountered symptoms, which were all transient, and the symptoms relieved after completion of radiotherapy; in the perioperative period, gross hematuria (100%) and abdominal pain (58.3%) were the most frequently encountered. Notably, no intraoperative major hemorrhage, rectal injury, or nerve severance was encountered. Three patients experienced lower extremity paresthesia and edema, and resolved after physical rehabilitation. One patient had prolonged drainage output, and appeared well on follow-up CT images after removal of the drainage tubes. During postoperative ADT, common anti-androgen-related complications, e.g., hot flashes (50.0%), fatigue (25.0%), gynecomastia (8.3%) were recorded along with other late-onset morbidities such as abdominal pain (25.0%), lower extremity edema (16.7%), urinary tract infection, cystitis, diarrhea, urinary retention, hematuria. Late GI and GU toxicities after 18 months occurred in 4 of 9 patients, in which patient #5 and #10 were grade II and the remaining were grade I.

Perioperative outcomes

All patients showed reduced tumor volume and/or reduced contrast uptake on consecutive ^{68}Ga PSMA-PET/CT or whole-body MRI images after neoadjuvant therapy (Fig. 1A–1L). Perioperative outcomes (documented from day of surgery to day of discharge) were also listed in Table 1. All patients underwent RARP plus ePLND successfully with no open conversion or re-admission. Mean operative time was 105.4 min (range, 80–185), with an estimated blood loss of 85 mL (range, 50–200). No blood transfusion was needed. Mean length of stay was 6.4 days (range, 4–9). Mean number of lymph nodes removed was 13.3 (range, 5–24). Positive surgical margin (pSM) rate was 33.3% (4/12), while 2 patients were marginally positive (< 0.1 cm). Pathological downstaging was 83.3% (10/12) for T staging and 41.7% (5/12) for N staging. MD Anderson TRG classification on final pathology showed that 66.7% (8/12) had no viable tumor cells after neoadjuvant treatment, i.e., TRG grade I (Fig. 1M and 1N), 3 patients (25.0%) showed TRG grade II, and 1 patient (8.3%) showed TRG grade III. Nevertheless, no complete response after treatment (pT0) was observed.

Follow-up

All patients were followed up to 1 year after surgery. Median follow-up time was 16.5 months (range, 15.2–24.5). All patients were alive. Mean RPFS was 21.3 months (95% confidence interval, 17.3–25.3, with both 1-year and 2-year RPFS of 83.3% (Fig. 1A–1L). BFS of 1

Table 2 Postoperative PSA, follow-up treatment, and treatment-induced toxicities in each individual patient.

ID	12mo PSA (ng/mL)	Latest PSA (ng/mL)	Salvage treatment	RT dose (Gy)	GU toxicities		GI toxicities		Clavien-Dindo
					Acute	Late	Acute	Late	
1	450	150 (20mo)	Abi + Dox + Zol	39.6			I (diarrhea)		I
2	0.004	0.004 (12mo)		39.6	I (frequency)		I (diarrhea)		I
3	0.02	0.02 (12mo)		39.6	I (radiation cystitis)		I (diarrhea)	I (diarrhea)	II
4	0.008	0.008 (24mo)		45	I (frequency)		I (diarrhea)		I
5	1.45	10.9 (19mo)	Abi + Dox + Ola	45			II (diarrhea, nausea)	II (abdominal pain)	II
6	0.01	0.01 (24mo)		45		I (frequency)	I (diarrhea)	I (abdominal pain)	II
7	0.001	0.001 (21mo)		50.4			I (nausea)		I
8	0.01	0.01 (14mo)		50.4					
9	0.01	0.001 (21mo)		50.4	I (frequency)		I (abdominal pain)	I (abdominal pain)	I
10	0.003	0.001 (21mo)	Abi	54		II (UTI)			II
11	0.01	0.001 (15mo)		54					
12	0.006	0.006 (12mo)		54	I (frequency, urgency)				I

PSA, prostate-specific antigen; Abi, abiraterone; Dox, docetaxel; Zol, zoledronic acid; Ola, olaparib; RT, radiotherapy; GU, genitourinary; GI, gastrointestinal; UTI, urinary tract infection.

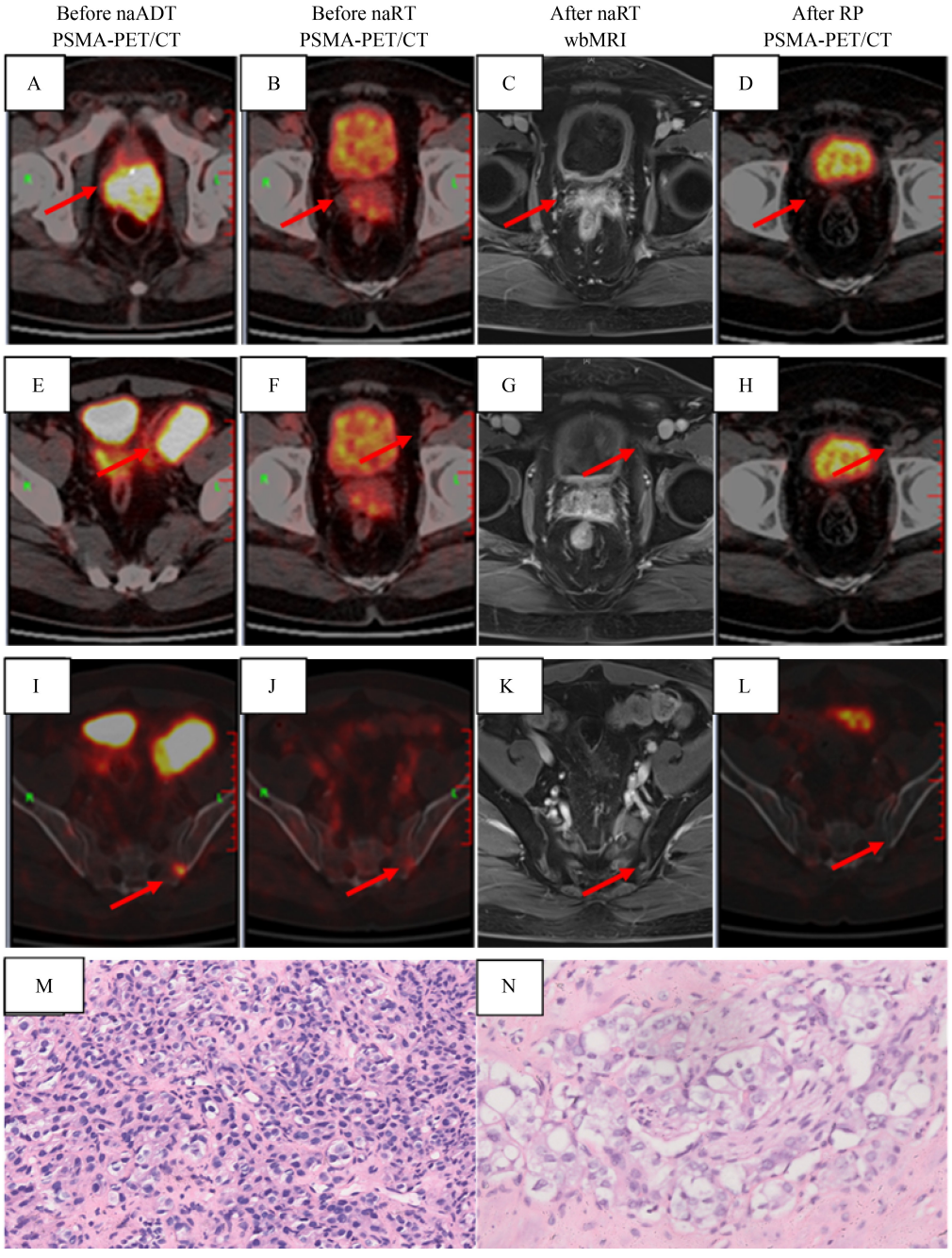

Fig. 1 Radiological manifestation on consecutive images during the treatment course, showing reduction of lesion size or contrast uptake, as well as histological tumor regression on prostate biopsy vs prostatectomy specimen. (A) Prostatic fossa before naADT; (B) prostatic fossa before naRT; (C) prostatic fossa after naRT; (D) prostatic fossa 1 year after RP; (E) left iliac lymph node before naADT; (F) left iliac lymph node before naRT; (G) left iliac lymph node after naRT; (H) left iliac lymph node 1 year after RP; (I) left S3 bone metastasis before naADT; (J) left S3 bone metastasis before naRT; (K) left S3 bone metastasis after naRT; (L) left S3 bone metastasis 1 year after RP (right); (M) histopathological changes in prostatic biopsy, showing adenocarcinoma; (N) pathology of the same patient after prostatectomy, showing tumor regression grade I (MD Anderson) with no viable tumor cells after neoadjuvant treatment. PSMA, prostate-specific membrane antigen; wbMRI, whole-body magnetic resonance imaging; naADT, neoadjuvant androgen deprivation therapy; naRT, neoadjuvant radiotherapy; RP, radical prostatectomy.

year after RARP was 83.3% (10/12). Patients' PSA, before enrollment, before neoadjuvant radiotherapy, after radiotherapy, before RARP, and after RARP, were documented in Fig. S3 (depicted as lgPSA; note that lg0.2 = −0.699). Two patients recorded biochemical failure and developed castration-resistant prostate cancer (CRPC), in which patient #1 was in 39.6Gy/22F dose level group, showing radiological progression with 2 newly identified metastatic lesions (third and fourth right anterior ribs), and undertook abiraterone, docetaxel

chemotherapy plus zoledronic acid 12 months postoperatively; patient #5 in 45Gy/25f dose level group had PSA and radiological progression after RARP, and was advised to receive SBRT for newly identified metastatic lesion in the left femur, combined with abiraterone followed by docetaxel and olaparib after genetic profiling. Another patient (#11) changed to abiraterone 9 months postoperatively, due to gynecomastia and breast soreness. For continence recovery, 3-, 6- and 12-month continence recovery were 41.7%, 75%, and 75%, respectively. On the 12th month postoperatively, 2 patients had moderate incontinence (3–4 daily pads use), and 1 patient had severe incontinence (≥ 5 pads use daily).

Discussion

Neoadjuvant therapy has become widely recognized over the years in treating advanced-stage malignant tumors, especially with the advent of new robotic platforms. In terms of prostate cancer, naADT has been carried out in many centers worldwide with mixed results, and its value in the comprehensive treatment of locally-advanced prostate cancer remains controversial. Some studies have reported reduction of prostate volume and downgrading of tumor stages [21], while some other studies have also shown no benefit regarding biochemical recurrence-free survival or cancer-specific survival [22,23], and may also lead to intraperitoneal adhesions [24] or neuroendocrine differentiation [25]. Postoperative radiotherapy has long been recognized for node-positive patients, but the treatment timing, prognostic value or dose-related toxicities are still inconclusive for oligometastatic PCa. Neoadjuvant radiotherapy, on the other hand, has become a promising regimen, in which case a systemic plus local therapy has shown its value for various types of malignant tumors in recent years. For prostate cancer, several clinical trials on naRT have been published, focusing on localized or high-risk PCa [14–17], but the study designs vary, and the optimal timing, dose, location and modality of naRT remains to be determined. That being said, it is still believed that the regimen of neoadjuvant therapy by combining local surgical removal of the primary site plus systemic and metastasis-directed therapy is worth exploring, given the fact that it may defer new metastases derived from primary site, control symptoms, as well as provide potential survival benefit [26].

The advantages of the current study lie in several folds. To the best of our knowledge, this is the first metastasis-directed clinical trial of naRT on oligometastatic PCa. We have obtained a dose-escalation regimen and treated metastatic lesions with SBRT and prostatic fossa with IMRT. First, compared with neoadjuvant ADT alone, neoadjuvant radiohormonal therapy is theoretically superior in reducing tumor burden and extraprostatic stem-cell viability, which may provide better downgrading of tumor itself, increasing R0 resection rate, and enhancing subsequent treatment sensitivity [22]. Second, IMRT can markedly reduce Grade 2–4 acute and chronic GI toxicity with better biochemical recurrence-free survival, according to the EAU guidelines [2]. Third, dose-escalation of radiotherapy may significantly reduce the risk of subsequent metastasis due to insufficient primary radiation dose, which is supported by various randomized clinical trials, showing markedly increased 10-year BFS and disease-specific survival [27]; also, the range of irradiation for SBRT was determined 2 cm above the highest plane of their respective lymph node or bone metastases. Compared with postoperative RT, the total dose and irradiation range of naRT may also be reduced, which may further reduce complication [21]. In terms of RARP, lymphadenectomy was performed with the help of da Vinci robotic platform for non-regional positive lymph nodes, as extensive as the level of the renal arteries, which may further reduce tumor burden after surgery. Finally, postoperative pathology and sequential PSMA-PET/CT provides urologists with more accurate disease evaluation and information for prognosis and prompt treatment adjustments in case of disease progression.

The primary objective of the current study was to assess the feasibility, safety and validity of naRT on OMPC. Our results indicated that preoperative radiohormonal therapy did not bring major complications, nor did dose escalation increase treatment-induced toxicities or surgical difficulties, compared with previous studies on OMPC patients undertaking radical prostatectomy [5,8]. Also, the different interval from RT to RP did not appear to affect blood loss, operative time, as well as intraoperative fibrosis, adhesion, ureteral or rectal injury, anastomotic leak or stricture, and other intraoperative morbidities. Moreover, the extensiveness of lymphadenectomy did not markedly increase risk of lymphocele, neurovascular injury, lower extremity swelling or dysfunction; additionally, postoperative continence was acceptable with a 6-month recovery of 75%. In terms of validity outcomes, the current study had a pathological downstage of 83.3% in pT stage and 41.7% in pN stage, which seemed superior comparing to other metastasis-directed or neoadjuvant therapies [28–30]. Of course, no definitive conclusions should be drawn before follow-up verifications with a larger sample size. All patients but one (8.3%) showed no response (i.e., TRG grade III) to neoadjuvant radiohormonal therapy, indicating an effective preoperative treatment, which can also be visualized on subsequent PSMA-PET/CT imagings. Note that this patient also recorded pathological downstaging, from cT4N1 to pT3bN1. Biochemical recurrence-free

survival and radiological progression-free survival also indicated that such treatment regimen may be effective for this patient population. Specifically, the two patients who encountered PSA failure were both in low-dose groups (39.6Gy and 45Gy), while no PSA failure was recorded in high-dose groups. The above results suggest that the current dose-escalation protocol is safe and efficacious, warranting the possibility of higher dose design of naRT, which should be verified by further studies with larger sample sizes and longer follow-up. Notably, some studies have reported complete pathological response (pT0) [31,32], which was not observed in the current study. It appears that no consensus has been reached so far regarding the timing and clinical value of such parameter; also under an oligometastatic setting, pT0 may be more challenging to achieve with unknown significance for follow-up treatment.

The two patients who experienced treatment failure also provided us with valuable information for further investigations. Patient #1 had early PSA recurrence, possibly due to higher tumor burden (5 oligometastatic lesions), suggesting that the current treatment protocol may better benefit patients with lower tumor burden (i.e., metastatic lesions $\leqslant 3$). Patient #5 also showed rapid disease progression, possibly due to accompanying high neuroendocrine differentiation on final pathology, suggesting that patient with adenocarcinoma, rather than neuroendocrine prostate cancer, may benefit better from naRT. These outcomes also require further studies to verify the best indications and patient population who may benefit most from this treatment protocol.

Several limitations may also be noted. Since the primary goal was to assess the feasibility and safety parameters, this trial was designed to be a single-center and non-blinded single-arm study with a relatively small sample size. Therefore, caution must be paid before drawing any conclusions for clinical practice. Also, we failed to provide statistically significant information regarding the potential benefit of naRT compared with neoadjuvant ADT or adjuvant RT. Further clinical trials and comparative studies should be designed to acquire higher-evidence data, so as to determine the best treatment indications for this treatment regimen, and whether it is more beneficial to patients with higher or lower tumor burden. Also, since postoperative ADT was still ongoing by the end of study follow-up, we believe that no conclusions should be drawn on treatment efficacy based on our current survival parameters. Longer follow-up is still mandatory to observe late toxicities and more mature prognostic parameters.

Conclusions

In all, the current study provides preliminary outcomes of neoadjuvant radiohormonal therapy for oligometastatic prostate cancer, indicating that the integration of preoperative radiotherapy to the primary plus metastatic site, together with local therapy to surgically remove the prostate is well tolerated for this patient population. Further investigations and higher-level clinical trials are on the way to provide data with higher evidence.

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Compliance with ethics guidelines

Yifan Chang, Xianzhi Zhao, Yutian Xiao, Shi Yan, Weidong Xu, Ye Wang, Huojun Zhang, and Shancheng Ren declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. Informed consent was obtained from all patients for being included in the study.

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