Original Article

Clinical characteristics and prognostic factors of low metastatic burden prostate cancer with non-regional lymph node metastases: role of cytoreductive radiotherapy?

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Background: Low metastatic burden prostate cancer (LMBPC) is a special transitional clinical status between localized and disseminated disease, but the clinical prognostic factors and potential therapeutic interventions of those with non-regional lymph node metastases (NRLNM) remain less understood. We aim to explore the prognostic factors and investigate the potential treatment strategy for LMBPC patients with NRLNM.

Methods: There were 88 patients retrospectively identified. Kaplan-Meier method and Cox proportional hazards model were used for prognostic analyses. Patients receiving non-regional lymph node (NRLN) radiotherapy (NRLN RT group) after prostate-directed local therapy were matched to patients without NRLN RT (control group) by propensity score matching (PSM).

Results: The majority of patients had Gleason score >8 (61.4%), retroperitoneal metastases (93.2%), upward NRLNM (78.4%) and hormone-sensitive prostate cancer (HSPC) (68.2%) at diagnosis. Patients with upward NRLNM showed better survival outcome (75.4 *vs.* 32.8 months, P=0.04). HSPC [hazard ratio (HR) =0.32, P=0.003], bone metastases (HR =3.79, P<0.001), androgen-receptor-axis-targeted agents (ARATAs) (HR =0.40, P=0.007), and notably, NRLN RT (HR =0.23, P=0.001) were independent prognostic factors of overall survival (OS). The median follow-up was 43.3 months. The prostate-specific antigen (PSA) response and median progression-free survival (PFS) after NRLN RT were 70.6% and 29.5 months. The 4-year OS for NRLN RT group and control group were 62% and 46% (P=0.04). After PSM, NRLN RT was still associated with improved OS (HR =0.39, P=0.04). No grade ≥3 NRLN RT-related adverse event was observed.

Conclusions: Upward NRLNM was the main pattern for LMBPC with NRLNM and associated with better clinical outcome. HSPC, bone metastases, ARATAs and NRLN RT were independent prognostic factors. Applying cytoreductive RT to NRLNM may benefit LMBPC patients. Further studies are still needed.

Keywords: Cytoreductive radiotherapy; low metastatic burden; metastatic prostate cancer (PC); non-regional lymph node (NRLN)

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Introduction

In metastatic prostate cancer (PC), low metastatic burden prostate cancer (LMBPC) is a special transitional clinical status between localized and disseminated disease. The STAMPEDE trial showed that prostate-directed radiotherapy (PDRT) can improve the overall survival (OS) of low-volume metastatic hormone-sensitive prostate cancer (mHSPC) (1-3). A secondary exploratory analysis of this study showed that M1a patients obtained OS and failure-free survival benefits from PDRT (4). Nevertheless, the understanding about the population of LMBPC patients with non-regional lymph node metastases (NRLNM), such as clinical characteristics, prognostic factors, and treatment strategy, remains largely unknown.

Nowadays, PDRT has been recommended in LMBPC by acknowledged guidelines. Regarding the oligometastatic PC, PEACE V-STORM (5) and ORIOLE (6,7) trials reported that metastatic-directed radiotherapy (MDRT) was associated with improved androgen deprivation therapy (ADT)-free survival and progression-free survival (PFS) for oligometastatic patients who had previously undergone curative local therapy. However, the previous studies mainly focused on MDRT to bone metastatic lesions, the evidence on MDRT to NRLNM is limited and yet to be investigated.

Therefore, this study aims to retrospectively identify the clinical characteristics and prognostic factors in LMBPC patients with NRLNM after prostate-directed local therapy (PDLT) and investigate the potential therapeutic interventions for this population in clinical practice. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-489/rc).

Highlight box

Key findings

- Upward metastasis is the main pattern of this studied population—low metastatic burden prostate cancer (LMBPC) with non-regional lymph node (NRLN) metastases (NRLNM) following prostate-directed local therapy, which is associated with better survival outcomes.
- Hormone-sensitive status, bone metastases, androgen-receptor-axis-targeted agents (ARATAs), and NRLN radiotherapy (NRLN RT) are independent prognostic factors.
- Applying cytoreductive NRLN RT may benefit this specific population.

What is known and what is new?

- LMBPC is a special transitional clinical status between localized and disseminated disease. Although it is currently well acknowledged that LMBPC gains survival benefits from prostate-directed radiotherapy, few studies have investigated the special group among this population—those with NRLNM and corresponding potential therapeutic interventions.
- Our research studies this specific group, demonstrates the clinical characteristics and prognostic factors and innovatively points out that applying cytoreductive NRLN RT may benefit these patients.

What is the implication, and what should change now?

- These findings advocate more attention to the clinical characteristics and prognostic factors of NRLNM in LMBPC patients, such as the metastases direction, castration status, accompanied bone metastases, ARATAs, which may improve the further treatment decision.
- Cytoreductive NRLN RT may play a role in cautiously selected NRLN-positive LMBPC patients

Methods

Patient selection and baseline evaluation

This study was approved by the ethics committee of Scientific Research Sun Yat-sen University Cancer Center (No. B2022-181) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The medical records of 202 metastatic PC (mPC) patients with NRLNM at Sun Yat-sen University Cancer Center between August 2009 and September 2022 were retrospectively analyzed. Patients with high metastatic volume according to the CHAARTED criteria, complicated with other malignancies, follow-up time <3 months, or those with missing key clinical data were excluded, leaving a total of 88 mPC patients in the analysis.

The diseases of all patients were staged or restaged according to the 8th edition of the American Joint Committee on Cancer staging. The staging of diseases was based on the primary and metastatic tumor lesions examined by conventional imaging including magnetic resonance

imaging (MRI) and/or computed tomography combined with Tc-99m bone scintigraphy. The direction of NRLNM such as those located in inguinal and/or mesenteric regions were nominated as others instead of upward NRLNM. High metastatic burden was defined as 4 bone metastases with one or more outside the vertebral bodies/pelvis or with visceral metastases. Low metastatic burden was defined as the metastatic burden without the condition of high metastatic volume. Castration-resistant prostate cancer (CRPC) was defined as biochemical or radiological progression in patients receiving ADT with castrate serum testosterone levels (<50 ng/dL) according to the Prostate Cancer Working Group 3 (PCWG3) criteria (8). Number of NRLNM used amount of 5 as a cutoff based on the results from ancillary studies of phase III trial STAMPEDE (9).

Treatment approaches

For the patients who had previously received PDLT (prostate radiotherapy or prostatectomy) and with regional lymph node metastasis, pelvic lymph node dissection and/or radiotherapy were also applied. All of the patients received lifelong ADT (either orchiectomy or gonadotropin-releasing hormone agonist/antagonist) immediately after the diagnosis of metastasis. The application of androgen-receptor-axis-targeted agents (ARATAs) and chemotherapy (CT) were according to the clinical guidelines, patients' wishes, and drug accessibility. In our study, ARATAs included abiraterone, apalutamide, enzalutamide. In the study, drug history was recorded after the diagnosis of NRLNM.

Patients receiving cytoreductive NRLN radiotherapy in addition to PDLT were categorized into the NRLN RT group, leaving others to the control group. In NRLN RT group, all of the patients were stimulated by supine or prone position with contrast-enhanced computed tomography scans for radiotherapy planning. Contouring and prescribed dose were based on the recommendations by the Radiation Therapy Oncology Group (RTOG). Gross tumor volume (GTV) was defined as positive lymph nodes detected by imaging. The positive lymph nodes were defined as those of short-axis diameter ≥1.5 cm in computed tomography based on criteria of Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 (10). The clinical target volume (CTV) included the GTV with a radial margin of 0.5 cm and also covered the whole involved nodal station. The planning gross tumor volume (PGTV) was generated by GTV plus a uniform margin of 0.5 cm expansion and the planning clinical target volume (PCTV) was obtained from CTV with a uniform margin expansion of 0.5 cm. The typical radiation dose was 60 Gy for PGTV and 45 Gy for PCTV in 25 fractions, once daily, 5 days a week. Prescription dose was required to cover more than 95% of the target lesion. Normal tissue constraints were based on RTOG. Intensity-modulated radiotherapy (IMRT) or volumetric intensity-modulated arc therapy (VMAT) was used for planning, and 6 MV X-ray beams were generated by Elekta or Varian linear accelerator.

Outcome evaluations

The duration of follow-up was calculated from the time of diagnosis of NRLNM. In most cases, patients were regularly followed up every 3 months with a prostate-specific antigen (PSA) assessment, and every 6–12 months with radiological evaluation. When a susceptible relapse occurred, both PSA and radiological evaluation were arranged. Acute and late adverse events were assessed according to the Common Terminology Criteria for Adverse Events Version 4.0.

OS was calculated from the time of diagnosis of NRLNM to the death due to any cause or the last follow-up. PFS after NRLN RT was measured from the beginning of NRLN RT until PSA or radiographic progression. PSA response after NRLN RT was defined as a >50% decline in serum PSA levels from the baseline before NRLN RT, according to PCWG3 (8).

Statistical analysis

Data were summarized by descriptive statistics [using frequency for categorical variables and median with interquartile range (IQR) for continuous variables]. Chi-squared test was used for comparing categorical data. Survival outcomes were estimated using the Kaplan-Meier method and compared with the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression. Propensity score matching (PSM) was used to balance confounding factors. One-to-one matching without replacement was utilized using nearest-neighbor matching, with a caliper value of 0.2, taking PSA when NRLNM, Gleason score, castration status, and number of bone metastases as covariates. A P value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 26.0 (IBM Corp., NY, USA) and the R statistical software (version 4.2.1).

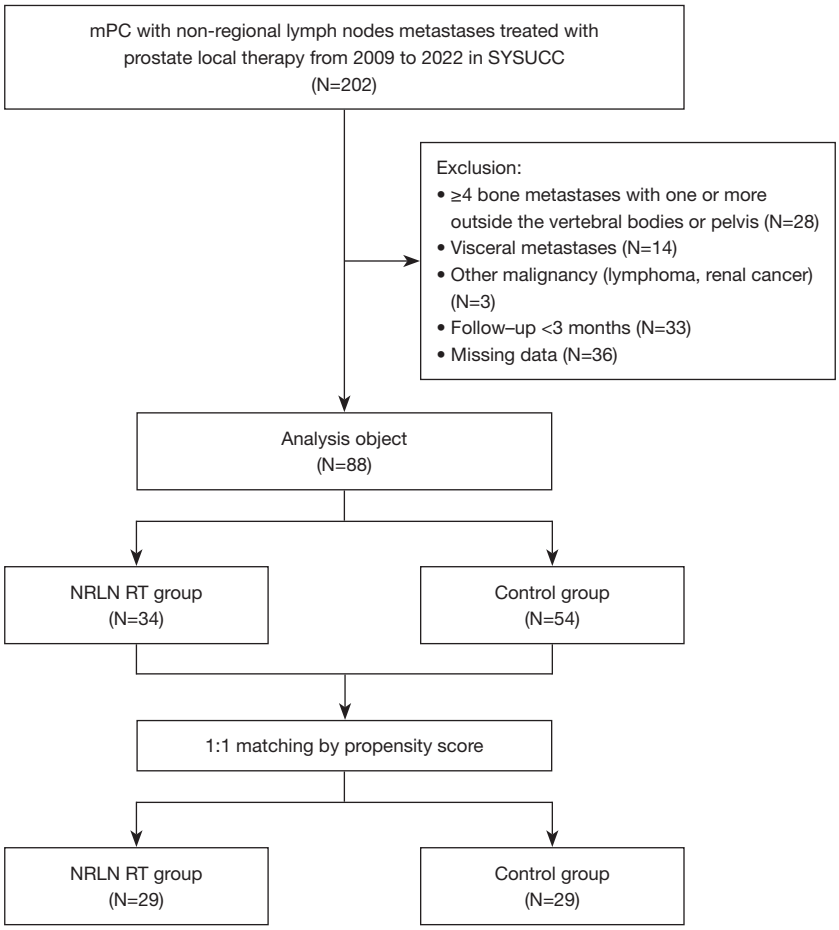

Figure 1 Study flow diagram. mPC, metastatic prostatic cancer; NRLN RT, non-regional lymph node radiotherapy; SYSUCC, Sun Yat-sen University Cancer Center.

Results

Patient and disease characteristics in the whole cohort

The study flow diagram is illustrated in *Figure 1*. The baseline characteristics of 88 LMBPC patients with NRLNM after PDLT for analysis are shown in *Table 1*. The distribution and corresponding percentages of NRLNM are shown as *Figure 2A*. In this investigated population, more than half of the patients had Gleason score >8 (54 patients, 61.4%). Forty-six-point-six percent patients demonstrated LMBPC with bone metastases. Of note, almost all the cases (93.2%) were accompanied by retroperitoneal metastases. The majority of patients (78.4%) shared the pattern of upward NRLNM. The percentage of patients with ≥5 NRLNM in bone metastases group was significantly lower than that in those without bone metastases (29.3% *vs.* 57.4%, P=0.008). The percentage of CRPC at the time of NRLNM was higher in patients with CT than in those without CT (56.0% *vs.* 22.2%, P=0.002).

Analysis of survival outcomes and prognostic factors

After a median follow-up of 43.3 months, 38 patients (43.2%) died leaving a total of 50 patients (56.8%) alive. The median OS was 48.3 months. Patients without bone metastases, treated with ARATAs had better survival benefits than those with bone metastases (75.4 *vs.* 26.0 months, P<0.001) or without ARATAs prescription (24.9 *vs.* 8.0 months, P=0.03). However, the site of NRLNM (P=0.95) or CT treatment (P=0.85) did not display any survival effect in the whole cohort. In both univariate and multivariate analyses, NRLN RT together with HSPC at the time of NRLNM, bone metastases, and application of ARATAs were evaluated to correlate closely with OS (*Table 2*).

Table 1 Baseline characteristics of the patients (n=88)

Parameter	Value
Age at diagnosis (years)	65 [61–71]
PSA (ng/mL) when NRLNM	
<20	28 (31.8)
≥20	60 (68.2)
Gleason score	
≤8	34 (38.6)
9–10	54 (61.4)
HSPC at the time of NRLNM	
No	28 (31.8)
Yes	60 (68.2)
Bone metastases	
No	47 (53.4)
Yes	41 (46.6)
Site of NRLNM	
Retroperitoneal involved	82 (93.2)
Others	6 (6.8)
No. of NRLNM	
<5	49 (55.7)
≥5	39 (44.3)
Direction of NRLNM	
Upwards	69 (78.4)
Others	19 (21.6)
ARATAs	
No	37 (42.0)
Yes	51 (58.0)
CT	
No	63 (71.6)
Yes	25 (28.4)

Data are presented as median [interquartile range] or number (percentage). ARATAs, androgen-receptor-axis-targeted agents; CT, chemotherapy; HSPC, hormone-sensitive prostate cancer; NRLNM, non-regional lymph node metastases; PSA, prostate specific-antigen.

Figure 2B-2H showed a representative patient diagnosed as M1a at first, received NRLN RT at metastatic CRPC (mCRPC) stage and there was no disease progression in the following 4 years. Thereafter, the bilateral cervical lymph nodes metastases were discovered along with biochemical progression and no effective medication was available after switching to multi-line ARATAs. Recently, he has been treated with selective cytoreductive NRLN RT to cervical region and again achieved a good PSA response.

Survival analysis before and after PSM

It was found that with regard to the direction of NRLNM, the median OS of upward group showed a higher survival rate than others (75.4 *vs.* 32.8 months, P=0.04) (*Figure 3A*). Among the 34 patients who received NRLN RT, 13 cases underwent NRLN RT concurrent with PDLT at metastatic stage, 12 cases received NRLN RT after PDLT at local stage and 9 cases had NRLN RT after PDLT at metastatic stage respectively. The site of treated NRLNM included retroperitoneal (28 cases), common iliac (5 cases), and inguinal (1 case) lymph nodes. As mentioned above, NRLN RT was evaluated as a prognostic factor in LMBPC patients. To eliminate the influence of selection bias, we further explored the role of NRLN RT in our cohort after PSM.

As shown in *Table 3*, patients were divided into NRLN RT group (34 patients) and the control group (54 patients). Four-year OS was 46% and 62% in control group and NRLN RT group (*Figure 3B*). The median NRLN RT-PFS was 29.5 months. Among NRLN RT group, 70.6% of patients showed PSA response after NRLN RT. The largest PSA change was depicted as a waterfall plot shown in *Figure 3C*. Patients who underwent NRLN RT for metachronous disease had a tendency of better OS than those who received NRLN RT for synchronous disease (P=0.09).

Before matching, the percentage of patients with a PSA <20 mg/mL at the time of NRLNM in NRLN RT group was higher than that in the control group (50.0% *vs.* 20.4%, P=0.004). After matching with covariates of PSA when NRLNM, Gleason score, castration status, and number of bone metastases, 29 patients in NRLN RT group were matched to 29 patients in control group, and no significant difference of baseline characteristics was observed between the two groups (*Table 3*). The median OS of NRLN RT group was significantly longer than that of control group (not reached *vs.* 39.6 months, P=0.03) (*Figure 3D*).

Adverse events related to NRLN RT

NRLN RT-related adverse events were observed in 16 of the 34 patients, and all were grades 1–2 (*Table 4*). Acute adverse

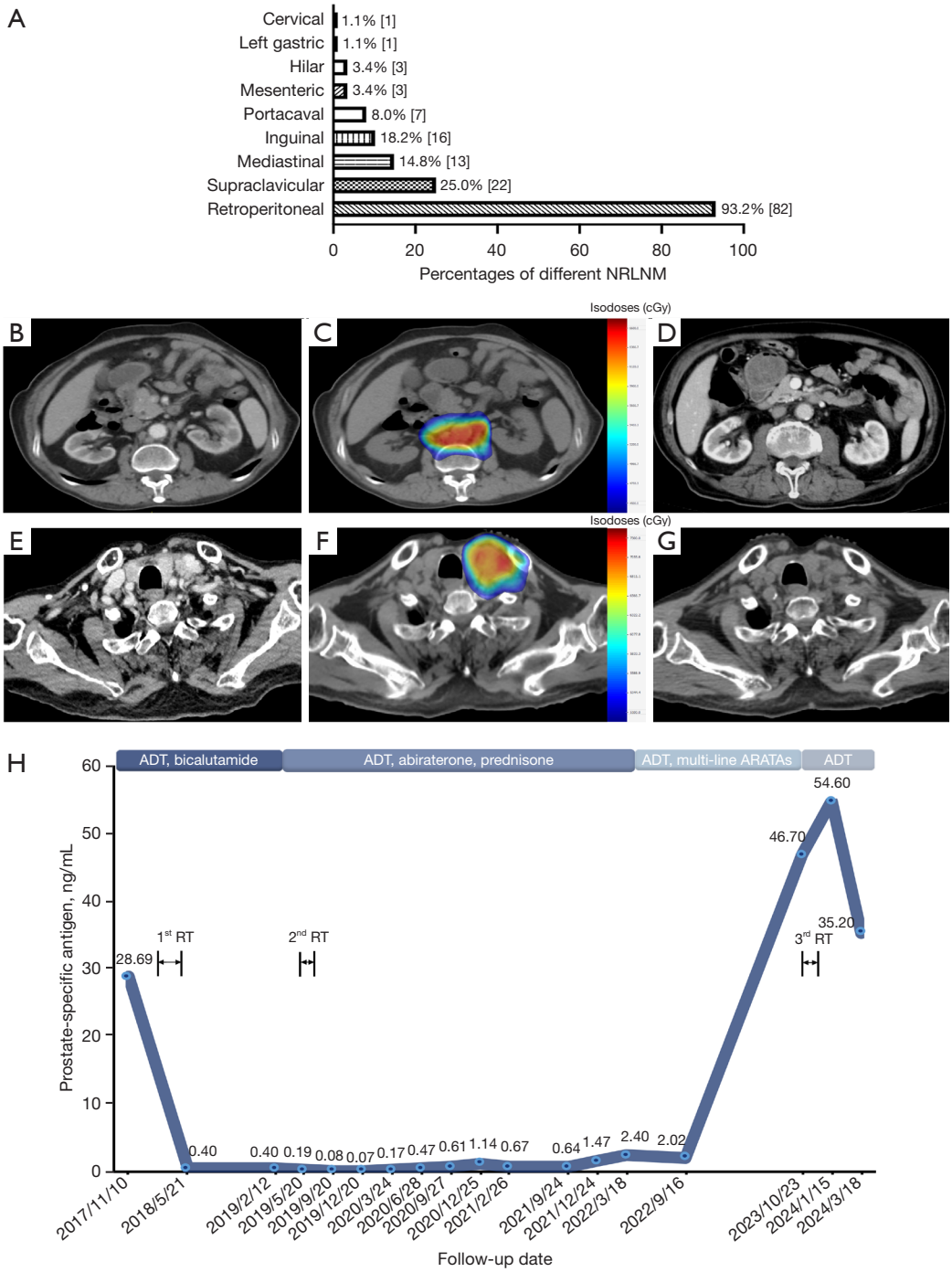

Figure 2 The pattern of NRLNM in our study and an illustrative case exemplifying the efficacy of treatment in a clinical context. (A) The percentages (numbers) of different distributions of NRLNM. Typical plane of a representative patient receiving retroperitoneal NRLN RT; (B) axial contrast CT image before NRLN RT; (C) treatment plan of retroperitoneal NRLN RT; (D) axial plain CT image 1 year after retroperitoneal NRLN RT. Four years later, cervical lymph node metastases typically showed on (E) axial contrast CT image; (F) treatment plan of cervical NRLN RT; (G) axial plain CT image 1 month after cervical NRLN RT with obvious tumor reduction; (H) prostate-specific antigen changes with different treatment interventions. 1st RT, radical radiotherapy; 2nd RT, retroperitoneal lymph node radiotherapy; 3rd RT, cervical lymph node radiotherapy; ADT, androgen deprivation therapy; ARATAs, androgen-receptor-axis-targeted agents; CT, computed tomography; NRLNM, non-regional lymph node metastases; NRLN RT, non-regional lymph node radiotherapy.

Table 2 Univariate and multivariate Cox hazard analyses of prognostic factors for the overall survival

Parameters	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
<65	1			–	–	–
≥65	1.59	0.84–3.04	0.16	–	–	–
PSA (ng/mL) at the time of NRLNM						
<20	1			–	–	–
≥20	1.48	0.71–3.06	0.30	–	–	–
Gleason score						
≤8	1			–	–	–
9–10	1.15	0.59–2.23	0.68	–	–	–
HSPC at the time of NRLNM						
No	1			1		
Yes	0.49	0.25–0.96	0.04	0.32	0.15–0.68	0.003
Bone metastases						
No	1			1		
Yes	3.11	1.60–6.03	0.001	3.79	1.88–7.62	<0.001
Site of NRLNM						
Retroperitoneal involved	1			–	–	–
Others	1.05	0.25–4.37	0.95	–	–	–
No. of NRLNM						
<5	1			–	–	–
≥5	0.98	0.52–1.85	0.94	–	–	–
Direction of NRLNM						
Upwards	1					
Others	2.04	1.02–4.07	0.04	–	–	0.23
ARATAs						
No	1			1		
Yes	0.50	0.26–0.94	0.03	0.40	0.21–0.78	0.007
CT						
No	1			–	–	–
Yes	0.94	0.46–1.90	0.85	–	–	–
NRLN RT						
No	1			1		
Yes	0.46	0.22–0.97	0.04	0.23	0.10–0.54	0.001

ARATAs, androgen-receptor-axis-targeted agents; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; HSPC, hormone-sensitive prostate cancer; NRLNM, non-regional lymph node metastases; NRLN RT, non-regional lymph node radiotherapy; PSA, prostate specific-antigen.

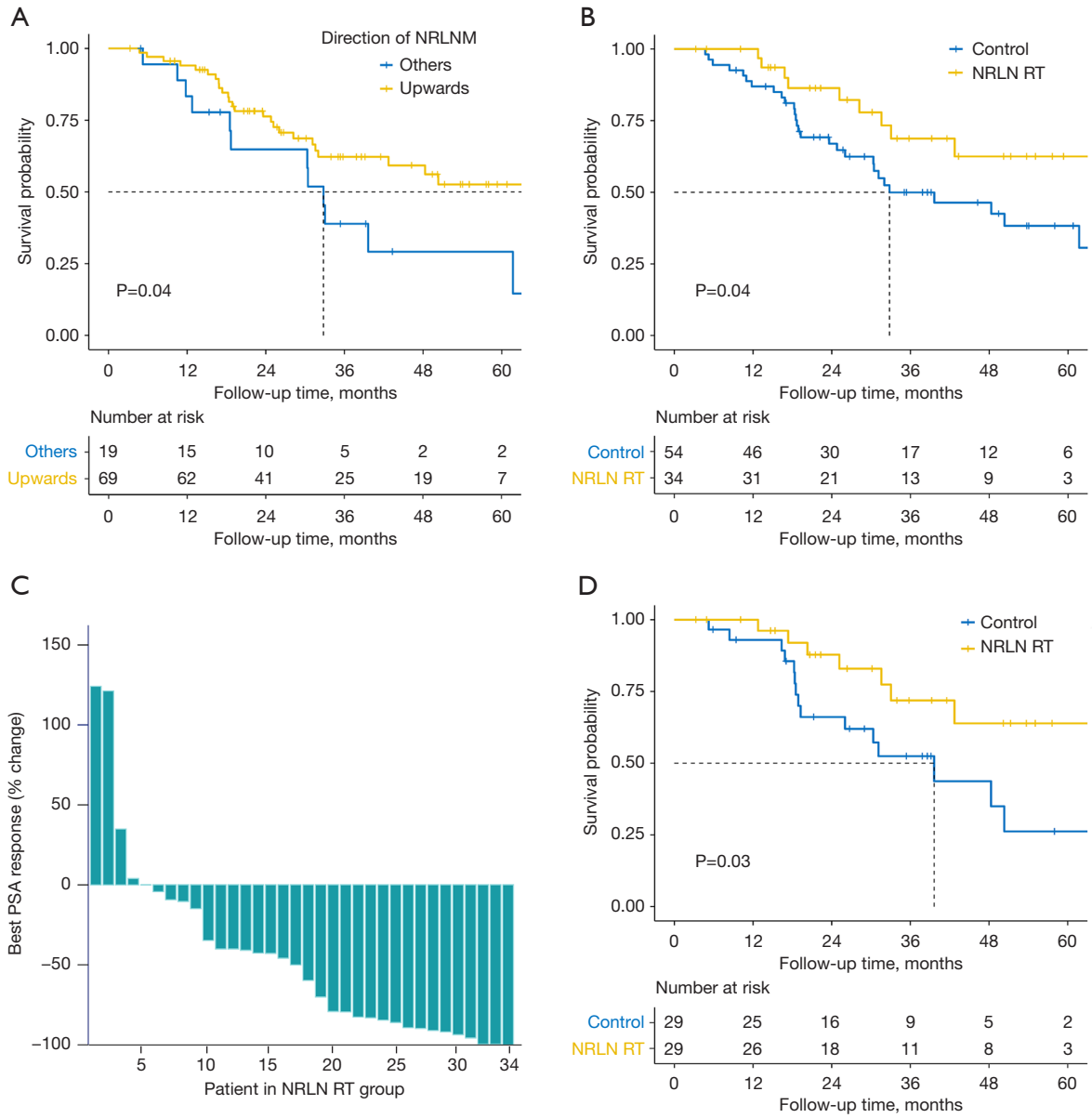

Figure 3 Survival outcomes and treatment response in the investigated patients. (A) Kaplan-Meier survival analysis calculating overall survival according to direction of NRLNM; (B) NRLN RT *vs.* control before propensity score matching; (C) best PSA response after NRLN RT; (D) NRLN RT *vs.* control after propensity score matching. NRLNM, non-regional lymph node metastases; NRLN RT, non-regional lymph node radiotherapy; PSA, prostate specific-antigen.

events (AEs) included gastrointestinal (GI) toxicity (grade 1: 9 patients, grade 2: 2 patients), skin toxicity (grade 1: one patient, grade 2: 2 patients), and bone marrow suppression (grade 1: 4 patients, grade 2: 6 patients). Regarding the late AEs, grade 1 and grade 2 late bone marrow suppression were observed in 2 and 3 patients, respectively.

Discussion

The population of LMBPC patients with NRLNM is a particular subgroup of mPC. In this study, we reported the clinical characteristics and prognostic factors, and identified NRLNM RT might be a potential therapeutic intervention for this population.

Table 3 Baseline characteristics of the patients before and after PSM

Parameters	Before PSM			After PSM		
	NRLN RT group (n=34)	Control group (n=54)	P	NRLN RT group (n=29)	Control group (n=29)	P
Age at diagnosis (years)	66 [53–87]	65 [45–91]	0.68	65 [59–74]	64 [61–69]	0.80
PSA (ng/mL) when NRLNM			0.004			0.59
<20	17 (50.0)	11 (20.4)		13 (44.8)	11 (37.9)	
≥20	17 (50.0)	43 (79.6)		16 (55.2)	18 (62.1)	
Gleason score			0.70			0.59
≤8	14 (41.2)	20 (37.0)		10 (34.5)	12 (41.4)	
9–10	20 (58.8)	34 (63.0)		19 (65.5)	17 (58.6)	
HSPC at the time of NRLNM			0.02			0.42
No	16 (47.1)	12 (22.2)		13 (44.8)	10 (34.5)	
Yes	18 (52.9)	42 (77.8)		16 (55.2)	19 (65.5)	
Bone metastases			0.94			0.79
No	18 (52.9)	29 (53.7)		15 (51.7)	14 (48.3)	
Yes	16 (47.1)	25 (46.3)		14 (48.3)	15 (51.7)	
Site of NRLNM			>0.99			0.60
Retroperitoneal involved	32 (94.1)	50 (92.6)		28 (96.6)	26 (89.7)	
Others	2 (5.9)	4 (7.4)		1 (3.4)	3 (10.3)	
No. of NRLNM			0.68			0.19
<5	18 (52.9)	31 (57.4)		14 (48.3)	19 (65.5)	
≥5	16 (47.1)	23 (42.6)		15 (51.7)	10 (34.5)	
Direction of NRLNM			0.48			0.52
Upwards	28 (82.4)	41 (75.9)		24 (82.8)	22 (75.9)	
Others	6 (17.6)	13 (24.1)		5 (17.2)	7 (24.1)	
ARATAs			0.90			0.43
No	14 (41.2)	23 (42.6)		14 (48.3)	11 (37.9)	
Yes	20 (58.8)	31 (57.4)		15 (51.7)	18 (62.1)	
CT			0.87			>0.99
No	24 (70.6)	39 (72.2)		20 (69.0)	20 (69.0)	
Yes	10 (29.4)	15 (27.8)		9 (31.0)	9 (31.0)	

Data are presented as median [interquartile range] or number (percentage). ARATAs, androgen-receptor-axis-targeted agents; CT, chemotherapy; HSPC, hormone-sensitive prostate cancer; NRLNM, non-regional lymph node metastases; NRLN RT, non-regional lymph node radiotherapy; PSA, prostate specific-antigen; PSM, propensity score matching.

Table 4 NRLN RT related adverse events

Grade of AEs	Acute GI AEs	Acute skin AEs	Acute BMS	Late BMS
Grade 0	23 (67.6)	31 (91.2)	24 (70.6)	29 (85.3)
Grade 1	9 (26.5)	1 (2.9)	4 (11.8)	2 (5.9)
Grade 2	2 (5.9)	2 (5.9)	6 (17.6)	3 (8.8)

Data are presented as number (percentage). AE, adverse events; BMS, bone marrow suppression; GI, gastrointestinal; NRLN RT, non-regional lymph node radiotherapy.

It is interesting to find that the direction of NRLNM was mostly upward, and upward NRLNM was associated with better survival outcome than other metastatic patterns. It has been widely accepted that the common nodal drainage pattern in PC is pelvic drainage pathway (11), but the direction of NRLNM has not been fully investigated. In some retrospective studies investigating the distribution of lymph node metastases (LNM) detected by ^{68}Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) (12,13), and also in a prospective study using conventional imaging (3,4,14), upward metastases of NRLNM, particularly retroperitoneal LNM, were identified as the predominant pattern in high-risk PC patients. In our cases, we also observed NRLNM in other directions, such as LNM to mesenteric or inguinal regions. These types of LNM were associated with poorer clinical outcomes, which may indicate more malignant biological behaviors. It is also possibly due to the disruption of the lymphatic network (15) after local treatment, which would lead to the onset of different nodal spread. Anyway, our cytoreductive radiotherapy to NRLNM covered the whole involved nodal stations, which may play a prophylactic role in delaying disease progression via the lymphatic drainage pathway.

Furthermore, NRLN RT together with ARATAs were evaluated as independent prognostic factors for OS in LMBPC in our study. After PSM to balance confounding factors, NRLN RT was still consistently associated with improved OS in LMBPC. According to the latest results from STAMPEDE, PDRT is most beneficial for LMBPC patients with NRLNM only or those with ≤3 bone metastases (4). Since MDRT in addition to PDLT may improve clinical outcomes in mPC (6,16-19), it is encouraging and reasonable to think about cytoreductive RT for NRLNM in selective LMBPC patients with previous PDLT. Recently, Chopade *et al.* (20) reported that oligometastatic common iliac-M1a could be treated with curative radiotherapy plus long-term ADT and yielded a 5-year OS of 90.1%, as high as those with cN1. Our study further suggested that NRLN RT after PDRT could decrease 54% of death risk in LMBPC with NRLNM. When it comes to the question who would be most likely to benefit from NRLN RT, the sample size of our cohort is too small to draw a conclusion, and further studies with larger sample sizes are needed.

Generally, it is safe to implement NRLN RT for LMBPC patients. AEs related to NRLN RT were relatively controllable and tolerable, mainly manifested as grade 1–2 toxic effects and without serious early or late side effects. GI toxicity is the most common side effect. It was noted that para-aortic lymph nodes irradiation regardless of prophylactical or therapeutic purpose in gynecologic cancers, had only a 3.9% incidence rate of grade 3 duodenal toxicity (21). In another study of cervical cancer about the safety of prophylactic extended radiation field, the incidence rates of grade 2 acute vomiting and nausea were only 13.3% and 6%, respectively (22), which was in accordance with our present results. Bone marrow suppression is another toxicity that we are concerned about. Apart from NRLN RT, several other factors, for instance, previous and concurrent medical prescriptions, and a history of pelvic radiotherapy, can also lead to bone marrow suppression. In our study, minor bone marrow suppression was detected in 29.4% of patients, yet 50% of these individuals were able to recover.

We concede that there are several limitations in this study preventing its generalizability. Firstly, the retrospective study with a small sample size is an inherent shortcoming. However, given the lack of evidence on the role of further cytoreductive NRLN RT in addition to PDLT in LMBPC, our study still provides some valuable information for current practice. Second, our patients represent a heterogeneous cohort of LMBPC patients who had undergone different treatments at different time points. Therefore, further studies are needed to validate our results. At the current time, we could expect results from a trial (ISRCTN36344989) (23) shedding light on the value of para-aortic lymph nodes radiotherapy in mHSPC.

Conclusions

Most LMBPC patients with NRLNM are manifested as high Gleason score, retroperitoneal metastases and HSPC at diagnosis. Upwards NRLNM is the main route

of metastasis and has better clinical outcome than others. HSPC, bone metastases, ARATAs and NRLN RT are independent prognostic factors. It may be beneficial to apply cytoreductive radiotherapy to NRLNM in LMBPC. Further studies are still needed.

Acknowledgments

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Scientific Research Sun Yat-sen University Cancer Center (No. B2022-181) and individual consent for this retrospective analysis was waived.

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