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LONG-TERM RADICAL PROSTATECTOMY ONCOLOGIC OUTCOMES IN PATIENTS WITH CLINICALLY LOCALLY ADVANCED PROSTATE CANCER: A SINGLE-CENTER STUDY

V. Grygorenko[1], Ye. Afanasiev[1,], R. Danylets[1], M. Vikarchuk[2], M. Kosyuchno[1], S. Pasichnyk[3]*
[1]*State Institution "Institute of Urology named after academician O.F. Vozyanov of the National Academy of Medical Sciences of Ukraine", Kyiv 04053, Ukraine*
[2]*Department of Urology of Medical Center "Dobrobut-Clinic", Kyiv 02000, Ukraine*
[3]*Danylo Halytsky Lviv National Medical University, Lviv 79010, Ukraine*

***Background*: Prostate cancer (PCa) is the second most frequently diagnosed cancer in males worldwide and placed fifth in cancer mortality among males. Between 14–24% of PCa patients have newly diagnosed advanced stages, which paradoxically has remained stable over time. *Aim*: To estimate and compare long-term radical prostatectomy (RP) oncologic outcomes in patients with clinically locally advanced prostate cancer (LAPCa), to determine the prognostic significance of common clinical-pathological parameters. *Patients and Methods*: The study included 105 patients with LAPCa who underwent RP with extended pelvic lymphadenectomy between September 2003 — April 2015. Kaplan — Meier method was used for calculating biochemical recurrence- (BRFS), progression-free- (PFS), overall (OS), and prostate cancer-specific survival (PCSS) rates. Analyses of features associated with outcomes were conducted using Cox proportional hazards regression model. *Results*: Patients from cT3b group had worse PFS, OS and PCSS rates in comparison with cT3a, while there was no significant difference in BRFS rates. Preoperative serum prostate-specific antigen level (hazard ratio (HR) 1.023, 95% confidence interval (CI): 1.014–1.033, $p < 0.001$), pT3a (HR 3,027, 95% CI: 1.449–7.096, $p < 0.01$), pT3b (HR 2.792, 95% CI: 1.133–6.881, $p < 0.05$) pT4 stage (HR 31.12, 95% CI: 7.646–126.6 $p < 0.001$) and positive lymph nodes status (HR 6.503, 95% CI: 3.190–13.25, $p < 0.001$) were significant factors in BRFS. Preoperative serum prostate-specific antigen level (HR 1.018, 95% CI: 1.007–1.030, $p = 0.001$) and positive lymph nodes status (HR 3.191, 95% CI: 1.672–6.088, $p < 0.001$) were significant factors in PFS and PCSS. *Conclusions*: RP as the initial treatment option of multimodal therapy in the management of LAPCa patients demonstrates encouraging oncologic outcomes. Patients from the cT3b group had the worse rates of PFS, OS, and PCSS in comparison with the cT3a group. Heterogeneity of LAPCa patients' outcomes reflects the insufficiency of the existing clinical risk classification for the prediction of systemic progression and cancer-specific survival.**
***Key Words*: locally advanced prostate cancer, radical prostatectomy, oncologic outcomes.**

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Prostate cancer (PCa) is the second most frequently diagnosed cancer in males worldwide and placed fifth in cancer mortality in males; in 2040 newly diagnosed PCa cases and PCa-related deaths are expected to double in comparison with 2020 [1]. In the past, PCa could be diagnosed only by clinical examination, and its manifestation as locally advanced or advanced stages was common [2]. Contemporary diagnostic and imaging tools have led to an increase in the proportion of men diagnosed with a low stage and low-grade disease, but between 14–24% of them have newly diagnosed advanced stages, which paradoxically remain stable over time [3, 4]. To date, the National Comprehensive Cancer Network, American Urological Association, as well as the European Urological Association of Urology follow well known predictors of disease outcome after primary treatment defined by D'Amico *et al*. [5]: clinical tumor stage, biopsy specimen Gleason score, and preoperative serum prostate-specific antigen (PSA) concentration. Patients with PSA above 20 ng/mL or biopsy specimen Gleason score of at least 8 or clinical tumor stage of at least T2c are defined as high-risk. Historically, surgical therapy (i.e., radical prostatectomy) for high-risk PCa was not considered to this cohort of patients, so most of them were managed by external beam radiation therapy (RT) or androgen deprivation therapy (ADT) or both considering the encouraging oncologic outcomes. Many retrospective studies and systematic literature reviews repeatedly demonstrated better oncologic outcomes in patients with locally advanced prostate cancer (LAPCa) after radical prostatectomy (RP) with adjuvant treatment in comparison with RT or/with ADT alone due to improvement of surgical technique and equipment, a better understanding of pelvic anatomy, understanding of tumor biology and disease kinetics. In a previous study, patients with clinically LAPCa who underwent RP demonstrated encouraging oncologic outcomes. Nevertheless, a short follow-up period in our previous study did not allow making strong conclusions [6]. Nowadays, there is no consensus in the definition of high-risk PCa [4, 7]. While it is imperative that all locally advanced cancers are of high-risk, not all high-risk cancers may be locally advanced. Lack of segregation has truncated the approach to treating such cancers [8–9].

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*Correspondence: E-mail: evhenii.afanasev@gmail.com
Abbreviations used: ADT – androgen deprivation therapy; BRFS – biochemical recurrence-free survival; CI – confidence interval; HR – hazard ratio; LAPCa – locally advanced prostate cancer; OS – overall survival; PCa – prostate cancer; PCSS – prostate cancer-specific survival; PFS – progression-free survival; PSA – prostate-specific antigen; RP – radical prostatectomy; RT – radiation therapy.

The aim of the study was to estimate and compare long-term RP oncologic outcomes in patients with clinically LAPCa among cT3a and cT3b groups along with evaluation of prognostic significance of common clinical-pathological parameters to determine the necessity of novel biomarkers.

PATIENTS AND METHODS

Study population. The study included 105 patients (40–74 years) with clinically diagnosed LAPCa who underwent RP with extended pelvic lymphadenectomy without any neoadjuvant therapies at our institution between September 2003 — April 2015. Before RP, PCa was diagnosed histopathologically using specimens obtained from systematic transrectal ultrasound-guided needle biopsy of the prostate. The clinical staging was performed by using digital rectal examination, transrectal ultrasonography, contrast-enhanced computed tomography, magnetic resonance imaging, and/or bone scan with Tc^{99} using the 2002 TNM classification of prostate cancer. LAPCa was defined as the one extending beyond the prostate capsule with the invasion of periprostatic tissue, apex, bladder neck, or seminal but without lymph node involvement or distant metastasis. Patients were divided into two subgroups cT3a (extracapsular extension but not to the seminal vesicles) and cT3b (seminal vesicle invasion), respectively.

The RP specimens including the prostate gland with seminal vesicles and bilateral pelvic lymph nodes were examined microscopically after routine preparation and were graded according to Gleason score. Microscopic extension of malignant cells to the inked surface of the resected specimen was interpreted as a positive surgical margin [10], invasion of malignant cells to the neurovascular bundle was defined as a perineural invasion. Differences between clinical and pathological Gleason score and TNM, in range of D'Amico stratification criteria, were interpreted as upstage or downstage.

Oncologic outcomes and adjuvant treatment. The follow-up period included digital rectal examination, measurements of serum PSA level at 4 weeks and quarterly after surgery during the first year, then once each 6 months; contrast-enhanced computed tomography, magnetic resonance imaging, or bone scan were performed if the clinical manifestation of local or distant recurrence occurs.

Biochemical recurrence was defined as a PSA level $\geqslant$ 0.2 ng/ml on 2 consecutive measurements. Local recurrence was defined as histologically confirmed evidence of cancer cells in targeted biopsies at the bladder-urethral anastomosis, distant metastasis was defined as a positive finding on bone scan or imagining examination [10]. Disease progression was defined as the development of either local disease recurrence or distant metastasis [8]. Cancer-specific survival was defined as the time from RP to death caused by PCa or its complications. Overall survival (OS) was defined as the time from RP to death from any cause.

Adjuvant treatment was defined as either ADT or RT was given within 3 months after surgery. Salvage treatment was defined as any kind of therapy (RT or ADT) given later than 3 months after surgery [8].

Statistical analysis. The data were summarized using descriptive statistics. Categorical variables were presented as contingency tables into statistical software. Continuous variables were presented as median and range. Comparison between groups was performed using the Chi-squared or Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. Kaplan — Meier method was used for calculating biochemical recurrence-free survival (BRFS), progression-free survival (PFS), OS, and prostate cancer-specific survival (PCSS) rates, all the differences were determined by the log-rank test. Univariate and multivariate analyses of features associated with outcomes were conducted using Cox proportional hazards regression model. All tests were two-sided, with $p < 0.05$ considered to indicate statistical significance. Statistical analysis was performed using SPSS version 22.0 (IBM SPSS Statistics 22.0).

RESULTS

The mean (range) follow-up was 101 (6–197) months. The patients' clinical-pathological features are presented in Table 1. There were significant differences between cT3a and cT3b groups regarding biopsy ($p < 0.05$), pathological Gleason score ($p < 0.05$), RP specimen tumor stage ($p < 0.001$), lymph node status ($p < 0.005$) and surgical margin status ($p < 0.05$), respectively. Pathological tumor, Gleason score understaging was in 19 and 10.5%, while overstaging occurred in 33 and 31.5% cases respectively. Also, positive lymph nodes and surgical margins were observed in 19 and 34.3% cases respectively. Moreover in cT3b group, upstaging of pathological parameters, positive lymph nodes and surgical margins occurred more often. Oncologic outcomes of LAPCa patients after RP are presented in Table 2. During follow-up period 44 (42%) patients died, including 22 (21%) who died from PCa. There were significant statistical differences between cT3a and cT3b groups in systemic progression ($p < 0.001$) and survival ($p < 0.05$). In cT3b groups systemic progression, death from PCa and any cause occurred more often.

The BRFS, PFS, OS and PCSS rates for cT3 PCa patients under study and separately for cT3a and cT3b patients are given in Fig. 1 and Fig. 2, respectively. There were significant differences between cT3a and cT3b groups regarding 5-, 10- and 15-year PFS rates (94.5; 76 and 27.5% *vs* 82; 40 and 4%; $p < 0.001$), OS rates (96; 94.5 and 93% *vs* 88; 81; 79.5% ($p < 0.05$) and PCSS rates (98; 89 and 75% *vs* 95.5; 68 and 58% ($p < 0.05$), while there was no significant difference between BRFS rates.

Univariate Cox proportional hazard analysis was performed to identify factors that could impact the

Table 1. Clinical and pathological features of LAPCa patients

Variable	Value			*p*
	Total (n = 105)	cT3a (n = 55)	cT3b (n = 50)	
Median (IQR)				
Age at RP, years	62 (40–74)	63 (40–70)	61 (40–70)	0.05
Preoperative PSA level, ng/mL	23.7 (2,5–150)	21.1 (2.5–100)	24.6 (3.0–150)	0.07
Prostate volume, mL	44 (21–123)	44 (21.8–123)	43.5 (21–88.6)	0.44
PSA density, ng/mL^2	0.5 (0.04–4.1)	0.5 (0.4–2.08)	0.62 (0.4–4.1)	0.12
N (%)				
Preoperative PSA level, ng/mL				0.16
< 10	8 (7.6%)	4 (7.2%)	4 (8%)	
10–20	31 (29.5%)	21 (38.3%)	10 (20%)	
20–50	54 (51.5%)	26 (47.3%)	28 (56%)	
> 50	12 (11.4%)	4 (7.2)	8 (16%)	
Biopsy Gleason score				< 0.05
⩽ 6	49 (46.6%)	32 (58.2%)	17 (34%)	
7	36 (34.4%)	15 (27.2%)	21 (42%)	
⩾ 8	20 (19%)	8 (14.6%)	12 (24%)	
RP Gleason score				< 0.05
⩽ 6	32 (30.5%)	24 (43.6%)	8 (16%)	
7	46 (43.8%)	20 (36.4%)	26 (52%)	
⩾ 8	27 (25.7%)	11 (20%)	16 (32%)	
Pathological stage				< 0.001
T2	20 (19%)	19 (34.5%)	1 (2%)	
T3a	28 (26.7%)	25 (45.5%)	3 (6%)	
T3b	49 (46.7%)	10 (18.2%)	39 (78%)	
T4	8 (7.6%)	1 (1.8%)	7 (14%)	
				<0.005
Lymph node status				
N-	85 (81%)	50 (91%)	35 (70%)	
N+	20 (19%)	5 (9%)	15 (30%)	
Perineural invasion				0.05
PNI-	54 (51.4%)	33 (60%)	21 (42%)	
PNI+	51 (48.6%)	22 (40%)	29 (58%)	
Surgical margin				0.05
R0	69 (65.7%)	42 (76.4%)	27 (54%)	
R1	36 (34.3%)	13 (23.6%)	23 (46%)	
Adjuvant treatment				0.15
No treatment	54 (51.5%)	34 (61.8%)	20 (40%)	
RT	2 (1.9%)	1 (1.8%)	1 (2%)	
ADT	20 (19%)	9 (16.4%)	11 (22%)	
RT+ADT	29 (27.6)	11 (20%)	18 (36%)	
Salvage treatment				0.22
No treatment	82 (78.1%)	47 (85.4%)	35 (70%)	
RT	7 (6.6%)	2 (3.6%)	5 (10%)	
ADT	15 (14.3%)	6 (11%)	9 (18%)	
RT+ADT	1 (1%)	0 (0%)	1 (2%)	

Notes: IQR – interquartile interval; PNI – perineural invasion; R – positive surgical margin.

Table 2. Oncological outcomes of LAPCa patients after RP

Clinical endpoint, N (%)	cT3 (n=105)	cT3a (n=55)	cT3b (n=50)	*p*
Biochemical recurrence				0.34
No biochemical recurrence	4 (3.8%)	3 (5.5%)	1 (2%)	
Biochemical recurrence	101 (96.2%)	52 (94.5%)	49 (98%)	
Systemic progression				< 0.001
No systemic progression	42 (40%)	31 (56.4%)	11 (22%)	
Systemic progression	63 (60%)	24 (43.6%)	39 (78%)	
Survival				< 0.05
Alive	71 (67.6%)	44 (80%)	27 (54%)	
Death from prostate cancer	22 (21%)	8 (14.5%)	14 (28%)	
Death from any cause	12 (11.4%)	3 (5.5%)	9 (18%)	

BRFS, PFS and PCSS of the LAPCa patients. The multivariate analysis was used to evaluate the significant variables in univariate analysis, $p < 0.05$ was considered statistically significant.

Age, preoperative serum PSA level, pT3a, pT3b, pT4 stage, and positive lymph nodes status were significant factors for BRFS (Table 3).

Age, preoperative serum PSA level, pT4 stage, and positive lymph nodes status were significant factors for PFS (Table 4) and PCSS (Table 5).

DISCUSSION

Historically, patients with LAPCa have been managed most often with RT or ADT or both [11, 12]. During the last two decades, the discussion about the

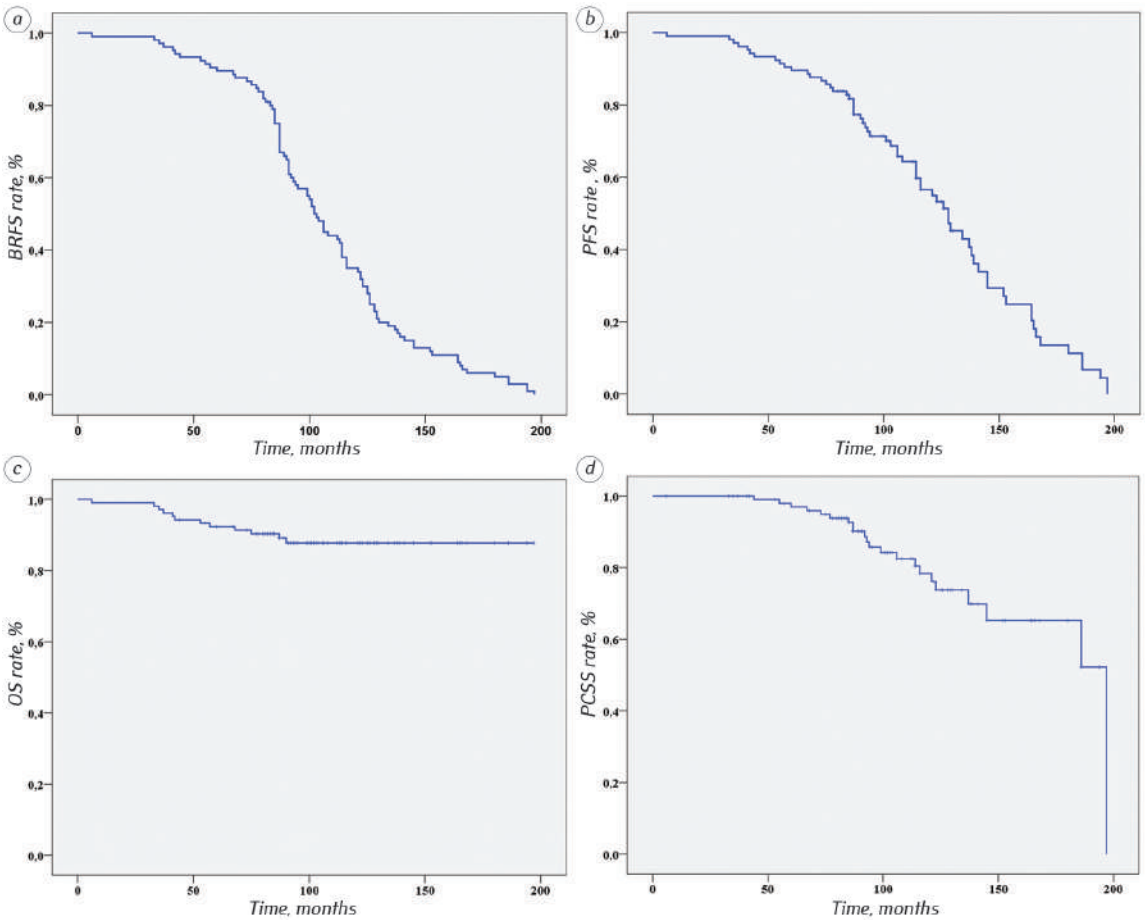

Fig. 1. BRFS rate (*a*), PFS rate (*b*), OS rate (*c*) and PCSS rate (*d*) among all cT3 PCa patients

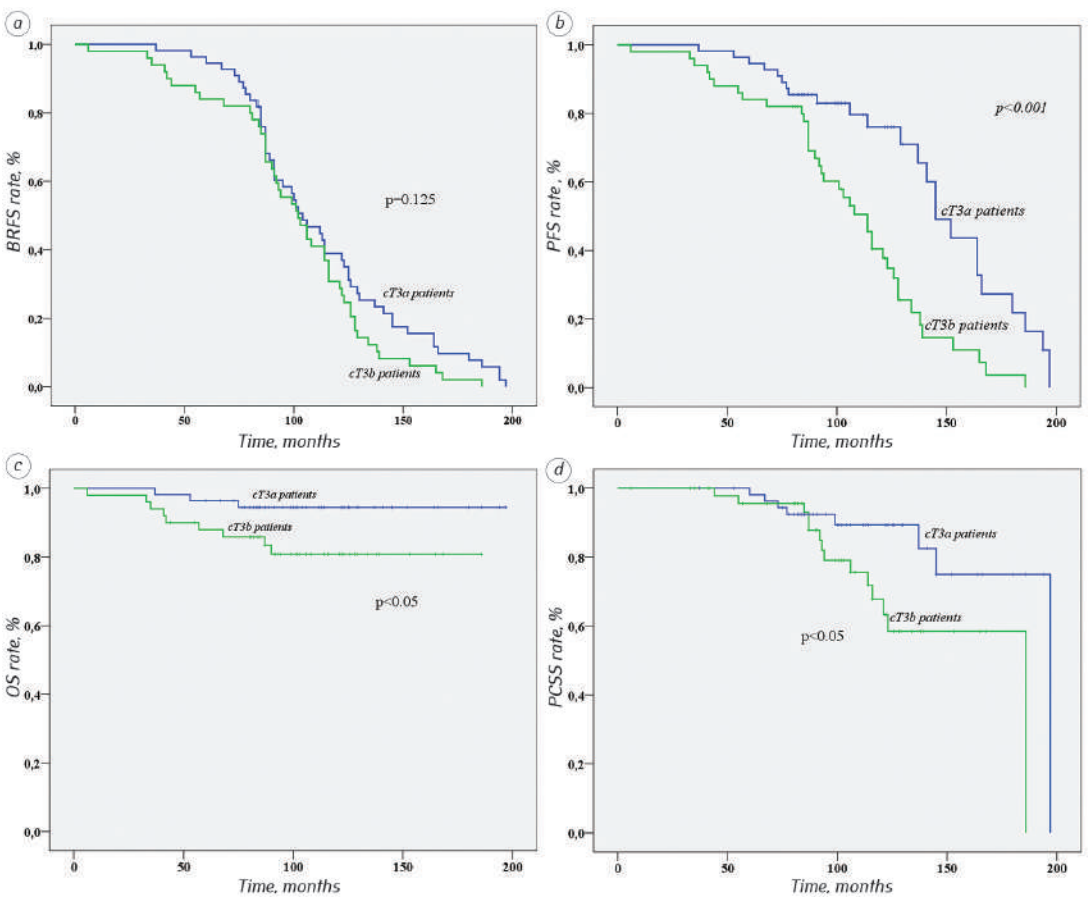

Fig. 2. BRFS rate (*a*), PFS rate (*b*), OS rate (*c*) and PCSS rate (*d*) in cT3 PCa patients segregated by groups

Table 3. BRFS prognostic factor analysis by Cox proportional hazard models of LAPCa patients

Covariate	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age at RP, years	0.959 (0.926–0.992)	< 0.05	0.958 (0.919–0.999)	< 0.05
Clinical T3 group	2.122 (1.416–3.180)	< 0.001	0.873 (0.433–1.760)	0.704
PSA, ng/mL	1.019 (1.005–1.03)	< 0.01	1.023 (1.014–1.033)	< 0.001
10–20 ng/mL	0.720 (0.308–1.681)	0.447		
20-50 ng/mL	0.829 (0.355–1.937)	0.666		
> 50 ng/mL	0.624 (0.136–2.825)	0.543		
Biopsy Gleason score	1.176 (1.003–1.380)	< 0.05	0.979 (0.765–1.255)	0.869
7				
⩾ 8	1.423 (0.907–2.233)	0.125	0.674 (0.333–1.366)	0.274
	2.133 (1.241–3.664)	< 0.01	1.078 (0.4–2.902)	0.883
Pathological tumor stage		< 0.001		<0.001
T3a				
T3b	3.349 (1.733–6.469)	< 0.001	3.207 (1.449–7.096)	< 0.01
T4	3.847 (2.087–7.093)	< 0.001	2.792 (1.133–6.881)	< 0.05
	23.63 (8.916–62.64)	< 0.001	31.12 (7.646–126,6)	< 0.001
Pathological Gleason score		< 0.001		0.111
7				
⩾8	2.208 (1.337–3.645)	< 0.01	1.887 (0.993–3.589)	0.53
	3.673 (2.080–6.487)	< 0.001	2.1 (0.936–4.710)	0.72
Lymph node status	5.657 (3.135–10.20)	< 0.001	6.503 (3.190– 3.25)	< 0.001
Surgical margin status	3.500 (2.252–5.442)	< 0.001	1.543 (0.678–3.512)	0.302
Perineural invasion	2.266 (1.517–3.386)	< 0.001	1.028 (0.577–1.834)	0.924
Adjuvant treatment	1.617 (1.375–1.900)	< 0.001	1.002 (0.731–1.374)	0.990

Table 4. PFS prognostic factor analysis by Cox proportional hazard models of of LAPCa patients

Covariate	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age at RP, years	0.931 (0.893–0.971)	0.01	0.924 (0.880–0.971)	<0.005
Clinical T3 group	3.022 (1.769–5.164)	< 0.001	2.091 (0.880–4.971)	0.095
PSA, ng/mL	1.018 (1.009–1.027)	< 0.001	1.018 (1.007–1.030)	0.001
10–20 ng/mL	0.467 (0.172–1.267)	0.135		
20–50 ng/mL	0.865 (0.348–2.154)	0.756		
> 50 ng/mL	1.104 (0.375–3.248)	0.857		
Biopsy Gleason score	1.058 (0.887–1.262)	0.53		
7				
⩾8	1.067 (0.594–1.917)	0.827		
	1.633 (0.864–3.086)	0.131		
Pathological tumor stage	2.154 (1.509–3.074)	< 0.001		< 0.01
T3a				
T3b	5.619 (1.645–19.18)	< 0.01	3.231 (0.835–12.49)	0.089
T4	6.135 (1.876–20.06)	< 0.005	1.370 (0.334)–5.622)	0.662
	25.764 (6.61–100.37)	< 0.001	6.569 (1.136–38.00)	< 0.05
Pathological Gleason score	1.683 (1.196–2.367)	< 0.01		0.351
7				
⩾8	1.749 (0.911–3.357)	0.093	0.994 (0.476–2.078)	0.988
	2.848 (1.425–5.694)	< 0.005	1.607 (0.701–3.681)	0.262
Lymph node status	4.132 (2.344–7.283)	< 0.001	3.191 (1.672–6.088)	< 0.001
Surgical margin status	3.838 (2.296–6.416)	< 0.001	0.865 (0.305–2.458)	0.786
Perineural invasion	3.258 (1.909–5.563)	< 0.001	1.185 (0.575–2.445)	0.645
Adjuvant treatment	1.829 (1.488–2.248)	< 0.001	1.320 (0.874–1.993)	0.187
Biochemical recurrence	21.768 (0.073–64.77)	0.289		
Salvage treatment	1.061 (0.768–1.465)	0.720		

surgery in LAPCa became increasingly active; however, the role of the RP, as an initial treatment option for this cohort, remains controversial [11–14]. Moreover, there is no clear consensus on stratification criteria and accurate prediction which individuals with LAPCa will benefit from surgery. Heterogeneous groups and selection bias for good or poor prognosis of LAPCa patients makes it difficult to individualize counseling for defining clinical trial enrollment criteria, and compare RP with other treatment modalities respectively, so it explains why there is no large-scale randomized controlled trial (RCT), which could demonstrate the superiority of surgery.

In meta-analyses of large retrospective series of RP for LAPCa, PCSS rates were greater than 85% at the end of 10 years follow-up, which consequently underscored the critical role of RP in these patients [2, 15, 16].

Swanson *et al*. [17] analyzed patterns of treatment failure in patients with LAPCa included in the SWOG 8794 study, and observed that most recurrences were local with only 16% distant metastases; they highlighted the sensitiveness of PSA following RP in identifying early failures and therefore ability to deliver early salvage therapy which improves PCSS and OS rates. Moreover, this conclusion is significantly different from the current RT + ADT standard of care: the data registry

Table 5. Prostate cancer specific survival prognostic factor analysis by Cox proportional hazard models of LAPCa patients

Covariant	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age at RP, years	0.920 (0.849–0.996)	< 0.05	0.882 (0.787–0.989)	< 0.05
Clinical T3 group	2.688 (1.070–6.749)	< 0.05	0.493 (0.119–2.045)	0.33
PSA, ng/mL	1.009 (0.998–1.021)	0.11		
10–20 ng/mL	0.534 (0.102–2.796)	0.458		
20-50 ng/mL	0.619 (0.133–2.874)	0.540		
> 50 ng/mL	1.063 (0.193–5.840)	0.944		
Biopsy Gleason score	1.321 (0.940–1.856)	0.109		
7				
⩾ 8	1.609 (0.557–4.648)	0.379		
	3.483 (1.198–10.127)	< 0.05		
Pathological tumor stage	1.930 (1.103–3.379)	< 0.05	1.520 (0.68–3.397)	< 0.05
T3a				
T3b		0.895	-	0.959
T4		0.9	1.067 (0.187–6.095)	0.942
		0.888	0.245 (0.067–0.904)	< 0.05
Pathological Gleason score	2.145 (1.177–3.909)	< 0.05		
7				
⩾8	3.631 (1.0–13.182)	0.05	0.195 (0.034–1.110)	0.065
	5.430 (1.358–21.713)	< 0.05	0.642 (0.211–1.949)	0.434
Lymph node status	3.659 (1.453–9.210)	< 0.01	1.272 (0.449–3.605)	0.605
Surgical margin status	1.908 (0.8–4.552)	0.142		
Perineural invasion	2.449 (0.866–6.928)	0.091		
Adjuvant treatment	1.386 (0.982–1.958)	0.064		
Biochemical recurrence		0.734		
Salvage treatment	1.474 (0.865–2.513)	0.153		
Systemic progression	11.185 (1.488–84.05)	< 0.05	0.145 (0.018–1.196)	0.073

derived from meta-analyses of CaPSURE showed local disease recurrence in 10–25% range [2, 18–20].

Shipley *et al*. [18] in RTOG9601 phase III study concluded that combination of ADT+RT as salvage following RP demonstrated good oncologic outcomes, a 10-year OS of 82% with a very low 2.3% cancer-specific mortality, which subsequently supports the role of RP as a key therapeutic approach being a part of multimodal therapy of LAPCa [2, 19–21].

In our previous study, we estimated RP oncologic outcomes in patients with clinically LAPCa, with a median postoperative follow-up of 48.9 months. Nevertheless, insufficient observation period did not allow us to adequately evaluate the role of RP in LAPCa along with the determination of significant risk factors [6].

All above studies demonstrate significant superiority of RP in LAPCa patients as an initial treatment option in multimodal therapy approach compared with RT or ADT or both. Nevertheless, the number of treatment failure cases still remains high due to the lack of preoperative prognostic criteria.

Limitations of clinical assessment and progression risk factor classification in LAPCa had occurred due to the routine using only three basic parameters: preoperative serum PSA level, biopsy Gleason score, and clinical TNM staging of the disease [13]. Clinical Gleason score and TNM stage could be biased due to human factor and often do not correspond to the pathological findings. Among T3a and T3b groups, there were 33.3 and 31.4% of TNM and Gleason score upstage, while downstage occurred in 21.9 and 10.5% cases, respectively.

In the case of systemic organ-specific marker (PSA), there are fluctuations according to the individual conditions, which include benign prostatic hyperplasia, prostatitis, and other nonmalignant conditions.

It is important that parameters such as age, PSA level, pathological tumor stage, lymph node status were significant factors in the prediction of biochemical recurrence development, while biochemical progression did not demonstrate any significant influence on progression and survival. Moreover, it should be noted that pathological T4 stage, PSA level, and lymph node status demonstrated significant prognostic potential in progression and survival.

According to the National Comprehensive Cancer Network, T3b stage is considered a very high-risk profile and there were no differences in BRFS rates among cT3a and cT3b groups, while cT3b patients have statistically significant lower 5-, 10-, and 15-year PFS, OS, and cancer-specific survival rates. Most likely, it can be explained by the fact of greater frequency of Gleason score, TNM upstaging, and positive surgical margins in the cT3b group, whereas cT3a patients demonstrated the higher frequency of Gleason score and TNM downstaging.

Nowadays, there is a lot of serum or whole-blood biomarkers (free PSA, PSA velocity, PSA doubling time, inactive PSA, proPSA, [-2]proPSA, NADIA, hexokinase, urokinase-type plasminogen activator, transforming growth factor-β1, interleukin-6, insulin-like growth factors), molecular, protein and metabolite urine markers, genetic markers which demonstrated encouraging sensitivity and specificity rates, but they have a lot of limitations in routine clinical practice due to their complexity and costs.

Heterogeneous RP oncologic outcomes among LAPCa patients demonstrate the necessity of searching, developing, and evaluating new systemic markers that could be effectively and routinely used at any level of medical care.

To sum up, RP as the initial treatment option of multimodal therapy in the management of LAPCa patients

demonstrated encouraging oncologic outcomes. Patients in the cT3b group had worse PFS, OS, and PCSS rates from comparison with cT3a group. Clinical tumor stage, Gleason score, lymph node status often mismatch with their pathological characteristics. Patients from the cT3a group had higher frequencies of TNM and Gleason downstaging, while cT3b — upstaging by the same parameters. Heterogeneity of LAPCa patients demonstrates the insolvency of contemporary clinical risk classification for the prediction of systemic progression and cancer-specific survival. The necessity of developing new available systemic markers for the oncologic outcomes of LAPCa is more urgent than ever.

ETHICAL APPROVAL

The study protocol was approved by the Ethics Commission of State Institution "Institute of Urology named after academician O.F. Vozianov of the National Academy of Medical Sciences of Ukraine".

DISCLOSURE

The authors declare that they have no competing interests.

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ВІДДАЛЕНІ ОНКОЛОГІЧНІ РЕЗУЛЬТАТИ РАДИКАЛЬНОЇ ПРОСТАТЕКТОМІЇ У ХВОРИХ З КЛІНІЧНО МІСЦЕВО-РОЗПОВСЮДЖЕНИМ РАКОМ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ: ОДНОЦЕНТРОВЕ ДОСЛІДЖЕННЯ

В.М. Григоренко[1], Є.І. Афанас'єв[1], Р.О. Данилець[1], М.В. Вікарчук[2], М.О. Косюхно[1], С. Пасічник[3]

[1]Відділ відновної урології та новітніх технологій ДУ "Інститут урології імені академіка О.Ф. Возіанова НАМН України", Київ, Україна

[2]Відділення урології МЦ "Клініка Добробут", Київ, Україна

[3]Львівський національний медичний університет імені Данила Галицького, Львів 79010, Україна

***Стан питання*:** Рак передміхурової залози (РПЗ) — друге за частотою онкологічне захворювання серед чоловіків у світі та посідає п'яте місце серед причин канцер-специфічної смертності. У 14–24% випадків РПЗ вперше діагностують

на етапі розповсюдженої стадії, і цей показник, що парадоксально, залишається стабільним протягом усього часу. ***Мета*:** Оцінити та порівняти віддалені онкологічні результати після радикальної простатектомії (РП) у хворих з клінічно місцево-розповсюдженим РПЗ (МРРПЗ), визначення прогностичної значимості загальних клініко-патологічних параметрів. ***Матеріали та методи*:** У дослідження включено 105 пацієнтів з клінічно МРРПЗ, яким було проведено РП з розширеною тазовою лімфаденектомією на базі нашого інституту в період з вересня 2003 до квітня 2015 р. Метод Каплана — Мейера застосовували для розрахунку ступенів біохімічної безрецидивної (ББВ), безпрогресивної (БВ), загальної (ЗВ) та канцер-специфічної виживаності (КСВ). Аналіз факторів, асоційованих з онкологічними результатами, проводили з використанням моделі пропорційних ризиків Кокса. ***Результати*:** У пацієнтів групи cT3b відмічали гірші показники БВ, ЗВ та КСВ в порівнянні з cT3a, у той час як статистично достовірної різниці в ступенях ББВ виявлено не було. Передопераційна сироваткова концентрація простатичного специфічного антигену (відношення ризиків (ВР) 1.023, 95% довірчий інтервал (ДІ): 1.014–1.033, $p < 0.001$), pT3a (СР 3,027, 95% ДІ: 1.449–7.096, $p < 0.01$), pT3b (СР 2.792, 95% ДІ: 1.133–6.881, $p < 0.05$) pT4 (СР 31.12, 95% ДІ: 7.646–126.6 $p < 0.001$) та наявність позитивних лімфатичних вузлів (СР 6.503, 95% ДІ: 3.190 — 13.25, $p < 0.001$) були значущими факторами у ББВ. Передопераційна сироваткова концентрація простатичного специфічного антигену (СР 1.018, 95% ДІ: 1.007–1.030, $p = 0.001$) та наявність позитивних лімфатичних вузлів (СР 3.191, 95% ДІ: 1.672–6.088, $p < 0.001$) були значущими факторами у БВ та КСВ**.** ***Висновки*:** РП як ініціальний компонент мультимодального підходу у лікування пацієнтів з МРРПЗ демонструє обнадійливі онкологічні результати. У пацієнтів з клінічною стадією T3b відмічено гірші результати в ББВ, БВ, ЗВ та КСВ в порівнянні з T3a. Гетерогенність пацієнтів з МРРПЗ демонструє недостатність сучасних клінічних стратифікаційних класифікацій ризику в прогнозуванні системного прогресування та канцер-специфічної смертності.
***Ключові слова*:** місцево-розповсюджений рак передміхурової залози, радикальна простатектомія, онкологічні результати**.**