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ONCOLOGIC OUTCOMES OF RADICAL PROSTATECTOMY AND PROGNOSTIC STRATIFICATION IN PATIENTS WITH CLINICALLY LOCALLY ADVANCED PROSTATE CANCER

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Abstract

Oncologic outcomes of radical prostatectomy in 106 patients with clinically locally advanced prostate cancer were demonstrated. The mean follow-up was 50.6 (12−129) months. 5-year recurrence-free survival was 47.7 %, 5-year cancer-specific and overall survival − 85.8 %. Patients were devided into three different risk groups: low risk patients had PSA level <20 ng/ml, biopsy Gleason score ≤6 and absence of the seminal vesicle invasion of cancer; intermediate risk was noted when the patient had only one of poor prognostic factors (PSA ≥20 ng/ml or biopsy Gleason score ≥7 or presence of cancer invasion to the seminal vesicle) and high risk patients had 2 or 3 poor prognostic factors. For patients of low, intermediate and high risk the biochemical reccurence rates were 14.3 %, 37.1 % and 70.2 %, respectively (p=0.002). The patients of intermediate and high risk had clinically significant higher risk of biochemical reccurence than those of low risk with odds ratio 3.0 and 8.5, respectively. Such grouping may help in guiding the individualized treatment for these patients.

Keywords: locally-advanced prostate cancer, prognostic stratification.

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1. Introduction

Locally advanced prostate cancer (PCa) is defined as a tumor that has extended beyond the prostatic capsule, including invasion of the periprostatic fat, bladder neck or seminal vesicles, but without regional or distant metastases. Nearly 20–25 % of cases present as locally advanced disease [1, 2]. Last years the incidence of PCa in locally advanced stage significantly decreased, primarily due to the early diagnosis improvement through the use of prostate-specific antigen (PSA) and needle biopsy. In 2013 in Ukraine, the percentage of locally advanced disease in the prostate cancer incidence was 23.1 % compared with 31.1 % in 2003 [3, 4].

The management of locally advanced PCa is one of the most compelling contemporary challenges. In the absence of randomized clinical trials comparing the effectiveness of radical prostatectomy (RPE), radiotherapy (RT), androgen deprivation therapy (ADT), or combination of these methods, it is difficult to determine the optimal treatment strategy for these patients. RPE with an extended pelvic lymphadenectomy is a proper treatment option of patient with locally advanced PCa accepted by international guidelines [5]. RPE benefits are to achieve the maximal tumor reduction and following pathological examination that allows to select patients who need adjuvant treatment. Prospective studies in this area allow only overall treatment strategies of this group of patients [6, 7].

Most of the studies devoted to the evaluation of oncological outcomes of RPE, RT or multimodality treatment of patients with locally advanced PCa face the challenge of heterogeneity within this group [8, 9]. When the most of these patients have the benefits of treatment, some patients die, despite the chosen option. Thus, it is necessary to review the current classification system and develop optimal stratification of locally advanced PCa.

2. Aim of research

To present the oncologic outcomes of RPE in patients with clinically locally advanced PCa and create a model of its prognostic stratification using combinations of accepted risk factors.

3. Material and methods

We identified and treated with RPE 106 patients with clinically locally advanced PCa (stage $cT_3N_0M_0$ according to the 2010 TNM system) between August 2002 and June 2015 at State Institution 'Institute of Urology of National Academy of Medical Sciences of Ukraine'.

Prostate biopsies were performed under transrectal ultrasound (TRUS) guidance, and pretreatment PSA was measured before digital rectal examination (DRE) or TRUS. A minimum of six biopsy cores was taken for each patient included in the study. All patients underwent a bone scan and a magnetic resonance imaging scan or pelvic computed tomography. Patients were excluded if they were found to have radiographic evidence of regional or distant metastatic disease.

Clinical stage was assigned according to the TNM system of 7th edition (2010) [10]. Clinical stage cT3a was determined in cases of tumor invasion beyond the prostate capsule without invasion of the seminal vesicles, cT3b – in cases of MRI or CT signs of tumor invasion in the seminal vesicles, cT4 – in case of tumor invasion in the external sphincter. **Table 1** presents the baseline characteristics of studying patients.

Out of all 106 patients, 31 (29.2 %) underwent laparoscopic RPE and 75 (70.8 %) underwent radical retropubic prostatectomy both with extended bilateral pelvic lymph node dissection. The RPE specimens including prostate, seminal vesicles, and bilateral pelvic lymph nodes were examined microscopically after routine preparation. The prostate was inked, weighted, and cut at 5-mm intervals. A positive surgical margin was defined as the presence of cancer cells extending into the inked surface of the prostate. A positive lymph node was defined as the presence of tumoral glands in at least one of the pelvic lymph nodes.

Follow-up included DRE, serum PSA measurement. Bone scan, MRI or CT were performed by indications. The serum PSA level was typically measured at 4 weeks and quarterly during the initial 2 years after surgery, semi-annually for an additional 3 years, and annually thereafter. Biochemical recurrence (BCR) was defined as evaluation of total PSA by >0.2 ng/ml. Biochemical recurrence free survival (BRFS) referred to time from RPE to biochemical reccurence constatation.

PCa-specific survival (PCSS) referred to time from RPE to death attributed to PCa or disease-related complications. Adjuvant therapy was defined as treatment received ≤90 days of RP, and was given at the discretion of the treating physician, while salvage therapy was defined as treatment received >90 days after RPE, and triggered by PSA recurrence or clinical progression.

The Kaplan-Meier method was used to estimate time-to-event outcomes and the log-rank method was used to compare survival. Cox proportional hazard regression was used to identify prognostic factors, which were employed in a stepwise selection approach. The assumption of proportional hazards was confirmed for each of the input variables. All P values are two-sided, and a level of 0.05 was considered statistically significant.

Table 1
Characteristics of the study population

Characteristic	Result
Mean age (range), years	62.2±0.6 (40–74)
Time of follow-up, months	55.7±3.2 (12–129)
Mean PSA (range), ng/ml	29.4±1.3 (2.5–150)
PSA<10 ng/ml, n (%)	8 (7.5)
PSA =10–20 ng/ml, n (%)	31 (29.2)
PSA >20 ng/ml, n (%)	67 (63.2)
Mean biopsy Gleason score	6.7 (5–9)
Gleason score 2–6, n (%)	49 (46.2)
Gleason score 7, n (%)	36 (34.0)
Gleason score 8–10, n (%)	21 (19.8)
Stage cT_{3a}, n (%)	52 (49.1 %)
Stage cT_{3b}, n (%)	55 (51.9 %)
Stage cT_{4}, n (%)	1 (0.9 %)

4. Results

Mean follow-up after RPE was 55.7±3.2 months, and 45 (42.5 %) patients had follow-up beyond 5 years. During the follow-up 55 (51.9 %) patients experienced biochemical recurrence, 18 died, with 16 dying of PCa. **Fig. 1** displays the BRFS and **Fig. 2** – PCSS for the entire cohort of clinically locally advanced PCa patients.

In univariable analysis the most important predictor of biochemical recurrence was clinical signs of tumor invasion in the seminal vesicles (hazard ratio (HR): 6.5; 95 % confidence interval

(CI), 2.8−13.3) followed by biopsy Gleason score ≥7 (HR: 1.7; 95 % CI, 0.8−3.6) and PSA ≥20 ng/ml (HR: 2.0; 95 % CI, 0.9−4.5).

On the basis of the three main clinical risk factors were established model of prognostic stratification of clinically locally advanced PCa into three subgroups: low, intermediate and high risk.

Low risk patients had PSA level <20 ng/ml, biopsy Gleason score ≤6 and absence of the seminal vesicle invasion of cancer (14 patients). Intermediate risk was noted when the patient had only one of poor prognostic factors (PSA ≥20 ng/ml or biopsy Gleason scor e≥7 or presence of cancer invasion to the seminal vesicle, 35 patients) and high risk patients had 2 or 3 poor prognostic factors (57 patients).

Oncological outcomes and pathomorphological features of tumors were significantly different in all three subgroups. For patients of low, intermediate and high risk the biochemical reccurence rates were 14.3 %, 37.1 % and 70.2 %, respectively (p=0.002) (**Fig. 3**), and the risk of its development in patients with intermediate risk grew 3.0, high − in 8.5 times.

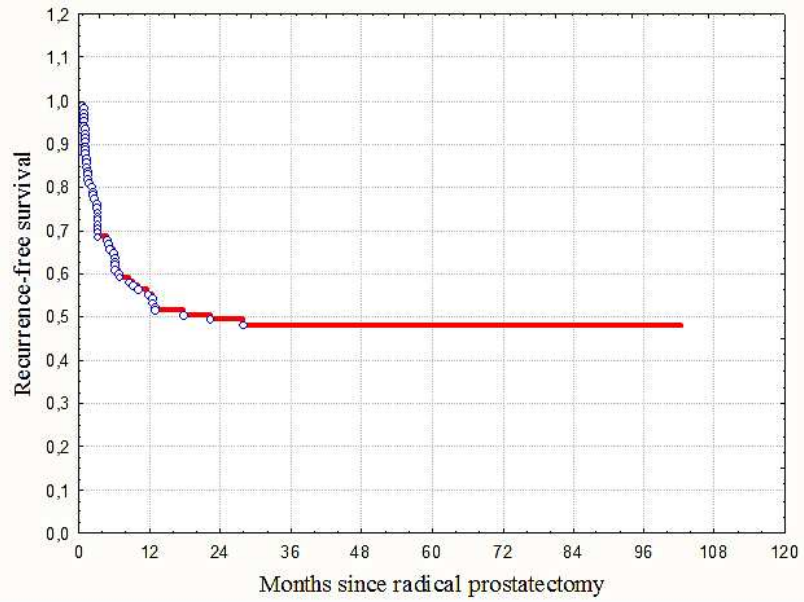

Fig. 1. Biochemical recurrence-free survival for the entire cohort of clinically locally advanced PCa patients

Proposed model demonstrated that most patients in low risk group were treated with RPE alone (adjuvant RT received 14.3 % of patients, adjuvant ADT − 26.8 %, and biochemical recurrence had only 2 of 14 patients (14.3 %)). In addition, 35.7 % of patients had pathologically organ-confined prostate cancer that occurred clinical overstaging of the disease.

On the other hand, a large number of high risk patients had poor pathomorphological characteristics of tumor. Positive surgical margin identified in 49.1 % of cases, perineural invasion − in 56.1 %, regional lymph nodes metastases − in 29.8 %. Most of patients in high risk group require multimodal treatment (adjuvant RT carried 40.4 % of patients, adjuvant ADT − 59.6 %) and had biochemical recurrence (40 of 57 patients, 70.2 %) (**Table 2**).

Obviously, the high-risk group includes patients with aggressive disease, regardless of the chosen treatment strategy. These patients should be in focus of the researchers of new treatment approaches of PCa.

The ambiguous place of intermediate risk in determining of optimal treatment option. Given the fact that 62.9 % of patients had no biochemical recurrence during the follow-up, adjuvant RT carried only 22.9 %, adjuvant ADT − 34.3 % of patients, and the frequency of poor prognostic features was lower than in the high-risk group, this group of patients can be offered RPE as a first-line method of treatment. Feasibility of adjuvant therapy should be decided after determining the pathological tumor characteristics.

Table 2
Pre- and postoperative patient characteristics related to prognostic subgroups

Characteristics	Risk group			p
	Low, n=14	Intermediate, n=35	High, n=57	
Mean age (range), years	64.4±1.6	61.8±1.0	61.9±0.8	0.351
Mean PSA level (range), ng/ml	13.0±1.1	23.8±1.9	36.9±3.6	0.0002
Mean Pathologic Gleason score	6.3	6.6	7.7	
Pathologic Gleason score ≤6, n (%)	9 (64.3)	18 (51.4)	5 (8.8)	0.0001
Pathologic Gleason score 7, n (%)	3 (21.4)	13 (37.1)	31 (54.4)	
Pathologic Gleason score ≥8, n (%)	2 (14.3)	4 (11.4)	21 (36.8)	
Pathologic stage				
pT_2, n (%)	5 (35.7)	11 (31.4)	4 (7.0)	
pT_{3a}, n (%)	4 (28.6)	15 (42.9)	9 (15.8)	0.0001
$pT_{3в}$, n (%)	4 (28.6)	8 (22.9)	37 (64.9)	
pT_4, n (%)	1 (7.1)	1 (2.9)	7 (12.3)	
Lymph node methastasis, n (%)	0	4 (11.4)	17 (29.8)	0.014
Perineural invasion, n (%)	5 (35.7)	15 (42.8)	32 (56.1)	0.262
Positive surgical margin, n (%)	1 (7.1)	8 (22.9)	28 (49.1)	0.002
Adjuvant RT, n (%)	1 (7.1)	8 (22.9)	23 (40.4)	0.027
Adjuvant ADT, n (%)	4 (28.6)	12 (34.3)	34 (59.6)	0.020
Salvage RT, n (%)	0	4 (11.4)	4 (7.0)	0.383
Salvage ADT, n (%)	2 (14.3)	5 (14.3)	9 (15.8)	0.977
Biochemal recurrence rate, n (%)	2 (14.3)	13 (37.1)	40 (70.2)	0.0001
Cancer specific deaths rate, n (%)	1 (7.1)	4 (11.4)	11 (19.3)	0.02

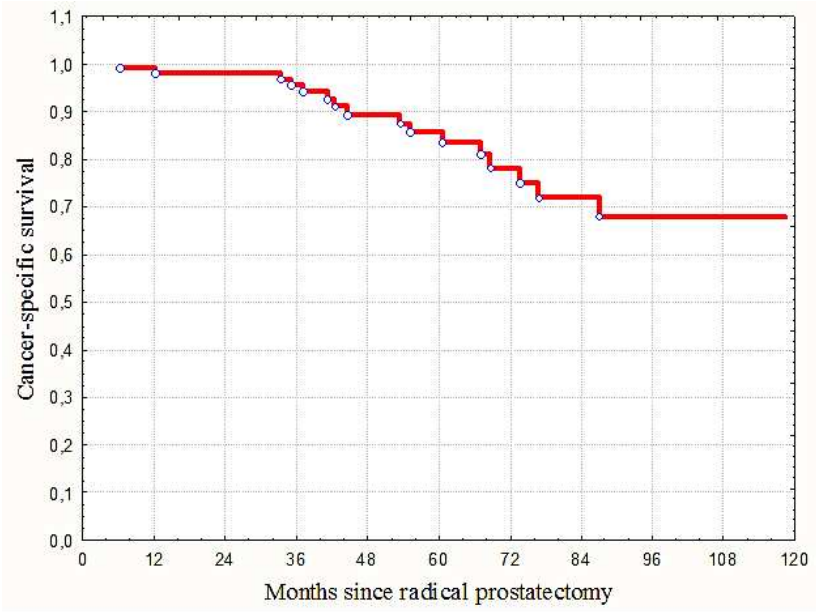

Fig. 2. Cancer-specific survival for the entire cohort of clinically locally advanced PCa patients

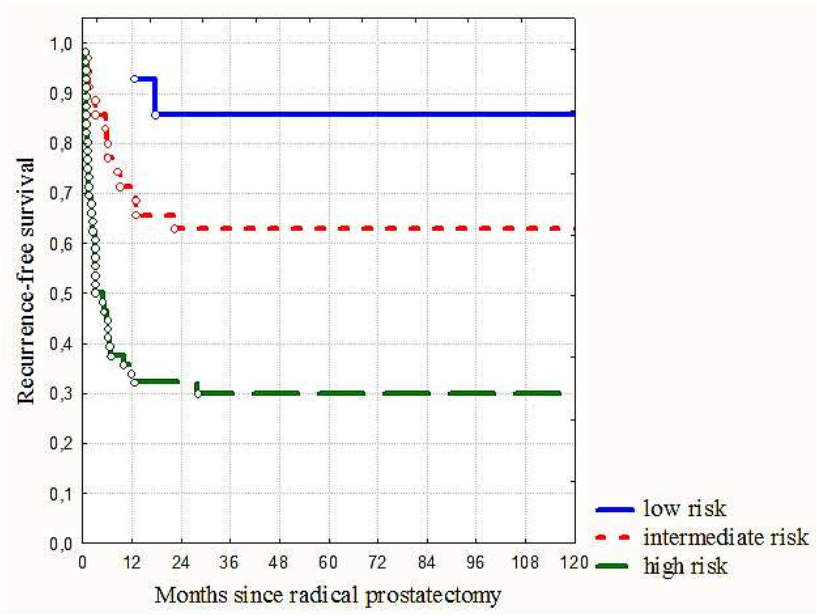

Fig. 3. Biochemical recurrence-free survival for the model of prognostic stratification of clinically locally advanced PCa with three prognostic subgroups

5. Discussion

Despite the clinical stage migration that has occurred with the advent of PSA screening, some patients continue to present with clinically locally advanced PCa [11]. The optimal treatment for this category of men remains controversial and is a matter of debate [12, 13].

The data on surgical management of locally advanced PCa has not been investigated or systematically reviewed and no large randomized controlled trial is available to show its superiority. Comparison of RPE with other treatment options for locally advanced PCa is questionable due to patients heterogenity and inherent selection bias of good prognosis patients in favor of surgery [8, 9, 14].

A few studies have shown promising results of RPE for locally advanced PCa [15, 16]. Xylinas et al. have shown oncologic outcomes in patients with T3 stage of PCa in few series of RPE. This meta-analysis has demonstrated 5-years BCRF, CSS and overall survival at 45−62 %,

84−98 % and 84−91 %, respectively [17]. Oncological outcomes of our study are similar to those reported in the literature series for clinically locally advanced PCa.

At diagnosis, PCa is usually classified into major risk categories based on TNM clinical stage, biopsy Gleason score and PSA level. It is generally assumed that patients with locally advanced PCa are at an elevated risk of experiencing biochemical recurrence, metastatic progression, and death from PCa [8, 18−20]. Our proposed model of prognostic stratification for patients with clinically locally advanced PCa was designed for use in clinical practice and comprises three prognostic subgroups: a low, intermediate and high risk. BCR rates and histopathologic features at RP were significantly different between the low, intermediate and high risk subgroups.

Also, proposed model demonstrates that many patients of low risk were treated with surgery alone and experienced exceptionally good 5-yr BRFS (85.7 %) and PCSS (92.8 %). Conversely, most individuals in the high risk subgroup necessitated a multimodal treatment (adjuvant RT: 40.4 %; adjuvant ADT: 59.6 %). Despite this much more intense treatment, 5-yr BRFS was significantly worse (29.8 %). Clearly, the subgroup of high risk patients includes men with aggressive disease despite more intense treatment. Ideally, these patients should be in target when studying new combined treatment approaches.

6. Conclusions

1. Patients with clinically locally advanced prostate cancer have higher risk of biochemical failure after radical prostatectomy but demonstrate good cancer-specific and overall survival.

2. The proposed stratification of locally advanced prostate cancer into three prognostic groups of low, intermediate and high risk is easy in use by urologists and researchers for selecting the optimal treatment strategy.

3. The patients of intermediate and high risk had clinically significant higher risk of biochemical reccurence than those of low risk with odds ratio 3.0 and 8.5, respectively.

4. The most of low risk patients can be treated with radical prostatectomy alone.

5. The most of patients in high risk has an aggressive disease, need for multimodality treatment and should be in focus of the researchers of new treatment approaches of prostate cancer.

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