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EVALUATION OF RISK FACTORS FOR BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY IN PATIENTS WITH HIGH RISK PROSTATE CANCER

Abstract. *Surgical treatment of locally advanced cancer is still controversial since radical prostatectomy RP has been regarded as technically difficult in these patients and also, due to the increased risk of positive margins and biochemical recurrence (BCR). The EAU guidelines on prostate cancer consider that radical prostatectomy in high risk disease represents an option for selected patients alone or in association with external beam radiotherapy (EBRT) and/or hormonal therapy (HoT).* ***Objective:*** *This article presents our experience in the management of men with locally advanced prostate cancer using open radical prostatectomy as the first step in a multimodal approach.* ***Material and Method:*** *We conducted a retrospective study during 2008-2014 which included 204 patients with locally advanced prostate cancer who underwent open radical prostatectomy with extended bilateral pelvic lymph node dissection (eLND) in our Center. Biochemical recurrence was considered an increase in postoperative PSA >0.2 ng/dl confirmed by a second measurement after a minimum of 2 weeks. Local recurrence was detected by digital rectal examination and/or imaging studies. Salvage treatment (EBRT±HoT) was decided by the urologists depending on*

pathological and imaging findings at the time of BCR. Primary endpoints were considered cancer specific survival (CSS), overall survival (OS), biochemical recurrence (BCR) at 5 years. In order to identify predictive factors in BCR we constructed several models using logistic, probabilistic regressions and Bayesian analysis (recognition of forms). ***Results:*** *In our study median age at surgery was 65 years (range, 52 to 74). Median prostate-specific antigen (PSA) was 17.9 ng/ml (interval 4.9-24.9) and median follow-up was 55.3 months (interval: 12-63). Mean time to biochemical recurrence was 21.11 months (interval 15-54), with a higher PSA doubling time in patients with multiple adverse characteristics (positive surgical margins, LNI, high pathological stage). High-risk patients with poorly differentiated tumors showed significantly lower survival and higher progression rates compared to those with well or moderately differentiated tumors. The biochemical recurrence-free survival at 5 years was 55.89% while cancer-specific survival varied only marginally from OS at 5 years (80.8% and 82.84% respectively). The results obtained by these regression models were similar in terms of parameter significance, thus confirming the validity and consistency of the results.*

Conclusions. *Our data showed excellent long-term outcome for patients with high risk prostate cancer treated with surgery as first step in a multimodal approach. High risk patients with multiple adverse factors have presented early biochemical recurrence and need adjuvant treatment following surgery.*

Keywords: *high risk prostate cancer, open radical prostatectomy, biochemical recurrence, oncologic outcomes, mathematical models.*

JEL Classification: I10 (Health-General)

Introduction:

Despite the introduction of PSA testing worldwide, 14-24% of men are still diagnosed with high risk disease and prone to develop biochemical recurrence (BCR)[1]. The EAU guidelines on prostate cancer (PCa) consider that surgical treatment represents an option for selected patients with locally advanced disease, but many urologist still consider external radiotherapy (EBRT) and hormonal treatment (HoT) as primary line of treatment for these patients [2, 3]. Historically, men with high risk PCa have been addressed to radiotherapy (EBRT) alone or in combination with hormones [4, 5]. However recent studies have shown excellent oncologic outcomes in these patients treated with radical prostatectomy alone or in combination with EBRT or hormonotherapy[6-8].This article presents our experience in the management of men with locally advanced prostate cancer using open radical prostatectomy as the first step in a multimodal approach.

Material and method:

We conducted a retrospective study during 2008-2014 which included 204 patients with locally advanced prostate cancer who underwent open radical prostatectomy with extended bilateral pelvic lymph node dissection (eLND) in our Center. Inclusion criteria were: minimum of T3a on clinical evaluation, negative bone scan, ASA score<IV, no neoadjuvant treatment (HoT and/or EBRT), no postvoidal residue at bladder ultrasound and a life expectancy of >15 years evaluated using the Karnofsky scale[9]. The follow-up after surgical treatment involved a PSA evaluation every 3 months for the first 2 years and every 6 month thereafter. Biochemical recurrence was considered an increase in postoperative PSA >0.2 ng/dl confirmed by a second measurement after a minimum of 2 weeks. Clinical or systemic recurrence was detected by digital rectal examination and/or imaging studies. Salvage treatment (EBRT±HoT) was decided by the urologists depending on pathological and imaging findings at the time of BCR. Primary endpoints were considered cancer specific survival (CSS), overall survival (OS), biochemical recurrence (BCR) at 5 years. Cox uni- and multivariate regression analyses were used to identify predictive factors in BCR.In order to identify the factors involved in the appearance of biochemical recurrence, a forwards-stepwise logistic regression analysis was used. A p value of <0.05 was considered to indicate a statistically significant difference.

Results:

In our study median age at surgery was 65 years (range, 52 to 74). Median prostate-specific antigen (PSA) was 17.9 ng/ml (interval 4.9-24.9)and median follow-up was 55.3 months (interval: 12-63). Preoperative patient characteristics, distribution of clinical staging and Gleason score are shown in Table 1.

Table 1. Preoperative patient characteristics

Preoperative patient characteristics	
No. of patients	204
Mean Age (interval)	65 years (52-74)

PSA (median)	17.9 ng/ml (4.9-24.9)
Follow-up (median)	55.3 months (12-63)
Preoperative Gleason score	
6 (%)	95 (43.13%)
7 (%)	68 (35.29%)
8-10 (%)	41 (21.56%)
Clinical stage	
T3a	104 (50.98%)
T3b	78 (38.23%)
T4	22 (10.78%)
ASA score	
II	165 (80.88%)
III	39 (19.11%)
Previous TURP	42 (20.58%)

Evaluating the postoperative data, we observed a predominance of T3a stage in 45.58% of cases, while bladder invasion was demonstrated in 7.48% of cases. Also, there was discordance between biopsy and prostatectomy specimens' Gleason score in 30.88% of cases, with a tendency towards a higher Gleason. All postoperative data is presented in Table 2.

Mean time to biochemical recurrence was 21.11 months (interval 15-54), with a higher PSA doubling time in patients with multiple adverse characteristics (positive surgical margins, LNI, high pathological stage). Salvage treatment was initiated in 106 (51.96%) consisting in pelvic EBRT or hormonal therapy.

Table 2. Postoperative patient's characteristics

Postoperative patients characteristics	
Pathologic stage	
T2 (%)	31 (15.19%)
T3a (%)	93 (45.58%)
T3b (%)	64 (31.37%)
T4 (%)	16 (7.48%)
Down staged (%)	35 (17.15%)
Upstaged (%)	21 (10.29%)
Pathologic Gleason	
6 (%)	88 (43.13%)
7 (%)	72 (35.29%)
8-10 (%)	44 (21.56%)
Downgraded (%)	27 (13.23%)
Upgraded (%)	36 (17.64%)
LNI (%)	28 (13.72%)
Positive surgical margins (PSM)	36 (17.64%)
Mean time to BCR (months)	21.11 months (15-54)
Salvage treatment	106 (51.96%)
EBRT	29 (14.21%)

HoT	20 (9.8%)
EBRT+HoT	57 (27.94%)

The biochemical recurrence-free survival at 5 years was 55.89% while cancer-specific survival varied only marginally from OS at 5 years (80.8% and 82.84% respectively).

In order to identify the factors involved in the appearance of biochemical recurrence, we created several logistic regression models using SPPSS Statistics software vs. 23. Any pre and postoperative parameter associated with BCR was eligible for entry into the models.

The 1st model was created using a logistic regression (logit). The general form of logit models is as following;

$$Y = \int_{inf}^{\beta 0+\beta 1X1+\beta 2X2+\beta nXn} f(x)dz + \varepsilon \quad (1)$$

where Y represents the dependent variable (PSA after surgery), X_1,X_2..X_n - independent variables (Clinical Stage, PSA at biopsy, Biopsy Gleason score, T stage, etc), β_1,β_2..β_n – models' parameters, ε-models' perturbation, and f(·)-probability density function (PDF), respectively:

$$f(z;\mu;\sigma) = \frac{e^{-\frac{z-\mu}{\sigma}}}{\sigma\cdot\left(1+e^{-\frac{z-\mu}{\sigma}}\right)} \quad (2)$$

where μ represents location and σ–scale (for example: standard deviation).

Taking into account the connection between the probability density and the repartition function, the model described above can be written as follows:

$$Y = F(\beta 1 + \beta 2X2 + \beta nXn) + \varepsilon \quad (3)$$

where F(·)represents the logistic repartition function (CDF).Moreover, considering the form of the logistic repartition function, the previous model can be described as following:

$$Y = \frac{1}{1+e^{-\frac{\beta 0+\beta 1X1+\beta 2X2+\beta nXn-\mu}{\sigma}}} \quad (4)$$

Loss function is: maximum likelihood
Convergence criterion: .0001000
Estimation method: Hooke-Jeeves and quasi-Newton
Start values: .100000 for all parameters
Initial step size: .500000 for all parameters
No. of 0's:90.00000 (44.11765%)
No. of 1's:114.0000 (55.88235%)
Loss function is: maximum likelihood
Final value: 105.44761424
-2*log(Likelihood): for this model= 210.8952 intercept only= 279.9740, Chi-square = 69.07874
df =4, p = .000000

M N=204 D F	Model: Logistic regression (logit)Nof 0's:901's:114 Loss: Max likelihood(MS-err.scaledto1)				
	Const.B0	Clinical_Sta	PSA_Biop	Biopsy_G	T_Stage
Estimate	4.323282	1.522707	-0.1601368	-0.2691138	-2.043665
StandardError	1.683301	0.6987008	0.0518068	0.1404873	0.3361272
t(199)	2.568336	2.179341	-3.091034	-1.915573	-6.080037
p-value	0.0109516	0.0304806	0.0022804	0.0568529	0.0000000060359
-95%CL	1.003886	0.1448997	-0.2622977	-0.5461487	-2.706494
+95%CL	7.642678	2.900515	-0.0579759	0.0079211	-1.380837
Wald'sChi-	6.596352	4.749527	9.554488	3.669422	36.96685
p-value	0.0102232	0.0293136	0.0019963	0.0554283	0.0000000012151
Oddsratio(unitc	75.43581	4.584621	0.8520272	0.7640563	0.129553
-95%CL	2.728867	1.155924	0.7692819	0.5791761	0.06677052
+95%CL	2085.32	18.18351	0.9436727	1.007953	0.251368
Oddsratio(rang		4.584621	0.0406508	0.3408015	0.002174413
-95%CL		1.155924	0.0052687	0.1125233	0.0002976831
+95%CL		18.18351	0.3136373	1.032192	0.0158829

C Parameter	Covariance Matrix of Parameter Estimates				
	Const.B0	Clinical_Stage	PSA_Biops	Biopsy_GS	T_Stage
Const.B0	2.833501	-0.657157	-0.039727	-0.145351	0.027355
Clinical_Stage	-0.657157	0.488183	-0.002636	-0.002138	-0.157346
PSA_Biops	-0.039727	-0.002636	0.002684	-0.000040	0.003952
Biopsy_GS	-0.145351	-0.002138	-0.000040	0.019737	0.008949
T_Stage	0.027355	-0.157346	0.003952	0.008949	0.112982

C	Correlation Matrix of Parameter Estimates				
Parameter	Const.B0	Clinical_Stage	PSA_Biops	Biopsy_GS	T_Stage
Const.B0	1.000000	-0.558748	-0.455554	-0.614639	0.048347
Clinical_Stage	-	1.000000	-0.072836	-0.021784	-0.669980
PSA_Biops	-	-0.072836	1.000000	-0.005549	0.226944
Biopsy_GS	-	-0.021784	-0.005549	1.000000	0.189501
T_Stage	0.048347	-0.669980	0.226944	0.189501	1.000000

Observed	Classification of Cases Oddsratio:7.1712Perc.correct: 73.04%		
	Pred.	Pred.	Percent Correct
1.000000	58	32	64.44444
0.000000	23	91	79.82456

The 2nd model was created using a probabilistic regression (probit). The general form of probit models is as following;

$$Y = \int_{inf}^{\beta 0+\beta 1X1+\beta 2X2+\beta nXn} f(x)dz + \varepsilon \quad (5)$$

where Y represents the dependent variable (PSA after surgery), X^1, X_2,…X_n - independent variables (Clinical Stage, PSA at biopsy, Biopsy Gleason score, T stage, etc), β_1, β_2, β_n– models' parameters, -models' perturbation, and f(·) - probability density function (PDF), respectively:

$$f(z;\mu;\sigma) = \frac{1}{\sqrt{2\pi\varepsilon}} e^{-\frac{1}{2}\left(\frac{z-\mu}{\sigma}\right)^2} \quad (6)$$

where μ represents location and σ–scale (for example: standard deviation).

Taking into account the connection between the probability density and the repartition function, the model described above can be written as follows:

Taking into account the connection between the probability density and the repartition function, the model described above can be written as follows:

$$Y = F(\beta 1 + \beta 2X2 + \beta nXn) + \varepsilon \quad (7)$$

where F(·)represents the normal repartition function (CDF).

Model is: probit regression
Number of parameters to be estimated: 5
Loss function is: maximum likelihood
Convergence criterion: .0001000
Estimation method: Hooke-Jeeves and quasi-Newton
Start values: .100000 for all parameters
Initial step size: 2.00000 for all parameters
No. of 0's:90.00000 (44.11765%)
No. of 1's:114.0000 (55.88235%)
Loss function is: maximum likelihood
Final value: 105.29841608
-2*log(Likelihood): for this model= 210.5968 intercept only= 279.9740
Chi-square = 69.37714 df = 4 p = .000000

M N=204 (	Model:ProbitregressionNof0's:901's:114 Loss: Max likelihood (MS-err. scaledto1)				
	Const.B0	Clinical_Stage	PSA_Biops	Biopsy_GS	T_Stage
Estimate	2.466658	0.948920	-0.09415	-0.15525	-1.24056
Std.Err.	0.954481	0.401897	0.03006	0.08328	0.19366
t(199)	2.584293	2.361104	-3.13214	-1.86426	-6.40589
-95%CL	0.584464	0.156397	-0.15342	-0.31946	-1.62244
+95%CL	4.348853	1.741444	-0.03487	0.00897	-0.85867
p-value	0.010474	0.019187	0.00200	0.06376	0.00000

Parameter	Covariance Matrix of Parameter Estimate Variances of Parameter Estimates were computed after rescaling MSerrorto1.				
	Const.B0	Clinical_Stage	PSA_Biops	Biopsy_GS	T_Stage
Const.B0	0.911034	-0.214875	-0.013027	-0.048147	0.020241
Clinical_Stage	-	0.161521	-0.000577	-0.001337	-0.053559
PSA_Biops	-	-0.000577	0.000904	-0.000058	0.000957
Biopsy_GS	-	-0.001337	-0.000058	0.006935	0.002541
T_Stage	0.020241	-0.053559	0.000957	0.002541	0.037504

Parameter	Correlation Matrix of Parameter Estimates Variances of Parameter Estimates were computed after rescalingMSerrorto1.				
	Const.B0	Clinical_Stage	PSA_Biops	Biopsy_GS	T_Stage
Const.B0	1.000000	-0.560149	-0.454060	-0.605739	0.109505
Clinical_Stage	-	1.000000	-0.047783	-0.039957	-0.688149
PSA_Biops	-	-0.047783	1.000000	-0.023270	0.164403
Biopsy_GS	-	-0.039957	-0.023270	1.000000	0.157532
T_Stage	0.109505	-0.688149	0.164403	0.157532	1.000000

Observed	Classification of Cases Oddsratio:7.5795		
	Pred.	Pred.	Percent
1.000000	58	32	64.44444
0.000000	22	92	80.70175

In order to construct a prediction tool, that is capable to assess probabilities concerning the two possible states of the patients, a specific form recognition method was used. This method uses the principles of automated learning theory, based on a Bayesian analysis. Patients were divided into 2 classes: ω_1– patients with a PSA<0.2 ng/ml and ω_2- patients with PSA≥0.2 ng/ml. Clinical stage, PSA at biopsy, biopsy Gleason score and T stage are the explicative variables which represent the elements of vector X. Thus, we are evaluating a conditional type probability, which is represented by the probability, that a variable random class X_ω (in our case PSA after surgery) to take a particular value k_ω, knowing that X=x, a probability conditioned by the following form, respectively:

$$P[\![X\omega = k\omega \mid X = x]\!] \tag{8}$$

which defines the aposterioric probability that the x form belongs to class ω_k.

Considering

$$\mathrm{P}[X = x]\, P[X\omega = k\omega | X = x] = P[X\omega = k\omega] P[X = x | X\omega = k\omega] \tag{9}$$

means that the searched probability is given by the following relation:

$$P = [X\omega = k\omega | X = x] = \frac{P[X\omega = kw] P[X = x | X\omega = k\omega]}{P[X = x)} \tag{10}$$

Taking into account the formula of total probability P[X=x], the aposterioric probability of form x for class ω_k takes the following shape:

$$P = (X\omega = k\omega | X = x) = \frac{P(X\omega=k\omega)P(X=x|X\omega=k\omega)}{\sum_{i=1}^{K} P(X\omega=i\omega)P(X=x|X\omega=i\omega)} \quad (11)$$

Known as the Bayes formula.

These functions are used to perform predictions regarding the allegiance of the forms to classes: for a form with an unknown allegiance, each of the K functions is evaluated by substituting the X_1 $X_2 \ldots X_n$ variables with values recorded at that form and the form will be adjudicated to the class for which the highest value was obtained. The values of these functions are also known as classification scores.

D N=204 N	Discriminant Function Analysis Summary No.ofvarsinmodel:4;Grouping:PSA_Group_after_Surgery(2 rps) Wilks'Lambda:.70163approx.F(4,199)=21.156p<.0000					
	Wilks'	Partial	F-remove	p-value	Toler.	1-Toler.
Clinical_Stage	0.726287	0.966051	6.99322	0.008835	0.545472	0.454528
PSA_Biopsy	0.739696	0.948539	10.79639	0.001202	0.966948	0.033052
Biopsy_GS	0.714330	0.982222	3.60188	0.059162	0.968729	0.031271
T_Stage	0.920725	0.762042	62.14058	0.000000	0.522562	0.477438

C Variable F P	Classification Functions; grouping:	
	G_1:0 p=.55882	G_2:1 p=.44118
Clinical_Stage	19.3810	17.6883
PSA_Biops	1.0783	1.2382
Biopsy_GS	4.8296	5.1010
T_Stage	-2.3203	-0.1076
Constant	-40.8388	-45.1678

Group	Classification Matrix Rows: Observed Classifications Columns: Predicted classifications		
	Percent	G_1:0	G_2:1
G_1:0	82.45614	94	20
G_2:1	64.44444	32	58
Total	74.50980	126	78

Discussions

High risk disease represents a very heterogeneous entity, especially since the correct definition of locally advanced prostate cancer is still under debate, thus making the counseling of these patients difficult [7]. Also, depending on the definition used, the oncological and functional outcomes of various treatment modalities are different [6, 10, 11]. The lacks of standardized definition and reported outcomes after surgery have profound implications in the risk adapted management of patients who are prone to develop biochemical recurrence after radical treatment. Also, a randomized prospective study comparing the oncological outcomes of various treatment modalities has never been conducted, thus limiting the quality evidence of present studies. Nevertheless, several well conducted studies have shown excellent long term outcomes, both oncological and functional[6, 8, 12]. In our series, cancer-specific survival and overall survival rates at 5 years were82.84% and 80.8% respectively, proving that surgery alone or in combination with EBRT or HoT provide excellent long term outcomes.

One of the potential benefits of using radical prostatectomy as the first step in a multimodal approach is the possibility of providing an accurate staging, allowing for a more coherent risk adapted management. As shown by many trials, clinical stage and Gleason score can be altered in ~50% of patients undergoing surgical treatment for high risk disease [13-15]. In our cohort, 27.45% of patients have been restaged, majority from T3a to T2a or T2b, while 17.64% were upgraded from Gleason 6 to 7-10. Also, in our experience, the 82.64% of patients initially classified as D'Amico high risk were found to have specimen-confined disease after radical treatment.

After the introduction of PSA testing, the incidence of node positive patients undergoing radical prostatectomy has dramatically decreased [16]]. However, even in highly selected cohorts the percentage of N+ patients treated with RP and eLND

has been reported up to 40% [17]. In our series, 13.72% of patients were node positive on the pathological examination. Although, the presence of lymphatic metastases has been shown to be a negative prognostic factor, not all patients with nodal disease carry the same risk of developing BCR and eventually die from prostate cancer. Several studies have shown excellent long term outcomes in these patients treated with surgery alone or with adjuvant treatment [12, 18, 19].

PSA after surgery was the resultative type variable which was the subject of the statistical models created in order to quantify the factors which influence it significantly. Since the critical cutoff point for this variable is 0.2 ng/mL, the patients were divided into 2 categories accordingly: PSA group after surgery < 0.2/mL and PSA group after surgery >0.2 ng/mL. Logit and probit regression are the most suitable analyses in order to describe dichotomous variables. The results obtained by these regression models were similar in terms of parameter significance, thus confirming the validity and consistency of the results.

The usage of radiotherapy after radical prostatectomy can, theoretically, eradicate residual microscopic disease, especially in patients with positive surgical margins thus improving the oncological outcomes [20, 21]. However, the timing of radiotherapy initiation is still unclear since most data regarding this topic is retrospective and current prospective trials are still ongoing [22, 23]. In our cohort, EBRT was used in 42.15% of patients, alone or in combination with HoT. Adjuvant hormonal treatment after radical prostatectomy is very common in high risk disease, 62% of urologist recommending hormones, as adjuvant or salvage treatment, especially to node positive patients[3].

Conclusions

Our data showed excellent long-term outcome for patients with high risk prostate cancer treated with surgery as first step in a multimodal approach. Salvage treatment appears to improve oncological outcomes and should be offered to patients with multiple adverse pathologic features.

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