Predictors of unfavorable pathological outcome in patients undergoing radical prostatectomy for high risk prostate cancer

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Abstract

Introduction and Objectives. Despite refinements in the initial evaluation and management of patients with newly diagnosed localized high-risk prostate cancer, urologist have difficulties to counsel their patients based upon currently used pretreatment parameters.
In this study, we investigate preoperative characteristics that can predict unfavorable pathological outcome in patients undergoing radical prostatectomy for clinically localized high-risk prostate cancer.

Materials and Methods. We analyzed a database of 279 patients diagnosed with prostate cancer and treated with radical prostatectomy in our institute between 2014 and 2017 and identified 83 patients with high-risk characteristics because of PSA > 20 ng/ml or biopsy Gleason score ^{3} 8. The following postsurgical parameters were considered unfavorable pathological outcome: seminal vesicle invasion, surgical margins, perineural invasion and lymph node invasion. To identify the determinants associated with unfavorable pathologic outcomes, we performed univariate and multivariate logistic regression in two models.

Results. 77.1% of patients (n=64) had unfavorable pathological outcome. In multivariate analysis, we pointed out that PSA > 20 ng/ml was an independent determinant associated with lymph node invasion (OR: 3.7, 95 % CI: 1.02-14.36, p=0.04), biopsy Gleason score ≥ 8 was independently associated with increased risk of perineural invasion (OR: 6.04, 95% CI: 1.09-33.31, p=0.03) and PSA > 20 ng/ml and biopsy Gleason score ≥ 8 were independent high risk factors for seminal vesicle invasion (OR: 11.10, 95% CI: 1.30-98.44, p=0.02; OR: 11.45, 95% CI: 1.28-102, p=0.02, respectively). Moreover, in the second model, we showed that Gleason score pattern 5 increased the risk of lymph node invasion by 3.21 (OR: 3.21, 95% CI: 1.03-9.99, p=0.04).

Conclusions. Newly diagnosed patients with PSA > 20 ng/ml or biopsy Gleason score≥ 8 are at increased risk of more extensive disease. Our data is important for urologist in the selection of patients with high risk characteristics proposed for radical prostatectomy and for patients to better understand their disease.

Key-words: high-risk localized prostate cancer, radical prostatectomy, seminal vesicle invasion, lymph node invasion

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Introduction And Objectives

In the era of changes in the widespread use of PSA-screening and epidemiology of prostate cancer [1], up to 15% of patients with newly diagnosed localized prostate cancer have a more aggressive disease at presentation based upon the presence of presumed extraprostatic extension on digital rectal examination, PSA > 20 ng/ml or biopsy Gleason score of 8 to 10 [2]. Conventional treatment options for these patients include radical prostatectomy, external beam radiotherapy or hormonal therapy used alone or in multimodality approaches. Some of these patients will experience favorable outcome after definitive treatment. In contrast, most of patients with characteristics mentioned above will have a worse prognosis including the risk of progression to metastatic disease or death due to prostate cancer. These patients should be counselled and properly informed about the frequent risk of disease relapse, need for additional therapy and also about the complications of initial therapies, some with substantial impact on quality of life. Today, the priority of clinicians is to identify the group of patients who will most benefit from every initial therapy.

In 1998, D'Amico and his colleagues showed that patients with PSA > 20 ng/ml or biopsy Gleason score ≥ 8 or cT≥ T2c are at high risk of biochemical recurrence or progression to metastatic disease [3]. However, data from the literature about the importance of individual or combined parameters used in D'Amico definition are contradictory [4]. Although the role of radical prostatectomy in the initial management of high risk prostate cancer is a subject of numerous disputes, it has been shown that surgery has major benefits over primary radiotherapy, since provides an accurate pathological staging with strongest predictors for cancer specific survival and guide secondary therapies more rationale [5].

In this study, we investigate preoperative data in relation to pathological outcome to better understand the disease behavior and counsel patients with high risk features proposed for radical prostatectomy.

Materials And Methods

We analyzed a database of 279 patients diagnosed with prostate cancer and treated with radical prostatectomy in our institute between 2014 and 2017 and identified 83 patients with high-risk characteristics because of PSA > 20 ng/ml or biopsy Gleason score ≥ 8. The following post-surgical parameters were considered unfavorable pathological outcome: seminal vesicle invasion, surgical margins, perineural invasion and lymph node invasion.

Statistical analysis

To analyze the data, we reported binary variables as percentages, continuous parametric variables as mean and standard deviation and continuous non-parametric ones as median and interquartile range. To identify the determinants associated with unfavorable pathologic outcomes, we performed univariate and multivariate logistic regression. Two models were made. Statistical significance was considered p <0.05. Statistical analysis was made with IBM SPSS 19 Software (Chicago, Illinois).

Results

The main characteristics of the study group were showed in Table 1. We analysed 83 patients with high-risk prostate cancer. Mean age of study sample was 65.3 ±5.7 years and 71 out of 83 patients (85.5%) had ≥ 60 years. Preoperative features showed a median PSA of 20.5 (IQR 9.7-28.5) ng/ml and a median biopsy Gleason score of 8 (IQR 7-8). Also, 49.4% of patients had PSA > 20 ng/dl, 66.3% had biopsy Gleason score ≥ 8 and 13 patients out of 83 (15.7%) had a combination of PSA > 20 ng/ml with biopsy Gleason score ≥ 8. Regarding pathological characteristic, we found a median pathological Gleason score of 7 (IQR 7-8), 32.5% of patients had lymph node invasion and 9.7% out of them had more than 2 nodes involved, 4.8% positive surgical margins, 60.2% perineural invasion and 59% seminal vesicle invasion with 40% out of them with bilateral invasion. Forty-five out of 83 patients had no difference between biopsy and pathological Gleason score, 15.7 % had upgrading and 30.1% had downgrading Gleason score.

Variables	No. of patients (n=83)
Age (mean, years)	65.3 ±5.7
≥ 60 years (%)	71 (85.5%)
PSA (median, ng/ml)	20.5 (9.7-28.5)
> 20 ng/ml (%)	41 (49.4%)
Biopsy Gleason Score (median)	8 (7-8)
≥8 (%)	55 (66.3%)
PSA >20 ng/ml and Biopsy Gleason Score ≥8 (%)	13 (15.7%)
Pathological Gleason Score (median)	7 (7-8)
Lymph node invasion (%)	27 (32.5%)
≤ 2ggl (%)	19(22.8%)
>2ggl (%))	8 (9.7%)
Positive surgical margins (%)	4 (4.8%)
Perineural invasion (%)	50(60.2%)
Seminal vesicle invasion (%)	49(59%)
Unilateral	15(18%)
Bilateral	34 (40%)

Table 1. General characteristics of study group

Determinants analysis

To identify the determinants associated with unfavorable pathological outcomes, we performed two models of binary logistic regression. In the first model, we evaluated the impact of age ≥ 60 years, PSA > 20 ng/ml and biopsy Gleason score ≥ 8 on lymph node invasion, perineural invasion and seminal vesicle invasion (Tables 2, 3, 4). In multivariate analysis, we pointed out that PSA > 20 ng/ml was an independent determinant associated with lymph node invasion and increased the risk of this unfavorable pathological outcome 3.7 times (OR: 3.7, 95% CI: 1.02-14.36, p=0.04), biopsy Gleason score ≥ 8 was independently associated and increased the risk of perineural invasion 6 times (OR: 6.04, 95% CI: 1.09-33.31, p=0.03) and PSA > 20 ng/ml and biopsy Gleason score ≥ 8 were independent high risk factors for seminal vesicle invasion (OR: 11.10, 95% CI: 1.30-98.44, p=0.02; OR: 11.45, 95% CI: 1.28-102, p=0.02, respectively).

In the second model, we analyzed the impact of age ≥ 60 years, PSA > 20 ng/ml and biopsy primary Gleason score pattern 5 on lymph node invasion (Table 5). By multivariate analysis, we showed that PSA > 20 ng/ml increased the risk of lymph node invasion 2.99 times (OR:2.99, 95% CI: 1.03-8.64, p=0.04) and primary Gleason score pattern 5 by 3.21 (OR: 3.21, 95% CI: 1.03-9.99, p=0.04).

Model 1

Table 2. Binary regression analysis to identify the determinants of lymph node invasion

	Univariate regression			Multivariate regression		
Variables	OR	95% CI	P value	OR	95% CI	P value
Age ≥ 60 years	0.28	0.08-0.96	0.04*	0.27	0.07-1	0.06
PSA > 20 ng/ml	2.26	0.88-5.82	0.08	3.7	1.02-14.36	0.04*
Biopsy Gleason score ≥ 8	0.65	0.30-2.01	0.65	2.24	0.57-8.92	0.24

Table 3. Binary regression analysis to identify the determinants of perineural invasion

	Univariate regression			Multivariate regression		
Variables	OR	95% CI	P value	OR	95% CI	P value
Age ≥ 60 years	0.25	0.05- 1.26	0.09	0.23	0.04-1.18	0.07
PSA > 20 ng/ml	1.06	0.44- 2.56	0.89	3.72	0.76-20.32	0.11
Biopsy Gleason score > 8	1.89	0.75-4.78	0.17	6.04	1.09-33.31	0.03*

Table 4. Binary regression analysis to identify the determinants of seminal vesicle invasion

	Univariate regression			Multivariate regression		
Variables	OR	95% CI	P value	OR	95% CI	P value
Age ≥ 60 years	0.24	0.05- 1.19	0.08	0.22	0.04-1.14	0.07
PSA > 20 ng/ml	1.75	0.72- 4.24	0.21	11.10	1.30-98.44	0.02*
Biopsy Gleason score ≥ 8	1.40	0.55-3.52	0.47	11.45	1.28-102	0.02*

Model 2

Table 5. Binary regression analysis to identify the determinants of lymph node invasion

	Univariate regression			Multivariate regression		
Variables	OR	95% CI	P value	OR	95% CI	P value
Age ≥ 60 years	0.28	0.08- 0.98	0.04*	0.24	0.06-0.91	0.03*
PSA > 20 ng/ml	2.26	0.88- 5.82	0.08	2.99	1.03-8.64	0.04*
Biopsy primary Gleason pattern 5	1.94	0.71-5.27	0.19	3.21	1.03-9.99	0.04*

Discussions

Nowadays, urologist have great interest in optimizing treatment for clinically significant prostate cancer. Although high risk prostate cancer carries a worse prognosis, under this definition there are neoplasms that have good prognosis or even can be cured. Despite numerous advances in biomarkers discovery or radiologic imaging for detection and staging of aggressive disease, urologists are using in their current practice mostly clinical parameters from D'Amico definition for risk assessment of newly diagnosed prostate cancer. However, it has been shown that PSA value or biopsy Gleason score or clinical assessment of tumor stage by digital rectal examination cannot accurately predict prognosis and subsequently help clinicians to counsel their patients about optimal treatment [4]. Further, patients with locally advance disease and high-risk characteristics at diagnosis were not considered good candidates for radical prostatectomy because of unfavorable outcomes [6]. In addition, surgery can be technically difficult for majority of urologists. Continuous efforts are made by researches to identify those patients who benefit mostly from surgical therapy in these group of patients. Pathological parameters have been shown to be more useful and more accurately predictors of prognosis [7]. Among them, the most important determinants are status of surgical margins, extraprostatic extension into seminal vesicle and lymph node involvement.

While some authors demonstrated PSA association with tumor volume, pathological stage and tumor extent others were not [8]. In our study, in multivariate analysis PSA > 20 ng/ml was a significant predictor for seminal vesicle invasion and lymph node invasion.

Likewise, biopsy Gleason sum has an important role for the prediction of adverse pathological outcome, disease recurrence or progression and was included in many nomograms [9]. It has been shown that Gleason sum can be downgraded in the surgical specimen and this finding encourage the urologists to perform radical prostatectomy as the primary treatment of high risk patients. Despite this positive finding, some men will experience poor outcome after radical prostatectomy. In our study, biopsy Gleason sum was a strong predictor for unfavorable pathology, increasing the risk of seminal vesicle invasion by 11.45 times and of perineural invasion by 6.04 times. Moreover, the presence of Gleason pattern 5 in our cohort of patients with biopsy Gleason sum≥ 8 increased the risk for lymph node invasion by 3.21 times. The significance of Gleason pattern 5 as a predictor for unfavorable outcome after radical prostatectomy or radiotherapy was demonstrated by numerous research studies [10].

Since it has been shown that pathological findings are the strongest predictors of biochemical recurrence or of more important clinical endpoints such as time to metastases or cancer specific survival, it is expected that patients with prostate cancer diagnosed at PSA > 20 ng/ml or with biopsy Gleason sum≥ 8, with or without pattern 5, will experience a poor prognosis. However, this is not mandatory, and it will be of importance to further explore the impact of our findings.

The retrospective analysis of our study and relative small number of patients in our cohort are the limitations of this study.

Conclusions

Newly diagnosed patients with PSA > 20 ng/ml or biopsy Gleason score≥ 8 are at increased risk of more extensive disease. Our data is important for urologist in the selection of patients with high risk characteristics proposed for radical prostatectomy and for patients to better understand their disease.

References

1. Lee DJ, Mallin K, Graves AJ, Chang SS, et al. *Recent Changes in Prostate Cancer Screening Practices and Epidemiology.* J Urol. 2017 Dec;198(6):1230-1240. doi: 10.1016/j.juro.2017.05.074. Epub 2017 May 25.
2. Cooperberg MR, Broering JM, Carroll PR. *Time trends and local variation in primary treatment of localized prostate cancer.* J Clin Oncol. 2010 Mar 1;28(7):1117-23. doi: 10.1200/JCO.2009.26.0133. Epub 2010 Feb 1.
3. D'Amico AV, Whittington R, Malkowicz SB, Cote K, et al. *Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era.* Cancer. 2002 Jul 15;95(2):281-6
4. Partin AW , Yoo J , Carter HB et al . *The use of prostate specific antigen, clinica stage and Gleason score to predict pathological stage in men with localized prostate cancer.* Journal Urol 1993 ; 150 :110 – 4
5. Van Poppel H. *Locally advanced and high risk prostate cancer: The best indication for initial radical prostatectomy?* Asian J Urol. 2014 Oct;1(1):40-45. doi: 10.1016/j.ajur.2014.09.009. Epub 2015 Apr 16.
6. Khan MA, Mangold LA, Epstein JI, Boitnott JK, et al. *Impact of surgical delay on long-term cancer control for clinically localized prostate cancer.* J Urol. 2004 Nov;172(5 Pt 1):1835-9.
7. Adamis S, Varkarakis IM. *Defining prostate cancer risk after radical prostatectomy.* Eur J Surg Oncol. 2014 May;40(5):496-504. doi: 10.1016/j.ejso.2014.02.221. Epub 2014 Feb 20
8. Stenman UH, Abrahamsson PA, Aus G, Lilja H, et al. *Prognostic value of serum markers for prostate cancer.* Scand J Urol Nephrol Suppl. 2005 May;(216):64-81.
9. Bastian PJ, Gonzalgo ML, Aronson WJ, Terris MK, et al. *Clinical and pathologic outcome after radical prostatectomy for prostate cancer patients with a preoperative Gleason sum of 8 to 10.* Cancer. 2006 Sep 15;107(6):1265-72.
10. Servoll E, Saeter T, Vlatkovic L, et al. *Impact of a tertiary Gleason pattern 4 or 5 on clinical failure and mortality after radical prostatectomy for clinically localised prostate cancer.* BJU Int109(10): 1489-94, May 2011