

Original Article

Characteristics and risk factors of biochemical recurrence after radical prostatectomy in patients with prostate cancer

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Abstract: Objective: To investigate the characteristics and risk factors of biochemical recurrence after radical prostatectomy in patients with prostate cancer in order to provide a basis for improving the therapeutic efficacy of the disease. Methods: A retrospective analysis was performed on clinical characteristics and follow-up data of the patients with prostate cancer treated with radical prostatectomy in our hospital between January 2008 and December 2012 to characterize the biochemical recurrence of the patients and explore the risk factors using the Cox regression model. Results: Among the 237 patients with prostate cancer treated with radical prostatectomy, 54 (22.8%) had biochemical recurrence during the follow-up period after surgery. The time to recurrence after surgery was 1.0~55.0 months, with a median of 23.0 months. The 1-, 2-, and 3-year biochemical recurrence-free survival rates after surgery were 94.9%, 88.2%, and 81.4%, respectively. The multivariate Cox regression analysis showed that high PSA level at diagnosis (10~20 µg/L and >20 µg/L) ($HR=1.52$, 95% CI : 1.01~2.30, $HR=3.02$, 95% CI : 1.54~5.90), high pre-surgical Gleason score (7 and ≥8) ($HR=1.61$, 95% CI : 1.05~2.49, $HR=2.15$, 95% CI : 1.21~3.84), late pathological stages ($HR=2.50$, 95% CI : 1.32~4.72) and pelvic lymph node metastasis ($HR=1.84$, 95% CI : 1.06~3.20) were risk factors of recurrence in the patients. Conclusion: There is still a risk of biochemical recurrence after radical prostatectomy in patients with prostate cancer. The patients with high PSA level, high pre-surgical Gleason score, late pathological stages, or pelvic lymph node metastasis were more likely to experience biochemical recurrence after surgery. These patients should be treated under comprehensive consideration to prevent recurrence and prolong survival time.

Keywords: Prostate cancer, radical prostatectomy, recurrence, risk factors

Introduction

Prostate cancer (PCa) is currently one of the most commonly seen male urinary system malignant tumors in the world, and it takes up 14.0% of the annual newly-diagnosed male cancer cases worldwide, and 6.0% of the annual cases of death induced by cancer [1]. Globally speaking, the mortality rate of prostate cancer in China is at an average level, but there are remarkable regional differences, and the annual mortality rate in some regions is as high as 28.6/100,000. With acceleration in population aging and changes in lifestyle during the recent years, the mortality rate of prostate cancer has a tendency of constant elevation [2, 3]. Radical prostatectomy (RP) is one of the most effective

methods to treat localized prostate cancer. With advances in technology and accumulation of experiences, it has been currently applied to clinical practice widely [4]. However, there are still some PCa patients who still face the risk of biochemical recurrence after surgical treatment. In case of recurrence, the prognosis of PCa patients will be poor [5]. Therefore, looking for the risk factors that influence recurrence in the patients after RP, adopting the corresponding measures to lower the post-surgical recurrence rate and improving patient's survival are the main focuses of clinical study. This study intends to explore the risk factors that influence the post-surgical recurrence of PCa, thus improving the level of clinical treatment and prolonging the patient's survival time by making

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a retrospective analysis on the clinical characteristics and follow-up data of the patients admitted in our hospital after RP and observing the post-surgical recurrence of the disease.

Materials and methods

Study subjects

The patients with prostate cancer that received radical prostatectomy at our hospital from January 2008 to December 2012 were selected as the subjects. The inclusion criteria were as follows: the patients who received radical prostatectomy; those who were pathologically diagnosed with prostate cancer; and those with detailed clinical and follow-up data. The exclusion criteria were as follows: the patients complicated with tumors at other sites; those with serious functional disorders in vital organs such as the heart, liver, brain and kidneys; and those with metastasis before surgery. A total of 237 patients with prostate cancer aged 42~79 years (with a median age of 67 years and a mean age of 68.3 ± 12.1 years) were included in the study. Regarding the clinical stages, there were 48 patients (20.3%) at T1 stage, 119 (50.2%) at T2 and 70 (29.5%) at T3. There were 76 patients (32.1%) with ≤ 6 points, 79 (33.3%) with 7 points and 82 (34.6%) with ≥ 8 points in pre-surgical Gleason score. The pre-surgical prostate specific antigen (PSA) was 3.6~255.9 $\mu\text{g/L}$. In pathological stages, there were 5 patients (2.1%) at T2a, 11 (4.6%) at T2b, 122 (51.5%) at T2c, 59 (24.9%) at T3a and 40 (16.9%) at T3b. There were 59 patients (24.9%) with ≤ 6 points, 92 (38.8%) with 7 points and 86 (36.3%) with ≥ 8 points in post-surgical Gleason score. There were 32 patients (13.5%) with positive surgical margins and 43 (18.1%) with pelvic lymph node metastasis.

Study methods

By reviewing the medical records such as inpatient records, various auxiliary examination reports and follow-up records, the clinical and follow-up data of the patients with prostate cancer were collected, and a uniform questionnaire was used to extract the relevant information, including mainly age, BMI, clinical and pathological staging of PCa, Gleason score, relevant examination results, treatment characteristics, biochemical recurrence and time of the last follow-up. Clinical and pathological

staging is based on the TNM staging system criteria.

Treatment methods

All PCa patients received radical prostatectomy, including 175 cases of open surgery (73.8%) and 62 cases of laparoscopic surgery (26.2%). In addition, whether adjuvant endocrine therapy was necessary and the treatment time, if necessary, were decided considering the presence and absence of pelvic lymph node metastasis, pathological staging and Gleason score etc. The patient with pelvic lymph node metastasis received adjuvant endocrine therapy for ≥ 2 years after surgery; those without pelvic lymph node metastasis, but with positive surgical margin, or with a post-surgical Gleason score ≥ 8 points, or clinical stage of T3 and above, received adjuvant endocrine therapy for 9 months after surgery.

Follow-up methods

All patients were followed up by the means of outpatient PSA review to collect the data. The follow-up cycle was once per month within 6 months after surgery, once every three months from 6 months to 2 years after surgery, and once every 6 months from 2 years afterward. The patients were followed up until biochemical recurrence (PSA increase for consecutively two times with a value higher than 0.2 $\mu\text{g/L}$) or December 2015, the follow-up rate of the included patients was 100%, and the biochemical recurrence-free survival time was the period from the day of surgery to the time of biochemical recurrence.

Statistical analysis

SPSS 21.0 software was applied for statistical analysis. Mean \pm SD and relative numbers such as rate and constituent ratio were used respectively for statistical description of measurement data and enumeration data. The Kaplan-Meier method was employed to estimate the biochemical recurrence-free survival rates after surgery for patients having prostate cancer with different characteristics and the log-rank test was used for comparison of the biochemical recurrence-free survival rates of patients with different characteristics. The Cox proportional hazard regression model ($\alpha_{\text{in}} = 0.05$, $\alpha_{\text{out}} = 0.10$) was used to explore the risk

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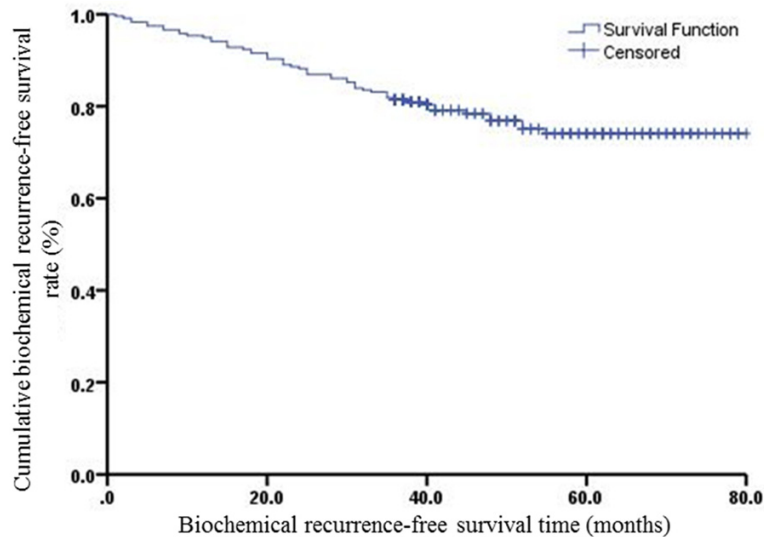


Figure 1. Biochemical recurrence-free survival curve of patients with prostate cancer after radical prostatectomy.

factors of post-surgical biochemical recurrence in the patients. Test level $\alpha=0.05$, and $P<0.05$ indicated statistically significant difference.

Results

Recurrence

A total of 237 patients were followed up after surgery for 1.0 to 80.0 months, with a median of 41.0 months. During follow-up, a total of 54 PCa patients experienced biochemical recurrence, with an overall recurrence rate of 22.8% (33/237). The earliest time of biochemical recurrence was 1.0 month after surgery, and the latest was 55.0 months after surgery, with a median of 23.0 months. The post-surgical 1-, 2- and 3-year biochemical recurrence-free survival rates were 94.9%, 88.2% and 81.4%, respectively (**Figure 1**).

Univariate analysis on recurrence

The log-rank test indicated that the differences in recurrence rate during the follow-up period after radical prostatectomy among the PCa patients with different PSA levels at diagnosis, pre-surgical Gleason scores, clinical stages, pathological stages and post-surgical Gleason scores, with or without pelvic lymph node metastasis and adjuvant endocrine therapy and negative/positive surgical margin were of statistical significance ($P<0.05$), whereas the

differences among the patients in different age groups and with different BMIs were of no statistical significance ($P>0.05$) (**Table 1**).

Multivariate analysis on recurrence

The variables that were meaningful to recurrence in the univariate analysis were included to perform a multivariate Cox proportional hazards stepwise regression analysis, and the results indicated that the overall difference in regression equation was of statistical significance ($\chi^2=45.682$, $P<0.001$). A high level of PSA at diagnosis (10~20 $\mu\text{g/L}$ and $>20 \mu\text{g/L}$), a high pre-surgical Gleason score (7 and ≥ 8), a relatively late pathological stage ($\geq T3a$) and the presence of pelvic lymph node metastasis were independent risk factors for biochemical recurrence after RP for PCa patients ($P<0.05$) (**Table 2**).

Discussion

With the development in technology and accumulation of experiences, radical prostatectomy (RP) has been widely applied in China. Currently, it has evolved into one of the most effective approaches to clinical treatment of localized prostate cancer [6]. There are more and more studies in this field, but the majority are focused on the discussion about the surgical methods, skills and experiences, and the domestic studies concerning the patient's post-surgical survival and recurrence are less than the similar foreign studies [7]. Exploring the risk factors that influence the post-surgical biochemical recurrence of PCa and establishing reasonable comprehensive therapeutic regimens against the risk factors are of important significance to preventing the post-surgical recurrence of PCa, optimizing the clinical therapeutic effect and improving the quality of life of the patients.

In this study, 237 PCa patients that received RP were followed up and the results showed that 54 patients experienced recurrence (22.8%), the post-surgical 1-, 2- and 3-year biochemical recurrence-free survival rates were 94.9%,

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Table 1. Univariate analysis results of biochemical recurrence in patients with prostate cancer after radical prostatectomy (n=237)

Variable	Total no. of patients	Post-surgical recurrence		χ^2	P
		No. of patients	Recurrence rate (%)		
Total	237	54	22.8		
Age (year)					
<65	110	20	18.2	2.472	0.116
≥65	127	34	26.8		
BMI (kg/m ²)					
<24	122	25	20.5	0.751	0.386
≥24	115	29	25.2		
PSA at diagnosis (μg/L)					
≤10	69	6	8.7	18.343	<0.001*
10~20	71	13	18.3		
>20	97	35	36.1		
Pre-surgical Gleason score					
≤6	76	8	10.5	15.656	<0.001*
7	79	16	20.3		
≥8	82	30	36.6		
Clinical stages					
cT1	48	7	14.6	9.736	0.008*
cT2	119	22	18.5		
cT3	70	25	35.7		
Pathological stages					
≤T2c	138	17	12.3	20.569	<0.001*
≥T3a	99	37	37.4		
Pelvic lymph node metastasis					
No	194	34	17.5	16.809	<0.001*
Yes	43	20	46.5		
Post-surgical Gleason score					
≤6	59	8	13.6	6.716	0.035*
7	92	19	20.7		
≥8	86	27	31.4		
Adjuvant endocrine therapy					
No	100	31	31.0	6.636	0.010*
Yes	137	23	16.8		
Surgical margins					
Negative	205	40	19.5	9.243	0.002*
Positive	32	14	43.8		

Note: *P<0.05.

88.2% and 81.4% respectively, obviously lower than those reported in relevant foreign studies [8, 9], and Menon *et al.* followed up 1,384 PCa patients and found that the patient's 3-year biochemical recurrence-free survival rate was up to 90.6% and the 5-year survival rate was over 85.0%. The reasons for the above difference were relatively late stage and higher grade

of tumor in the PCa patients of this group, with 41.8% of the patients at T3 in pathological stage, whereas in foreign studies, less than 5.0% of the patients were at T3; in addition, 34.6% of the patients in this group had a Gleason score ≥8 points, whereas in foreign studies, the proportion was not more than 15.0%. The previous studies [10] and multivari-

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Table 2. Multivariate Cox regression analysis results of biochemical recurrence in patients with prostate cancer after radical prostatectomy (n=237)

Independent variable	Regression coefficient	SE	Wald χ^2	P	HR (95% CI)
PSA at diagnosis (reference group ≤ 10 $\mu\text{g/L}$)			25.671	<0.001*	
10~20 $\mu\text{g/L}$	0.423	0.209	6.009	0.014*	1.52 (1.01~2.30)
>20 $\mu\text{g/L}$	1.105	0.342	18.556	<0.001*	3.02 (1.54~5.90)
Pre-surgical Gleason score (reference group ≤ 6)			22.359	<0.001*	
7	0.478	0.221	5.745	0.016*	1.61 (1.05~2.49)
≥ 8	0.767	0.295	9.219	0.002*	2.15 (1.21~3.84)
Pathological stage $\geq T3a$ (reference group $\leq T2c$)	0.915	0.325	9.518	0.001*	2.50 (1.32~4.72)
Pelvic lymph node metastasis (reference group = no)	0.611	0.281	19.425	<0.001*	1.84 (1.06~3.20)

Note: * $P < 0.05$.

ate analysis in this study demonstrated that the patients at relatively late stage or with higher grade of tumor had obviously increased risks of post-surgical biochemical recurrence. The main reason for differences in tumor stages and grades of the PCa patients between China and abroad is the difference in early screening for prostate cancer [11]. Due to the difficulties in economy and healthcare and personal health awareness, although in recent years China has recommended the use of early screening for prostate cancer, the majority of patients visit the doctors only in case of dysuria, hematuria and generalized pain when the disease has evolved into the advanced stage, even with metastasis, and the therapeutic effect is relatively poor.

In the meantime, the multivariate analysis in this study has demonstrated that a higher level of PSA at diagnosis, relatively late pathological stage and pelvic lymph node metastasis are independent risk factors for biochemical recurrence after RP for PCa patients, which are consistent with the reports in relevant domestic and foreign studies [3, 12, 13]. However, it has been found in this study that positive surgical margin is not an independent risk factor for biochemical recurrence after RP, which is different from the reports in relevant foreign studies [15]. The reasons may be as follows: (1) a bigger proportion of patients in this group were at a relatively late pathological stage, T3, and the risk of positive surgical margin in PCa patients at this stage is relatively high, thus subject to the influence of factors such as pathological stage; (2) in addition, active adjuvant therapy was given to the patients with positive surgical

margin in our hospital, delaying the occurrence of biochemical recurrence. This study has also showed that a higher pre-surgical Gleason score is an independent risk factor for biochemical recurrence after RP, consistent with the report in the previous relevant studies [12]. However, post-surgical Gleason score is not an independent risk factor for biochemical recurrence of the PCa patients, which is inconsistent with the relevant domestic and foreign studies [14, 15]. The foreign studies has shown that the HR of biochemical recurrence for post-surgical Gleason score ≥ 10 relative to ≤ 6 is 7.91 (95% CI=4.37-14.25), likely due to the differences in basic pathological characteristics, and the specific reason is to be further investigated.

In summary, the PCa patients still have a certain risk of biochemical recurrence after RP. The risk of post-surgical biochemical recurrence is increased in the patients with a late clinical stage, poor differentiation and non-squamous carcinoma in pathological type, lymph node metastasis and no post-surgical adjunctive therapy. Therefore, in clinical practice, treatment should be comprehensively considered for the patients with above characteristics to prevent post-surgical recurrence and prolong the patient's survival time.

Disclosure of conflict of interest

None.

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