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RESEARCH

Watchful Waiting and Active Surveillance Approach in Patients with Low Risk Localized Prostatic Cancer: An Experience of Out-Patients Clinic with 12-Year Follow-Up

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Abstract In this study we evaluated the safety of expectant approach in the patients with low risk prostate cancer in the reality of community based out-patients clinics. 48 men were enrolled into the study. The inclusion criteria were age ranged from 60 to 75 years and the Epstein criteria for low risk prostate cancer. Patients were managed expectantly while curative treatment was offered when indicated. Initial and final Charlson comorbidity index (CCI) and BMI were assessed for all men. Patients' median follow-up was 81.1±29.1 years. During this study 41.7% of the patients chose active forms of treatment. Cancer was found in 20.8% (n-10) of our patients. Two first sessions of re-biopsy diagnosed 92% of T1c upgrading. Six men with CCI ≥2 died from concomitant disease and no one died from PCa. Significant correlation was found between BMI and final CCI ≥2 (p-0.001). Expectant approach can be considered as self alternative to active treatment model in selected group of patients with well differentiated PCa, however 20.8% of these patients are still at risk of having aggressive form of cancer. Expectant approach is particular beneficial for the patients with CCI 1–2 and high BMI.

Keywords Prostate · Cancer · Expectant management · Body mass index · TRUS-biopsy

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Introduction

Nowadays the liberal use of PSA screening has doubled the detection rates of prostate cancer (PCa). The European Randomized Screening Trial for PCa reported a 20% reduction in mortality in the screening arm. However, this study had shown that 48 prostatectomies were performed to prevent one death [1]. Consequently, it would be worthwhile to identify patients with low risk PCa in whom curative-intent therapy could be postponed until the time of tumor progression. To accomplish this task, Epstein proposed a set of decisive factors based on the PSA and biopsies characteristics [2]. These criteria had been successfully adopted by others for identification of men eligible for expectant management [3, 4].

In this study we investigate the place of expectant management in the patients with low risk PCa who were treated in the community out-patient clinics of two medical insurance companies.

Materials and Methods

From October 1998 through March 2006, men with "low risk" PCa were enrolled into the study. All patients were seen in the community outpatient clinics of two health insurance companies. The follow-up was completed

through March–June 2010. The inclusion criteria were patients age ranged from 60 to 75 years, PSA ≤10 ng/ml, T1a/T1c, Gleason score ≤6, <3 cores involved with cancer with <30% involvement of each core.

Several objects were chosen as the end points of our study. First, we assessed the value of current tools for expectant management, such as increase in PSA and PSA doubling time (PSA DT). Second, we tried to unveil the long-term consequences of delayed treatment. Third, it appeared interesting to set up the optimal number of re-biopsy's sessions for expectant protocols. Finally, we evaluated if concomitant diseases and body mass index (BMI) help to categorize patients who might benefit from expectant approach. For the purpose of the latter task, patients' comorbidity index was assessed according to Charlson system (CCI) [5].

Until 2004 patients were on the watchful waiting (WW) protocol with *curative intention*. This protocol presumed every 3-month visits with PSA assessment and digital rectal examination (DRE). Curative intervention was offered to the patients with rising PSA levels >30% in at least one of 3 consecutive measurements and/or changes on DRE. Starting from 2004 all remained and new enrolled patients (n-30) were shifted to the active surveillance (AS) protocol. Patients were followed every 3 months by PSA and DRE. Repeat TRUS-biopsies were recommended every 18 months or in case of changes in PSA or DRE. Incline in Gleason score (Gl.score) and/or number of positive cores was considered as indication for active forms of treatment. During the follow-up patients were free to obtain "second opinion" and their decisions to be actively treated was considered as additional indication. We assigned causes that swung patients to active forms of treatment as "medical indication" (WW/AS protocols), "second opinion" and/or anxiety.

To systemize the biopsy protocol all TRUS –biopsies were taken according to the prostate volume and varying the biopsy site from session to session according to a pre-established schema (Table 1). Consequent re-biopsies during AS were performed based on the above mentioned protocol.

In all sessions we used periprostatic nerve block for local anesthesia [6]. We also assessed pain scores for every patient after each session of biopsies. For these purposes within 2 min of procedure completion patients were asked to grade their pain perception via a linear scale (range 0 to 10) without numbers to avoid superimposing of numbers on a visual analog scale. For analysis visual analog score was converted to digital score by simple measurement.

Statistics

The statistical analysis was performed using SPSS 13.0. For the first step descriptive statistical techniques were used in order to describe the study population. For the second step univariant statistical techniques were used: *T*-test and Chi Square test in respect to the variables nature. ANOVA and multiple comparisons analyses were used for different independent variables in order to assess their correlation with various dependent factors. For the small volume variables we used Fisher exact test and $p<0.05$ was considered significant.

Table 1 Protocol of TRUS-biopsy, based on the prostate volume and number of session

Prostate volume	1st session: laterally directed	2nd session: medially directed	3rd session: inclusion of TZ	>3 sessions: increased biopsies
<40 ml	8	8	10	14
40–60 ml	10	10	12	16
>60–80 ml	12	12	14	18
>80–100 ml	14	14	16	20
>100 ml	16	16	18	22

TZ transitional zone

Results

Of the 332 men who were diagnosed with PCa, 59 (17.8%) met the inclusion criteria and 48 (81.4%) agreed for expectancy treatment. Patients' mean age was 68.4±4.2, and mean PSA at the start of the study was 7.4±1.9 ng/ml. The mean prostate volume was 59.4±25.4 ml. Mean BMI was 27.6±4.6. At the beginning of the study 75% of the patients had no comorbidity, while CCI ≥1 was calculated in 25% of the patients (CCI −1 and CCI ≥2 in 7 and 5 men, respectively). T1c was diagnosed in 41 patients and in most of them the diagnosis was made on the 1st and 2nd sessions (n-20; 41.7% and n-13; 27%, respectively). Additional seven (14.6%) patients were diagnosed with T1a.

Mean follow-up was 81.1±29.1 months. Based on the AS protocol 28 patients underwent 65 session of re-biopsy with mean 35.92±15 biopsies taken on these sessions. As a result, higher Gl. score was revealed in 5 patients (Gl. score - 7 in 4 patients and 8 in one) whilst in 4 patents more cores with the same Gl. score were involved with cancer. In 92% the above mentioned changes were discovered on the 1st two sessions of re-biopsies.

During this study 41.7% of the patients underwent active forms of treatment (7 WW and 13 AS). Only half of them met medical indications for active intervention. Eleven underwent radical prostatectomy (RP), 5 patients chose radiotherapy and four were treated with cryo ablation. Cancer focus of ≤1 cm in diameter was reported in 6 of 11 patients who underwent RP, in 3 cases Gl. score on pathological exam was 7 and 8, while in 2 of these cases

reported cancer diameter was >1 cm or multifocal areas of cancer were found. Mean follow up after active treatment was 50.25±15.6 months. Only in one patient after radiation therapy and adjuvant hormonal deprivation PSA raised to1.5 ng/ml. His re-biopsies showed Gl. score 7 (4+3) and salvage cryo ablation of prostate was used in this case. He remains under follow-up and his recent PSA stabilized on the 0.2 ng/ml.

In nearly 25% of our patients (n-12) PSA rose >30%. Potentially aggressive cancer was diagnosed in 75% of these patients and in 55% of them PSA DT was ≤3 years. Mean PSA doubling time (PSA DT) was 8.25±3.7 years. Nine of ten patients with the features of potentially aggressive cancer had PSA DT 1–5 years (Fig. 1). In contrast, the majority of patients who remained under WW/AS were with PSA DT >5 years.

In addition, we decided to investigate subgroup of patients (n-10, 20.8%) with potentially aggressive cancer (higher Gl. score on re-biopsies, increased cancer involvement of cores, pathological Gl. score ≥7, cancer diameter >1 cm or mulifocal areas of cancer on pathological specimens). Mean PSA DT in this group was 2.6±1.2 years (Table 2). When PSA DT ≤3 years was compared with the other variables, statistical analysis had shown that only PSA increase >30% had a weak statistical correlation with the potentially aggressive cancer characteristics (Fisher's exact test *p*-0.72).

Twelve patients started this study with CCI ≥1 (25%), while final CCI ≥1 was registered in 21(44%) men: CCI-1 in 4 patients and CCI ≥2 in 5 men with initial no-comorbidity/CCI-1 and high BMI (mean 32.2±2.4). Six men with CCI ≥2 died from the other causes and no one died from cancer. Two of them had PSA DT ≤3 years and 3 PSA DT 4–5 years. Mean BMI in this group of patients was 33.51±3.57. In general, BMI was differed significantly between the groups with different CCI (p-0.03). In particular, it was significantly higher in patients with CCI ≥2 (35.4±3.83) than in CCI −1 (27.87±4.8) group and patients with no comorbidity (p-0.001 and 0.011, respectively). Significant correlation was found between BMI and final CCI ≥2 (p-0.001).

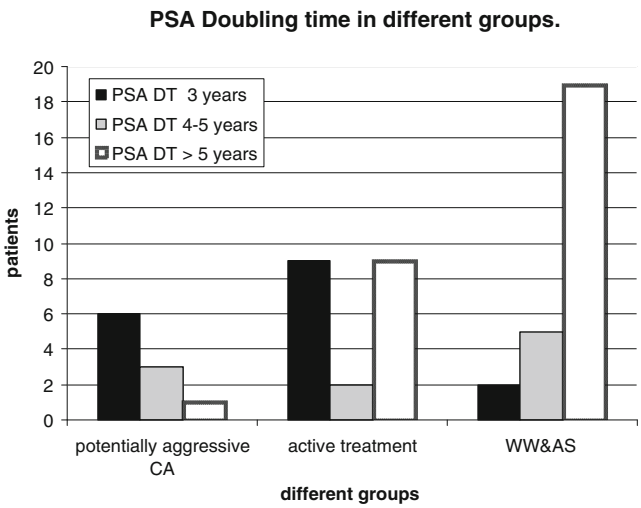

Fig. 1 PSA Doubling time in different groups of patients. WW – watchful waiting; AS – active surveillance

After mean follow-up of 78.82±34.3 months 22 (45.8%) patients remained on WW/AS protocol. Only 9 (18.8%) remained on AS, while 13 refused AS protocol on different stages of follow-up: 8 refused swing to AS and 5 declined repeat biopsies after the 1st/2nd sessions of re-biopsies. These patients explained their decision by old age, coexisting illness and anxiousness associated with re-biopsies. In fact, 61.5% (n-8) of these patients had CCI ≥1, their mean age was 76.9±3.48 years and each of them underwent ≥3 sessions of biopsies (before diagnosis of cancer and re-biopsies during AS). In this context it would be worthwhile to emphasize the results of statistical analysis, which showed that pain scores were significantly higher when more than 3 sessions of biopsies were performed (Table 3). The statistic analyses showed that the number of re-biopsy sessions >3 correlated with patient's decision to stop re-biopsies (Fisher's exact test $p - 0.001$).

Discussions

Previous studies had shown that application of Epstein criteria might underestimate biological significance of PCa in 20–24% of patients [3, 7]. However, these factors have PPV of 92% for organ confined disease that still could be successfully managed by active forms of treatment [7–9]. In our study we enrolled only patients who met the Epstein criteria for low risk PCa, yet nearly 21% had features of aggressive cancer based on the pathological reports and re-biospies. All of these patients underwent active forms of treatment and in nine of ten we failed to identify biochemical failure up to mean 50.25±15.6 months after treatment. Thus, we agree with Lee et al. that Epstein criteria can predict organ-confined PCa but additional tools should be used for identification of potentially aggressive disease [9].

In the study dedicated to expectant management of low risk PCa Klotz used PSA DT threshold <2 years as indication for curative treatment. It should be emphasized that he used less strict inclusion criteria and reported that 58% of patients who underwent RP had locally advanced disease. Therefore, he suggested to extend PSA DT cut-off to 3 years and predicted that in these circumstances 22% of low risk patients might need curative treatment [10]. Nearly 21% of our patients with strict Epstein criteria showed the features of aggressive PCa and most of them had PSA DT 1–5 years. None of the patients, who underwent RP showed

Table 2 Patients with potentially aggressive prostate cancer

P. No.	age	P-te V	Gl. score re-biopsy	> cores with Ca	>% Ca	psa >30%	psa dt	T-t	P Gl.	Ø Ca >1 cm	T-t f.	Follow up after T-t
12	68	67.2 ml	Not done	–	–	√	4–5	RP	6	–	–	52 mon.
21	63	42.5 ml	7	√	√	√	≤3	RP	7	–	–	63 mon.
25	68	51 ml	7	–	–	√	≤3	R-t	–	–	√	42 mon.
27	67	39.7 ml	6	√	–	–	4–5	AS	–	–	–	54 mon.
30	65	63.7 ml	8	√	√	–	≤3	RP	7	–	–	32 mon.
33	65	57.9 ml	6	–	√	√	≤3	RP	6	–	–	68 mon.
36	73	78.4 ml	6	–	√	–	>5	R-t	–	–	–	69 mon.
40	69	48.6 ml	7	√	√	–	≤3	RP	8	√	–	22 mon.
41	65	62.4 ml	6	√	–	–	4–5	RP	6	√	–	25 mon.
47	69	71 ml	7	–	√	√	≤3	Cry	–	–	–	41 mon.

P. No. – patients' number; P-te V – prostate volume; Gl. – Gleason score; Ca – prostate cancer; > cores with Ca – greater number of cores with cancer; >% Ca – higher percent of cancer; PSA DT – PSA doubling time; T-t –treatment; P Gl. - pathological Gleason score; Ø Ca – cancer diameter; T-t f. – treatment failure

evidence of locally advanced disease and only one patient who underwent radio therapy had biochemical failure. This man received salvage cryo ablation and remains up to 42 months without PSA progression. These results are better than those reported by Roemeling et al. who also used the Epstein criteria except PSA ≤15 ng/ml [11]. Consequently, we suggest that in patients with the strict Epstein criteria for low risk PCa, PSA DT cut-off should be raised to 5 years and this is in line with the data reported by Al Otaibi et al. [12].

The results of screening for PSA led to the inappropriate rate of overdiagnosis and overtreatment of potentially insignificant PCa [1, 13, 14]. Moreover, those men will most likely to die with PCa from other causes of death. As it was shown by Albertsen et al. the non-cancer related survival rate among men with CCI >1 was 11%, 6% and 3% in 15, 20, and 25 years, respectively [15]. He also had shown that non-PCa mortality had obviously overlapped PCa mortality in patients with Gl. score 5 and 6. Our results had shown that nearly 44% of our patients had final CCI ≥1. We also found that elevated BMI had a high correlation with final CCI incline. Six of our patients with CCI ≥2 died during follow-up from comorbid diseases, while most of the patients with CCI ≥1 refused re-biopsy and remained under WW. Based on these data, we suggest that patients who meet the Epstein criteria and have CCI ≥1 and BMI >30 will be good candidates for WW without re-biopsies.

Table 3 Pain scores in different sessions of re-biopsy

Number of sessions	Mean score	S.D.	Comparison of pain scores in different sessions		
1st	2.12	0.81	2nd: p=0.29	3rd :p=0.998	>3: p>0.05
2nd	2.51	1.05	1st : p=0.29	3rd :p=0.215	*>3: p= 0.057*
3rd	2.1	0.71	1st : p=0.998	2nd :p=0.215	>3: p>0.05
>3	3.17	1.29	1st:p>0.05	2nd : *p= 0.067*	3rd :p>0.05

It is generally accepted to obtain 1st round of re-biopsy 1 year after the start of AS and then every 12–24 months or if PSA/DRE change [16]. However, there is still no agreement on the number of re-biopsy sessions. Interesting, in a study in which high-risk patients with ≥3 previous negative biopsies underwent additional session of saturation biopsies, PCa was diagnosed only in 3 men and in all Gl. score 6 involved a small percent of single core [17]. In our study higher Gl. score and more cores with the same Gl. score were discovered in 32% (9 of 28) of the patients on AS and in 92% of the cases changes were revealed on the 1st two sessions of re-biopsies. We also found that pain scores were significantly higher in patients who underwent >3 sessions of biopsies, although other study failed to find any significant difference in discomfort on the repeat biopsies [18]. Most of the patients who remained on WW/AS after 3rd session of re-biopsies had PSA DT >5 years. Consequently, we suggest that 3 sessions of re-biopsy is a reasonable cut-off for AS protocols.

Recent study of the CaPSURE records found that even if 16% of men with newly diagnosed PCa met the Epstein criteria for low risk cancer, only 9% of them chose AS and a substantial percentage of these men would prefer active treatment due to the anxiety [4]. In addition, Post et al. had shown that serious comorbidity is present in about half of the patients with PCa, but barely influences the choice of treatment [19]. Our results showed that 17.8% of patients who were diagnosed with PCa met the Epstein criteria and 81.4% of them chose WW/AS. However, 41.7% of these men finally chose active form of treatment. It is worthwhile to emphasize that only half of them had medical indications for intervention. Anxiety supported by "second opinion" caused them to stop WW/AS. In this context, we would like to encourage the urologists to make their treatment approach to the patients with low risk PCa more balanced.

Several limitation of our study should be presumed. All previous studies dedicated to this issue were based on the experience of referral centers. Our study was performed in

the community outpatient clinics, where patients can change urologist every 3 months and as a result are more open to the "second opinion". This fact causes a bias in indications for active forms of treatment. We also agree that this study might be considered as "low volume" and accept this drawback.

Conclusion

Expectation approach can be considered as a reasonable model of treatment in patients who meet strict Epstein criteria for low risk PCa. However, some of these men might need active treatment and PSA increase >30% with PSA DT of 5 years help to discriminate this group. Patients with high comorbidity as well as those with less serious accompanying diseases and high BMI are best candidates for WW. More than 3 sessions of re-biopsies possess higher pain score with low diagnostic weight and might be considered as a cut-off number for expectation protocols. Community urologists should be less reluctant to WW/AS approach.

Conflict of interest The authors declare no conflict of interest

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