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DEFERRED TREATMENT IN PROSTATE CANCER: A MEDIAN 3-YEAR FOLLOW-UP OF 48 PATIENTS IN KARLOVAC GENERAL HOSPITAL

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Summary

The increasing number of localized, low-risk prostate cancers (PCa) detected on the basis of widespread prostate specific antigen (PSA) testing and PCa screening, as well as cognition that many of these tumors will not progress or will progress very slowly, face the urologists with dilemma to treat an early PCa immediately or to postpone active tumor-specific treatment until the signs of tumor progression. The concept of deferred treatment in terms of active surveillance (AS) or watchful waiting (WW) has become one of the most intriguing issues in urologic oncology. Despite many investigations, there is still no definitive conclusion about reliability and possible risk of deferred treatment for the patients with PCa. In our study we analyzed the outcome of 48 patients with low-risk PCa on deferred treatment (24 on AS and 24 on WW). Median age of the patients in the study was 74 years (56-85) with median PSA 7.7 ng/mL (0.4-29.0). The Gleason score was ≤6 in 97.5% patients with 75% of the patients with one positive core on biopsy or with less than 5% tumor in biopsy material after transurethral or transvesical prostatectomy. During a median follow-up of 36.5 months (2-196), in 12 (25.0%) patients a progression of the tumor was assessed. Median time to progression was 36 months (7-110) with probability to stay treatment-free after 5 years of 72.1%. In conclusion, the results of our study support the attitude that deferred treatment, in well selected patients with low-risk disease, can offer a safe option in treatment of PCa patients saving some of them from unnecessary procedures with a possible negative impact on the quality of life.

KEYWORDS: *prostate cancer, deferred treatment, active surveillance, watchful waiting*

ODGOĐENO LIJEČENJE ZA BOLESNIKE S KARCINOMOM PROSTATE: TROGODIŠNJE PRAĆENJE 48 BOLESNIKA U OPĆOJ BOLNICI KARLOVAC

Sažetak

Sve veći broj lokaliziranih karcinoma prostate niskog rizika, otkrivenih na osnovi široke primjene određivanja prostatičnog specifičnog antigena (PSA) i skrininga na karcinom prostate, kao i spoznaja da mnogi od tih tumora neće napredovati ili će napredovati vrlo sporo, suočava urologe s dvojbom treba li takav rano otkriveni karcinom prostate liječiti odmah ili se liječenje može odgoditi do pojave znakova tumorskog napredovanja. Pojam odgođenog liječenja, bilo kao aktivno nadgledanje (AN) ili budno praćenje (BP) postao je jedno od najizazovnijih pitanja urološke onkologije. Usprkos provedenim mnogim ispitivanjima na ovom području, konačnog zaključka o pouzdanosti i mogućim rizicima ovakvog terapijskog pristupa još uvijek nema. U našem smo ispitivanju analizirali ishod odgođenog liječenja kod 48 bolesnika s karcinomom prostate niskog rizika (24 kao AN i 24 kao BP). Medijan starosti svih bolesnika u ispitivanju iznosio je 74 godine (56-85) s medijanom vrijednosti PSA 7,7 ng/mL (0,4-29,0). Gleason zbroj iznosio je ≤6 kod 97,5% bolesnika, s manje od jednog pozitivnog cilindra ili s manje od 5% tumora u ukupnom biopsijskom materijalu u 75% slučajeva. Tijekom medijana praćenja od 36,5 mjeseci (2-196) u 12 (25%) bolesnika primijećeno je napredovanje tumora. Medijan vremena do nastupa progresije bolesti iznosio je 36 mjeseci (7-110) s vjerojatnošću da će nakon 5 godina 72,1% bolesnika ostati u skupini koja ne zahtijeva nikakvo liječenje. U zaključku možemo istaknuti da rezultati našeg ispitivanja podupiru stajalište da odgođeno liječenje,

kod dobro odabranih bolesnika s karcinomom prostate niskog rizika, može predstavljati pouzdan izbor koji neke od ovih bolesnika može poštedjeti nepotrebnog liječenja s mogućim nepovoljnim posljedicama na kvalitetu života.

KLJUČNE RIJEČI: *karcinom prostate, odgođeno liječenje, aktivno nadgledavanje, budno praćenje*

INTRODUCTION

The incidence of PCa has dramatically increased over the past decades. PCa has become the most common cancer in men in the European Union, accounting for more than a quarter (27.1%) of all the reported cancer cases in men in 2008 (1). Parallel with the increase of the overall incidence of PCa, a shift toward small, localized, well-differentiated PCa has been noticed mainly as the result of the introduction of PSA testing and screening for PCa (2). It is estimated that as many as 50% PCa cases detected by screening may be „over-detected" with 5-12 years of lead time before treatment becomes necessary (3). Several studies of people dying from different causes have shown that while 60-70% of older men have histologic evidence of PCa, a large proportion of these tumors will not progress (2).

These facts make management of PCa, even in clinically localized disease, more and more complex. In many cases it is not easy to decide which patient with early PCa will benefit from immediately definitive treatment and which will live his life-span with untreated PCa, without signs of tumor progression. It is still impossible to answer the question how many patients with localized PCa suffer from complications of unnecessary „overtreatment". There is a similar dilemma in the treatment of older patients and patients with locally advanced PCa, who are not candidates for a definitive treatment. Who of these patients will benefit from early treatment? In whom of them a tumor-specific treatment could be deferred without negative impact on the quality of life and survival, sparing them from adverse effects of hormonal or other palliative treatment?

With the aim of reducing the risk of overtreatment of these two subgroups of patients, two conservative treatment options have been proposed by the official EAU Guidelines in 2009 (4):

1. Active surveillance (AS) which assumes active decision not to treat the patient with localized, low-risk tumor, who is a candidate for curative treatment, immediately, but to follow him closely and to treat him by curative procedure when and if he develops pre-defined signs of progressive disease.
2. Watchful waiting (WW) which refers to conservative management of patients with PCa, who are not candidates for curative treatment, until appearance of local or systemic progression at which time the patient will be treated palliatively.

During the last decade there is an increased interest between urologists for deferred treatment in patients with PCa. There are many recently published studies, including some with meta analysis surveys, comparing the outcome of patients with early PCa undergoing radical prostatectomy with those on AS or WW (2,3,5-7).

The aim of this study is to assess reliability and validity of deferred treatment in the group of our patients with PCa who meet the pre-defined criteria for WW or AS. The results of our study are compared with similar studies published on this issue.

MATERIAL AND METHODS

A retrospective search of computer database of PCa patients diagnosed in the Karlovac General Hospital between January 1994 and April 2011 was done. Of overall 814 patients in this database, there were 48 patients in whom tumor-specific treatment was initially deliberately deferred. In 26 cases, the diagnosis of PCa was assessed by prostate biopsy indicated for clinically suspected tumor. In the remaining 22 patients, PCa was diagnosed incidentally after transurethral resection of the prostate (17 patients) or transvesical prostatectomy (5 patients) indicated for presumed benign prostatic hyperplasia. All patients underwent a standard work-up which consisted of routine laboratory tests, chest x-ray, bone scintigraphy, pelvic CT scan and cystoscopy. The inclusion criteria for deferred treatment were stage $<T_2N_0M_0$, PSA level <15 ng/mL, <3 positive cores on transrectal

ultrasound-guided biopsy and a Gleason score of ≤7 (with a Gleason score of 4+3 as excluding criterion). In patients on WW there were some exclusions of these criteria. Before the decision of deferred treatment was taken, every patient was informed in details about possible treatment options and risks and only patient who gave informed consent for deferred treatment were included.

The follow-up consisted of 3- to 6-month checkups with rectal examination, PSA testing, transrectal ultrasound and transrectal ultrasound-guided repeat biopsy a year after initial diagnosis and every two years further. Repeat bone scintigraphy or pelvic CT scan was indicated on an individual basis. Repeat biopsies were routinely indicated only in patients who were potential candidates for a radical treatment (SA group).

The criteria for tumor progression were: for biochemical progression, <2-year PSA doubling time, for clinical progression, obvious progression in tumor size on rectal examination or on transrectal ultrasound or appearance of lesions on bone scintigraphy, and for histologic progression an increased number of positive cores on repeat prostate biopsy and/or progression in the Gleason score of the tumor.

Statistics: Student´s T-test was used for testing differences between quantitative parameters. Survival rates were calculated using Kaplan-Meier product-limit method.

RESULTS

There were 814 patients diagnosed with PCa in the Karlovac General Hospital, Dept. of Urology between January 1994 and April 2011. Initial treatment for 14 of the 814 patients was not recorded, 186 (22.8%) patients were treated radically (105 underwent radical prostatectomy and 81 radical radiotherapy), 566 (69.5%) patients initially underwent hormonal therapy and in 48 (5.9%) patients, who met criteria and gave informed consent, any tumor-specific treatment was deferred. Twenty-four of these 48 patients were considered potential candidates for a radical treatment (AS) and the other 24 patients, because of their age and stage were considered candidates for palliative hormonal therapy (WW).

Median age of the patients on deferred treatment was 74 years (range 56-85). Patients on AS were significantly younger (median 71.5 years, range 56-74) than patients on WW (median 78 years, range 74-85) ($p<0.01$). Incidentally detected patients with PCa on deferred treatment were younger (median 72 years, range 56-85) than the patients with PCa diagnosed after biopsy for suspected cancer (median 76 years, range 69-85). Median PSA for all the patients on deferred treatment was 7.7 ng/mL (range 0.4-29.0). In the AS group, median PSA was lower (median 4.9 ng/mL, range 0.7-12.9) than in the WW group (median 8.4 ng/mL, range 0.4-29.0), but the difference was not significant ($p=0.08$). Nonincidentally diagnosed cases had significantly higher median PSA (8.1 ng/mL, range 1.8-29.0) than incidentally detected patients (4.2 ng/mL, range 0.4-12.9). In 9 patients with incidentally diagnosed PCa, PSA level was not recorded preoperatively and these cases were not included in statistic analysis (Table 1).

Forty-six patients (95.8%) were classified as stage $T_{1-2}N_0M_0$, and two patients (4.2%) as $T_3N_0M_0$. Both patients with $T_3N_0M_0$ tumor were in the WW group (Table 1).

The Gleason score was assessed in 41 patients and it was ≤6 in 40 cases and =7 in one case.

The number of biopsy cores positive on PCa was reported in 18 of 26 nonincidentally diagnosed patients. In 12 (66.6%) of them, PCa was assessed in only 1 core, in 3 cases 2 cores contained PCa and in 3 patients 3 cores were positive for PCa. The percent of biopsy material containing PCa was assessed in 14 of 22 incidentally diagnosed tumors. In 12 cases, PCa was found in less than 5% of biopsy material, and in 2 cases the portion of cancer in overall biopsy material was between 5 and 10 percent (Table 1). During the follow-up, overall 10 rebiopsies were done, all in the AS group patients. In 6 cases, rebiopsies were negative for PCa. In the other 4 rebiopsies PCa was confirmed; in 3 cases without signs of tumor progression, and in one patient third biopsy, 49 months after initial biopsy, showed progression in tumor grade and in the number of positive cores.

Median follow-up for all the patients on deferred treatment was 36.5 months (range 2-196). There was no significant difference in follow-up between the AS (median 39 months, range 3-196) and the WW group (median 36.5 months, range 2-134). Median follow-up in incidentally detected patients was significantly longer than in nonincidentally diagnosed patients (50.5 months, range 3-196 vs. median 36 months, range 2-134). During

Table 1.

DEMOGRAFIC, CLINICAL AND PROGNOSTIC CHARACTERISTICS OF PATIENTS ON DEFERRED TREATMENT, ACTIVE SURVEILLANCE AND WATCHFUL WAITING.

	Deferred treatment	Active surveillance (AS)	Watchful waiting (WW)	p
No. of patients	48	24	24	
Nonincidental Incidental	26 22	8 16	18 6	<0.01
Age, years Median Range	 74 56-85	 71.5 56-74	 78 59-77	<0.001
PSA, ng/ml Median Range	 7.7 0.4-29.0	 4.9 0.7-12.9	 8.4 0.4-29.0	0.08
Stage $T_{1-2}N_0M_0$ $T_3N_0M_0$	 46 2	 24 0	 22 2	NS
Pathologic grade Gleason score ≤6 Gleason score 3+4 Gleason score x	 40 1 7	 21 0 3	 19 1 4	NS
No of positive cores 1 2 3 x	 12 3 3 8	 5 0 1 2	 7 3 2 6	NS
Follow-up, months Median Range	 36.5 2-196	 39.0 3-196	 26.5 2-134	
Patients with progression (%)	12 (25.0)	4 (16.6)	8 (30.0)	NS
Time to progression Median, months Range	 36.0 7-110	 75.0 42-110	 14.5 7-84	

the follow-up, progression of the disease was noticed in 12 (25%) patients (Table 1). In 9 patients there was only a biochemical progression, in two patients a clinical progression requiring additional surgical intervention was reported and in one patient there was histologic progression on repeat biopsy. Progression of the disease was reported more frequently in the WW group (8 patients, 30.0%) than in the SA group (4 patients, 16.6%), but the difference was not significant. Both patients with clinical progression were in the WW group, and the patient with histological progression was on AS. There was no significant difference in the incidence of the progression between incidentally (5 patients, 22.7%) and nonincidentally diagnosed patients (7 patients, 26.9%). Median initial PSA level of the patients with tumor progression was 7.7 ng/mL (range 0.7-11.6) and it was not significantly higher than in the patients who showed no signs of tumor progression (median 5.6 ng/mL, range 0.4-29.0). Median time to progression for all 12 patients who progressed was 36 months (range 7-110) and it was significantly longer for the patients on AS (75 months, range 42-110) than in the patients on WW (14.5 months, range 7-84). Nonincidentally diagnosed patients had shorter median time to progression (30 months, range 9-72) than the patients with incidentally diagnosed PCa (84 months, range 7-110) (Table 1). Actuarial probability to stay treatment-free after five years for all the patients on deferred treatment was 72.1% and it was significantly higher for the patients on AS (79.9%) than for the patients on WW (66.8%) (Figure 1). After the progression was assessed, all the patients in the WW group were treated hormonally. Because of their

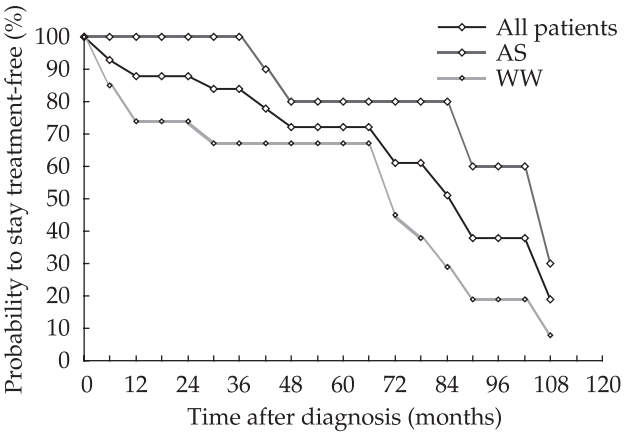

Figure 1. Kaplan-Meier treatment-free survival curve for all patients on deferred treatment(—), patients on active surveillance (AS) (—) and patients on watchful waiting (WW) (---).

age at the time of progression, three of four patients with tumor progression in the AS group were treated hormonally, while in one patient a radical prostatectomy was done. During the follow-up, no patient died from PCa. In the same time, 10 patients died from diseases not related to PCa, 8 patients in the WW group, and 2 patients in the AS group.

DISCUSSION

After an initial enthusiasm with radical treatment of PCa at the end of the last century, very soon, it became obvious that natural history of PCa is remarkably heterogeneous and still not completely understood. An increasing number of small, low-risk, localized PCa, detected as a result of widespread use of PSA testing and multicore transrectal ultrasound-guided biopsies, faced urologists with a doubt if it is necessary to treat each detected PCA. A concept of deferred treatment of early PCa became one of the most challenging issues in urologic oncology, initiating many new investigations. First consistent reports on expectant management of PCa came from Johansson et al. in 1992 (8) and 1994 (9). Choo and coworkers were the first who presented their study with 206 patients on AS with probability of remaining progression-free of 81% and 67% at 2 and 4 years, respectively (10). Two landmark Scandinavian studies of Holmberg et al. (6) and Bill-Axelson et al. (7) comparing outcome of 695 patients with early PCa randomized in RP and WW groups, demonstrated that RP significantly reduces the risk of metastases and local tumor progression, while the reduction in the risk of tumor-specific death was small. The authors (6,7) identified the group of patients younger than 65 years to benefit most from radical treatment in comparison with WW.

The treatment of patients in our study was characterized by a high rate of patients on hormonal treatment (69.5%), and relatively low rate of patients underwent radical treatment (22.8%) or deferred treatment (5.9%). It is significantly different from the data in the Stattin´s study from Sweden where 69% of patients with PCa underwent a radical treatment and in even 26% the tumor-specific treatment was initially deferred (11). Median age of our patients on AS (71 years) was higher than in other published studies where the range of the patients' age was between 64 and 70 years (3,6,10,12). All of these differences could be explained by the fact that patients from the cited studies were screen-detected, while our patients were not. There was no significant difference in the PSA value between patients on AS in our study (4,9 ng/mL) and patients on AS in some other recently published studies (range 4,8-6,5) (3,10). Patients on AS in the Holmberg´s and Bill-Axelson´s studies had a significantly higher median PSA (13 ng/ml), with 18% of patients with PSA >20 ng/mL (6,7).

According to pre-defined criteria for deferred treatment of PCa, most published studies include predominantly patients with a Gleason score of ≤6. In our study, only one patient with a score =7 was included. Van der Bergh and coauthors in their trial of 50 patients screen-detected a Gleason score of 7 and otherwise favorable tumor characteristics, assessed that in selected patients with a Gleason score of 3+4 AS might be a treatment option, especially in those with co-morbidity and/or short life-expectancy (13). They found a significantly shorter treatment-free survival in patients with Gleason score 4+3 in comparison with patients with Gleason 3+4 tumors (13). Most authors accept including a criterion of two or less positive biopsy cores for candidates for SA in patients with otherwise localized, low-graded PCa (3,5,12,13). The question of an optimal number of cores on initial biopsy for these patients remains to be answered. In our study, the number of positive cores on initial biopsy was not a significant prognostic parameter.

Repeat biopsies have an important role in the follow-up of PCa patients on AS (3,5,10,14). In our study, because of a relatively short follow-up, there was only one patient with histological signs of tumor progression on repeat biopsy with progression both in the tumor grade and the number of positive cores. Al Otaibi et al. concluded that the result of first repeat biopsy appears to have a strong impact on disease progression, with first negative rebiopsy associated with low-volume disease and favorable prognosis, and with first positive rebiopsy associated with a significantly lower 5-year actuarial progression-free probability (14). Most investigators propose 1-year period as a rational interval between repeat biopsies in patients on deferred treatment for PCa (3,5,10).

Probability to stay treatment-free after 5 years in our patients on AS (79,9%) was comparable with the results of the Soloway´s (85.2%) and Eggener´s study (75.0%) (3,15). Choo and coauthors in their trial of 206 patients from 2002 assessed that only 48% patients after 4 years remained on AS protocol (10).

The characteristic of our patients on deferred treatment was a significant number of patients with incidentally diagnosed PCa, especially in the AS group. We assessed no significant difference in the incidence of progression between incidentally and nonincidentally detected patients with PCa. There is no data in the literature on this issue. We believe that patients with incidentally diagnosed PCa, because of their more reliable histologic evaluation in comparison with nonincidentally detected cancers, represent a very suitable group of patients for deferred management.

Because of specific prolonged natural history of PCa and requirement for long-lasting investigations, there is a limited number of reports on overall survival, cancer-specific survival and metastasis-free survival with 10- or 15-year follow-up of patients on deferred treatment. There are some ongoing clinical trials comparing AS versus immediate treatment such as START, PIVOT and PROTECT, whose results are expected in future years (5).

CONCLUSION

The results of our study, although characterized by a limited number of patients and a short follow-up, support the attitude that deferred treatment, in well selected patients with low-risk disease, can offer a safe option in the treatment of prostate cancer patients saving some of them from unnecessary procedures with possible negative impact on the quality of life. In spite of that, it is obvious that, between these patients, selected on the basis of our present criteria, there will be cancers that harbor aggressive disease and that some of them will progress after a time. Although we are predicting the biologic behavior of low-risk tumors with increasing accuracy, the need for more reliable instruments to assess malignant potential of PCa is a condition to improve our selection of patients suitable for deferred management.

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