Acta Clin Croat 2015; 54:337-344 Review

LOW RISK PROSTATE CANCER: ACTIVE TREATMENT OR ACTIVE SURVEILLANCE?

Igor Tomašković

Clinical Department of Urology, Sestre milosrdnice University Hospital Center, Zagreb; School of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia

SUMMARY – The widely used screening for prostate cancer with prostate specific antigen has resulted in identification of potentially lethal prostate cancers at a much more curable stage and has been associated with significant falls in prostate cancer mortality. In spite of the fact that prostate cancer is one of the deadliest malignancies in men, the advent of sensitive diagnostic testing has also resulted in detection of low risk cancers due to the high incidence of latent prostate cancer in aging men and prolonged natural history of the disease. This, in turn, has entailed the problem of cancer overdiagnosis and subsequent overtreatment. Approximately 6 times as many men will be diagnosed with the disease as will die from it. Active surveillance appeared as a response to the clearly documented risks of overdiagnosis and overtreatment of low risk prostate cancer for localized prostate cancer. It entails initial expectant management rather than immediate therapy, with 'curative-intent' treatment deferred until there is evidence that the patient is at an increased risk of disease progression. This approach attempts to balance the risks and side effects of overtreatment against the possibility of disease progression and lost opportunity for cure. A systematic literature review brings current knowledge on the subject.

Key words: *Prostate cancer – diagnosis; Early detection of cancer – standards; Population surveillance; Prostate-specific antigen; Pathology – standards*

Introduction

The natural history of prostate cancer is highly variable and can range from indolent to very aggressive disease. Lifetime risk of acquiring the disease is 16%-20% and the risk of dying is about 3%[1]. It is obvious that there is great difference between the incidence and mortality. Autopsy studies have shown that the incidence of prostate cancer in men who died of other causes is by far greater than the incidence of clinically manifest prostate cancer in the population[2,3]. The best approach to treatment of localized prostate cancer remains a controversial issue[4].

Correspondence to: *Igor Tomašković, MD, PhD*, Clinical Department of Urology, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: igor.tomaskovic@kbcsm.hr

Received June 8, 2015, accepted July 1, 2015

The Problem of Early Detection and Overdiagnosis

The wide use of prostate specific antigen (PSA), which was introduced in clinical practice in the 1990s, has revolutionized early detection of prostate cancer. Its use has resulted in detection of a larger number of prostate cancers and significant increase in the incidence of this disease. In addition, modified biopsy protocols with an increased number of biopsy cores have also resulted in a higher rate of cancer detection. The reduction of mortality by up to 40% in some countries is a possible result of earlier detection and/or better treatment of this disease[5]. However, a parallel unwanted phenomenon is detection of indolent cancers, which do not pose threat to the patient health and life, and without measures of early detection they would never have clinical manifestations. Consequently, a large number of patients are undergoing treatment that does not bring any benefit to them, and

the complications thus entailed can even reduce their quality of life. For these phenomena, excessive diagnosis (overdiagnosis) and excessive treatment (overtreatment) are commonly used terms. The question of the benefit of the mass use of PSA for early detection of prostate cancer, which in places is reaching the extent of screening, has failed to be clarified even with two randomized, prospective studies, the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial[6,7]. While the ERSPC has shown a 27% reduction in mortality (0.73, 0.61-0.88; p<0.0007), the PLCO study failed to show benefit from screening. The objection to the PLCO study was the high rate of contamination of PSA testing in the control group, which reached about half of the respondents. The objection to screening lies in the fact that even with mortality reduction, the screening takes a very high price; the latest results of monitoring after 13 years in the ERSPC have shown that it is necessary to call 781 men to the screening program and to treat 27 men to avoid one death from prostate cancer[6]. It is believed that the excessive rate of diagnosis (overdiagnosis) is around 50% and it is the major adverse effect of screening. The use of PSA as a screening test has shown all its weaknesses, especially low specificity. With a threshold value of 3 ng/mL, which was used in the ERSPC, 25% of men aged 55-69 were 'positive', and in the remaining 75% where the test was negative (PSA <3 ng/mL), prostate cancer was not definitely excluded[8].

Active Treatment *versus* Active Surveillance

When a patient is diagnosed with prostate cancer, chances of being actively treated exceed 80% and it is very important to distinguish between the potential benefits and harms of such approach and understand the contemporary population of patients with prostate cancer. Although active treatment has contributed to reduced prostate cancer mortality in some countries, it is important to emphasize that the inclusion of a large number of patients with indolent prostate cancer (which would do well without treatment) have falsechanged performance statistics of 'active approach'. Direct comparisons of therapeutic modalities for localized prostate cancer with long-term monitoring were studied in two multicenter, randomized studies[9,10].

In the randomized Scandinavian Prostate Cancer Group Study-4 (SPCG-4), which enrolled 695 patients with localized prostate cancer, mortality was compared between the groups subjected to radical prostatectomy or active control. After 18 years of follow up, significant absolute reduction in the rate of death from any cause (relative risk (RR)=0.71, p<0.001), death rates from prostate cancer (RR=0.56, p<0.001) and the risk of metastasis was found in the group subjected to radical prostatectomy. Overall, there were 13% fewer deaths from any cause and 11% fewer deaths from prostate cancer in the group subjected to radical prostatectomy in 18 years of monitoring. The effect was limited to men younger than 65. The absolute risk reduction in total mortality and prostate cancer mortality was 25.5% and 15.8%, respectively, in this age group. Among men aged 65 and older, radical prostatectomy did not reduce mortality, but significantly reduced the risk of metastasis and the need of palliative treatment. With longer follow up, the number of patients who should have been treated to prevent one death from prostate cancer fell to eight. The advantage of this study was a randomized and prospective design. It provided the highest quality of evidence that active treatment saved lives. However, it did not provide an answer when to reach for active treatment in order to balance the consequences and complications of active treatment. Its population was heterogeneous and included patients with high, medium and low risk. A more detailed analysis shows that the most pronounced reduction in mortality was among patients with tumors of intermediate risk (RR=0.38, p<0.001), while the reduction of mortality in the two groups with high and low risk was not significant (RR=0.54, p=0.17 and RR=0.87, p=0.84, respectively). When analyzed according to age, the effects were more pronounced in men younger than 65, suggesting that not only the characteristics of the tumor, but also life expectancy play a role in the choice of therapeutic approach. It is important to note that the study was initiated in 1989 and that the majority of patients came from the so-called 'pre-PSA' period. Thus, only 5% of patients were T1c stage, and the median PSA was 13 ng/mL. Given the low proportion of patients detected only by elevated PSA, this population was very different from the contemporary population of patients with prostate cancer. In addition, a

restriction of stratifying patients according to the risk was that the number of patients in the subgroups was too small[9].

Unlike the SPCG-4, the Prostate Cancer Intervention *Versus* Observation Trial (PIVOT), launched in the early era of PSA testing, showed that radical prostatectomy for localized prostate cancer was not significantly reducing cancer-specific and/or overall mortality after 12-year follow up[10]. PIVOT study started in 1994 and compared radical prostatectomy with surveillance. Of the 731 respondents, three-quarters had cancer diagnosed based on elevated PSA. Half of the patients had stage T1c disease (only elevated PSA, impalpable cancer) and 45% had stage T2 disease. The median age was 67 years and median PSA 9 ng/mL. About one-third of patients were African Americans. Such a mixed population of patients, including 45% of low risk, 34% of intermediate risk and 21% of high risk patients, was more representative of contemporary populations of patients with prostate cancer, and inclusion of African Americans is not negligible either[11]. Unlike SPCG-4, this study failed to show reduction in the mortality benefit of radical prostatectomy for the whole study population. Additional analysis of the risk groups in the PIVOT study showed that in low risk patients (PSA <10, Gleason score ≤6), radical prostatectomy did not contribute to better overall or disease-specific survival, or the rate of progression to metastatic disease. This is a very important finding with relevant implications for the choice of treatment for low risk cancer. In contrast, in higher risk patients (intermediate and high; PSA >10), radical prostatectomy resulted in a decrease of total (hazard ratio 0.67; 95% CI 0.48-0.94) and cancer-specific mortality (5.6% *vs.* 12.8%, p=0.02). However, analysis of the intermediate risk group only showed reduction in total but not in cancer-specific mortality, whereas in the high risk group, cancer-specific mortality was reduced, but not all-cause mortality in favor of radical prostatectomy[12]. This result is a possible consequence of insufficient power of the study due to the small sample[11].

In addition, the results of PIVOT may not be replicated in younger patients with localized prostate cancer. One-third of patients in this study were older than 70, and half died before completion of 10-year follow up; 85% of deaths were not associated with prostate cancer. Therefore, it is difficult to extrapolate the PIVOT results to 40% of patients with prostate cancer who are diagnosed with the disease before age 65[11,12]. Critical analysis points to the fact that due to difficulties with patient enrollment, PIVOT failed to recruit initially planned 2000 patients and the study design was then revised. Only 15% of patients that met the inclusion criteria were included in the study[9]. In about one-third of patients there was no appropriate death certificate, so there is certain methodological doubt about the use of cancer-specific mortality in studies like the PIVOT[13]. Despite criticisms, some analysts suggest that even PIVOT study favors surgical treatment because 60% less metastases and 37% lower mortality were found in the surgical group[11].

On considering active treatment *versus* surveillance, it is necessary to mention radiotherapy as a possible active approach to patients with localized prostate cancer. Although data are scarce, a randomized study that compared these two approaches from the pre-PSA era did not demonstrate significant differences in mortality after 16-year follow up[14].

In the light of contradictions in the above mentioned studies, it becomes more difficult to recommend an optimal approach. The Canadian randomized Standard Treatment Against Restricted Treatment (START) study was launched in 2007 with the aim to compare directly the effectiveness of active treatments and active surveillance, but unfortunately, it was stopped for failing to reach satisfactory inclusion of patients[15]. Another prospective, randomized study that compared the effectiveness of radical prostatectomy *versus* radiotherapy *versus* active surveillance in patients with localized prostate cancer detected in the PSA era was launched at the end of the 1990s in the UK as the Prostate Testing for Cancer and Treatment (PROTECT)[16]. This study successfully recruited and tested by PSA over 82,000 men aged 50-69, with more than 500 respondents in each of the three study groups. Compared with the PIVOT and SPCG-4, the PROTECT study had a lower mean PSA value (5.8 ng/mL), age (61 years), higher stage of cancer, and randomized 62% of eligible patients (unknown in SPCG-4 and 15% in PIVOT). The first results of this study will be published in 2016, after 10 years of follow up. They will provide key information on the approach to patients with localized prostate cancer predominantly detected by PSA testing

and the potential benefits as well as the potential harmful effects of excessive detection and overtreatment in this population.

When to Consider Active Surveillance, When to Treat?

It is important to stress that the above mentioned studies investigated a heterogeneous group of patients with clinically localized prostate cancer but different clinical characteristics, represented as low, medium and high risk stratification. Contrary, therapeutic approach to patients with low risk prostate cancer is a separate topic. As noted above, the wide use of PSA and new protocols of prostate biopsy increased the incidence of prostate cancer, particularly low risk prostate cancer subgroup. This is a homogeneous group, although it also failed to be uniformly defined, as current possibilities of risk stratification are limited by imperfection of the existing methods[17]. Stratification of patients according to the risk level was first proposed by D'Amico *et al*.[18], and then the proposed division was several times adjusted (Table 1)[4,18-20]. It is estimated that, depending on the prevalence of PSA testing in certain areas, up to 45% of newly diagnosed patients are eligible for active surveillance[18].

Active surveillance means that patients at low risk are not treated aggressively (surgery or radiation), but are followed by PSA, imaging modalities and repeat biopsy, and in the event of disease progression to a more aggressive form of prostate cancer, the patient is subjected to active treatment with the intention to cure. All others in the group are thus spared the morbidity of therapeutic procedures of radical prostatectomy or radiation, which is not negligible. It is certainly important to distinguish the active surveillance approach from watchful waiting, which for decades has meant observation in the selected group of patients with the application of palliative treatment in the event of progression. The concept of active surveillance has important implications for patient counseling about their disease, treatment and related quality of life, and the cost of treatment. The parameters defining the patients eligible for active surveillance are shown in Table 2[18,21-28]. There are several ongoing studies that follow patients at low risk that have been subjected to active surveillance[23]. Noteworthy is that the screening criteria in these studies are quite different, just like the criteria for decision on active treatment when clinical parameters change during follow up. Most studies include low risk cancer (small

Table 1. Risk groups (adapted from Heidenreich et al.*[4])*

	Very low risk	Low risk	Intermediate risk	High risk	
D'Amico[18]		T1-T2a and GS ≤6 and PSA ≤10	T2b or GS 7 or PSA 10-20	≥T2c or PSA >20 or GS 8-10	
NCCN[19]	T1c and GS ≤6 and PSA <10 and <3 positive cores and ≤50% cancer in the core	T1-T2a and GS 2-6 and PSA ≤10	T2b or T2c or GS 7 or PSA 10-20	T3a or PSA >20 or GS 8-10	T3b-4
CAPSURE[20]		T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS 7 or PSA >10-20	T3- 4 or PSA >20 or GS 8-10	
EAU[4]		GS ≤6 and PSA ≤10 and T1c	T2b-2c and/or GS ≤7 and/or PSA ≤20	≥T3a or PSA >20 or GS 8-10	

NCCN = The National Comprehensive Cancer Network; CAPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; EAU = European Association of Urology; GS = Gleason score; PSA = prostate-specific antigen

volume, low grade, stage and PSA), and some include even 'insignificant' cancers adding a small number of biopsies (<3 or <33%), length of cancer in biopsy specimens (<50%), and PSA density (PSAD <0.15 or 0.20) to the current criteria. The patients are followed by PSA, digital rectal examination, and depending on the protocol, repeat biopsies are performed after 6 or 12 months. More recently, increasing importance is given to repeat biopsy. The emergence of an increase in PSA, unfavorable doubling time of PSA (<2 or 3 years, depending on the study), and emergence of Gleason score 4 or 5 on repeat biopsy reclassify patients and initiate active treatment at a stage when the disease is still curable. Results of one of the studies with longest follow up, conducted by Klotz *et al*. from The University of Toronto, showed that one-third of patients diverted to active treatment, and the mortality from other causes in this cohort was 19 times higher than the mortality rate of prostate cancer after 8-year follow up[23]. During the follow up, five of 450 (1.1%) patients died from prostate cancer. It is important to emphasize that among patients actively treated after active surveillance, 50% had biochemical relapse. The reason for this may lie in more liberal inclusion criteria in the study (Gleason score 7). The authors of the Göteborg randomized trial (part of ERSPC study) have recently reported on 442 middle-aged patients (65 years of age) under active surveillance who were followed-up for 6 years[29]. An important feature of this study is that it included a small number of patients at very low (51%), low (26.7%), medium (21%) and high (1.4%) risk, and the patient population was significantly different from the modern population under active surveillance. In this study, one-third of patients subsequently underwent active treatment, mostly due to progression, and only four patients because of anxiety. Of the 60 deaths, only one patient died from prostate cancer. The patient was under active surveillance for 8.6 years, and subsequently received androgen deprivation therapy and died 12.7 years after the diagnosis of the disease. One patient had bone metastases. Both patients had a medium risk at the time of diagnosis. Currently, the largest multicenter prospective study, the Prostate Cancer Research International: Active Surveillance (PRIAS) study, has been launched in 17 countries with much stricter entry criteria (T1c-T2b,

Table 2. Preoperative criteria for low risk prostate cancer

Study (authors)	Criteria
Epstein *et al*.[21]	cT1c-2, Gleason score ≤6, PSAD ≤0.15 ng/mL/mL, 2 and less positive biopsy cores, <50% cancer in the core
Bastian *et al*.[22]	cT1c-2, Gleason score ≤6, PSAD ≤0.15 ng/mL/mL, 2 and less positive biopsy cores, <50% cancer in the core
Klotz *et al*.[23]	PSA ≤10 ng/mL, Gleason score ≤6
D'Amico *et al*.[18]	cT2a, PSA ≤10 ng/mL, Gleason score ≤6
Patel *et al*.[24]	cT2, Gleason score ≤7
Soloway *et al*.[25]	cT2, Gleason score ≤6, PSA ≤0.15 ng/mL, 2 and less positive biopsy cores, <50% cancer in the core
Van den Bergh *et al*. (PRIAS)[26]	T1c-T2b, Gleason score ≤6, PSA ≤10 ng/mL, PSAD ≤0.20 ng/mL/mL, 2 and less positive cores
Van As *et al*.[27]	cT1-T2a, PSA ≤15 ng/mL, Gleason score ≤7(3+4), ≤50% positive cores
Dall'Era *et al*.[28]	PSA ≤10 ng/mL, Gleason score ≤6, ≤33% positive biopsy cores, <50% cancer in the core

PSA = prostate-specific antigen; PSAD = prostate-specific antigen density

Gleason score ≤6, PSA ≤10 ng/mL, PSAD ≤0.20 ng/mL/mL, and 2 or less positive biopsy cores)[30]. Follow up (median 1.6 years) is still short and the results of the study are immature, thus it is too early to draw any conclusions.

It is obvious that modern tools to distinguish indolent, low risk and aggressive disease require improvement[31]. The use of new biomarkers and their combinations in the future could solve this problem. The Early Detection Research Network of the National Cancer Institute conducts a research for this purpose[32]. A promising research comes from prostate cancer imaging, particularly in the field of magnetic resonance imaging[33,34].

Conclusion

Paucity of high-quality studies and their contradictory results hamper clinicians' selection of optimal treatment for patients with localized prostate cancer. Early diagnosis and successful treatment are certainly responsible for a mortality decline by 40% in some countries. The problem is that such a result comes at a high cost. A large number of people need to be tested, a significant part of them biopsied and a non-negligible number treated to prevent one death from prostate cancer. Results of these studies suggest that in patients younger than 65 whose prostate cancer was diagnosed not only based on PSA but also by positive digital rectal examination, active treatment can bring cure, so it is necessary and advisable. Results are less certain in patients older than 65 or those with significant comorbidity or life expectancy of less than 10 years. Considering tumor differentiation, it appears to be a reasonable option to offer active treatment to medium risk and high risk patients, taking into account the fact that the results of SPCG-4 do not support the latter category. In low risk tumors, benefit from aggressive treatment is dubious because the SPCG-4 and PIVOT studies showed no reduction in mortality for this group, and the questionable benefits must be compared with the complications that such an approach carries, such as change in the quality of life of patients who did not need treatment. Looking at the absolute number of patients that fall into this category, this problem becomes one of the burning problems of the contemporary treatment of this disease. Active surveillance is the legitimate approach for patients at low and very low risk, noting that the problem of proper patient classification exists and is well known, but that the results in properly selected patients are encouraging. Caution is needed in younger people. Neither inclusion criteria nor follow up protocols are unique, and there is still no agreement about them, whereas the follow up period in current studies is still too short. News in the field of imaging and new tumor markers could bring significant change in the approach to this issue.

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Sažetak

NISKORIZIČNI RAK PROSTATE: AKTIVNO LIJEČENJE ILI AKTIVNI NADZOR?

I. Tomašković

Široka uporaba za prostatu specifičnog antigena (PSA) rezultirala je otkrivanjem potencijalno smrtonosnih karcinoma prostate u nižem, lječivom stadiju te je povezana sa značajnim padom smrtnosti od raka prostate. Unatoč činjenici da je rak prostate jedna od najsmrtonosnijih malignih bolesti u muškaraca, pojava osjetljivih dijagnostičkih testova također je rezultirala otkrivanjem karcinoma niskog rizika zbog visoke učestalosti latentnog raka prostate u muškaraca starije dobi i dugog prirodnog tijeka bolesti. Dakle, pojavio se i problem pretjeranog dijagnosticiranja indolentne bolesti i posljedičnog suvišnog liječenja. Kod šest puta više ljudi će biti dijagnosticirana bolest nego što će ih umrijeti od nje. Aktivni nadzor pojavio se kao odgovor na jasno dokumentirani rizik pretjerane dijagnoze i pretjeranog liječenja kod lokaliziranog raka prostate niskog rizika. To podrazumijeva početno praćenje s odgodom "pristupa s namjerom liječenja" dok se ne pojave dokazi povećanog rizika za progresiju bolesti. Ovaj pristup pokušava uravnotežiti rizike i nuspojave pretjeranog liječenja u odnosu na mogućnost napredovanja bolesti i izgubljenu priliku za liječenje. Sustavni pregled literature donosi današnje spoznaje o ovoj temi.

Ključne riječi: *Prostata, tumori – dijagnostika; Rano otkrivanje tumora – standardi; Stanovništvo, praćenje; Antigen specifičan za prostatu; Patologija – standardi*