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Long-term Surveillance Outcomes of Prostate Cancer Patients Eligible for Active Surveillance but Who Underwent Radical Prostatectomy

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What's known on the subject? and What does the study add?

Active surveillance has been introduced as an alternative to avoid unnecessary treatment and related side effects. No cancer-related deaths were observed in patients who is eligible for active surveillance but underwent radical prostatectomy. This may suggest that active surveillance criteria are suitable for detecting low-risk prostate cancer patients.

Abstract

Objective: We aimed to investigate the long-term surveillance outcomes (biochemical recurrance, survival) and adequacy of active surveillance criteria to detect low-risk prostate cancer patients who were eligible for active surveillance but underwent radical prostatectomy.

Materials and Methods: Data of patients who underwent radical prostatectomy for prostate cancer between January 2005 and January 2019 were retrospectively evaluated. Upstaging, upgrading, surveillance periods, and survival status of patients with clinical stage T1c and T2a, serum prostate-specific antigen below 10 ng/mL, International Society of Urological Pathology grade 1, number of tumor-positive cores in biopsy 2 and below, tumor percentage in tumor-positive cores 50 and below were inclusion criteria for active surveillance.

Results: The study included 606 patients. Of these patients, 184 (30.4%) met the inclusion criteria for active surveillance. Upgrading was detected in 77 (41.8%) patients and upstaging in 29 (15.8%) patients who met the criteria for active surveillance. The prostate-specific antigen (PSA) and PSA density values of the patients who met the active surveillance criteria were significantly lower than those of the other patients ($p<0.05$). The mean surveillance period was 127.6±49.6 (8-227) months, and 123 patients died during this period. Among them, 18 (3%) patients died because of related causes of prostate cancer. None of the patients who met the criteria for active surveillance died because of prostate cancer ($p=0.018$).

Conclusion: No cancer-related deaths were observed in patients who is eligible for active surveillance but underwent radical prostatectomy. This may suggest that active surveillance criteria are suitable for detecting low-risk prostate cancer patients.

Keywords: Active surveillance, prostate cancer, radical prostatectomy

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Introduction

Prostate cancer (PCa) has become an early-diagnosed disease with the common use of prostate-specific antigen (PSA) and has even led to overdiagnosis and overtreatment (1). Because curative treatment options for PCa carry the possibility of morbidity and mortality, active surveillance (AS) has been introduced as an alternative to avoid unnecessary treatment and related side effects (2). AS aims to monitor patients closely without losing the option of curative treatment (2). The inclusion criteria for AS are generally accepted as serum PSA less than 10 ng/mL, International Society of Urological Pathology (ISUP) grade 1, biopsy positive core less than 3, and involvement less than 50%. There are studies that include ISUP grade 2 patients with limited criteria (3).

There has been no randomized controlled study comparing AS with curative treatments. In AS studies, one-third of patients require reclassification and curative treatment (4). In one of the most extensive and longest-duration AS studies, curative treatment was required in 20% of the patients. Only 23% of the treated patients were ISUP grade 1 (5). In this study, which has the highest number of patients in the literature, the mean surveillance period was approximately 50 months, similar to other AS studies (4).

Screening for PCa reduces mortality, but this gain is associated with overdiagnosis and overtreatment (1). When we detect and treat insignificant PCa, overdiagnosis and overtreatment occur (1). Although AS protocols protect patients from overtreatment, upgrading in some patients and the delay and inability to predict this is important issues. Upgrading increases the risk of biochemical recurrence, and its rate is around 30-45% (6,7). In addition, the relatively short surveillance periods in the literature for a slowly progressive disease such as PCa should not be ignored. In our study, we aimed to investigate the long-term surveillance outcomes (biochemical recurrance, survival) and adequacy of active surveillance criteria to detect low-risk PCa patients who may be eligible for AS but who underwent radical prostatectomy (RP).

Materials and Methods

Following Dokuz Eylül University Faculty of Medicine Institutional Review Board Ethics Committee approval (decision no: 2023/34-02, date: 25.10.2023), the data of patients who underwent RP for PCa between January 2005 and January 2019 were retrospectively evaluated. The patients' ages at the time of surgery, preoperative PSA values (ng/mL), prostate volumes (mL), and PSA densities (PSADs) (PSA/prostate volume) were recorded. The number of cores sampled during biopsy, the number of positive cores, and the percentage of tumors in positive cores were evaluated. The biopsy and RP pathology results were evaluated according to the ISUP 2014 grading system (8).

Patients whose surveillance data were not available were excluded from the study. RP results were evaluated as upgrading if the ISUP grade was increased according to the biopsy pathology result, and upstaging if the RP result was T3a, T3b, or greater. The surveillance period was calculated in months by subtracting the date of RP from the date of death in patients who died and in months by subtracting the date of RP from January 2024, the date of the last surveillance in other patients. A PSA value >0.2 ng/mL after RP was considered a biochemical recurrence. Causes of death were determined from patient data.

Inclusion criteria for AS included clinical stage T1c and T2a, PSA below 10 ng/mL, ISUP grade 1, number of tumor-positive cores in biopsy 2 and below, and tumor percentage in tumor-positive cores 50 and below (3).

Statistical Analysis

The SPSS program was used for statistical analysis. In the study, numerical data were calculated as mean ± standard deviation, and categorical data were calculated as percentages. The significance between categorical groups was analyzed using the chi-square test. The difference between numerical data was evaluated with the Student's t-test. A value of $p<0.05$ was considered statistically significant.

Results

Seven hundred and thirteen patients underwent RP. One hundred and seven patients were excluded from the study because surveillance data were unavailable, and 606 patients were included. The mean age at the time of surgery was 63.1±6.5 years, serum PSA value was 8.8±7.5 ng/dL, number of biopsy cores was 11.5±2.2, prostate volume was 52.3±21.6 mL, and PSAD was 0.19±0.18. The mean surveillance period was 127.6±49.6 (8-227) months.

Of the 606 patients in the study, 184 (30.4%) met the inclusion criteria for AS. There was no statistically significant difference in age, surveillance period, prostate volume, and number of biopsy cores between patients who met the criteria for AS and other patients ($p>0.05$). The PSA, PSAD values, and number of positive biopsy cores of the patients who met the AS criteria were significantly lower than those of the other patients ($p<0.05$). A comparison of the preoperative data and surveillance periods of patients who met the AS criteria and other patients is given in Table 1.

Among patients eligible for AS, 77 (41.8%) patients had upgraded according to RP pathology. In other patients, upgrading was detected in 117 (27.7%) patients and downgrading in 63 (14.9%).

Upgrading was statistically significantly higher in patients who met the criteria for AS [$x^2(1)=35.467$ $p\leq0.001$]. Upstaging was detected in 29 (15.8%) patients eligible for AS and 234 (55.5%) in other patients. Among patients eligible for AS, 14.1% were T3a and 1.6% were T3b; among other patients, 41.9% were T3a and 13.5% were T3b. Upstaging was statistically significantly less in patients who met the AS criteria [$x^2(1)=82.168$ $p\leq0.001$]. Surgical margin positivity was statistically significantly lower in patients who met AS criteria [9.8% vs 30.8%; $x^2(1)=30.681$ $p\leq0.001$].

When the RP pathologies of patients who met the criteria for AS were evaluated, 58.2% were ISUP grade 1, 39.1% ISUP grade 2, 2.1% ISUP grade 3, 0.5% ISUP grade 4, and no patient had an ISUP grade 5 pathology result. When the RP pathologies of the other patients were evaluated, 12.6% were ISUP grade 1, 62.6% were ISUP grade 2, 14.2% were ISUP grade 3, 4.5% were ISUP grade 4, and 6.2% were ISUP grade 5.

While the biochemical recurrence rate was 2.7% in patients who met the criteria for AS, this rate was 16.1% in other patients, and this result was found to be statistically significant [$x^2(1)=20.457$ $p\leq0.001$]. When patient data were accessed, it was seen that 123 patients died. Eighteen (3%) of the deceased patients died because of PCa (progression of of and related complications). None of the patients who met the criteria of AS died of PCa [$x^2(1)=8.09$ $p=0.018$]. A comparison of the pathology and surveillance data of patients who met the criteria for AS and other patients is given in Table 2.

Discussion

Treatment of localized PCa can be likened to a double-edged knife; curative treatment can lead to morbidity, whereas if the disease is left untreated and progresses, we may have missed the chance of early treatment. The important point is to be able to predict which patients have a low risk of PCa.

The biopsy and final RP pathology results are only sometimes compatible and identical. In the literature, the rate of upgrading after RP is reported to be around 30-45% (6). The high probability of upgrading requires us to appropriately evaluate patients with AS and minimize this risk. In addition, upgrading increases the probability of biochemical recurrence of PCa (7). A recent systematic review investigating the risk factors for upgrading found that patient age, serum PSA value, prostate volume, PSAD, number, and percentage of biopsy-positive cores were significantly effective on upgrading (9). These risk factors form the basis of the inclusion criteria for AS. In our study, upgrading was found in 41.8% of patients who met the criteria for AS, which is similar to the literature. In other words, no matter how much we apply the risk factors for upgrading, this condition still develops at a high rate, and this risk should be reduced as much as possible in patients with AS. Upgrading in patients who were removed from AS and underwent RP varies between 14% and 51% (10).

The probability of positive surgical margin increases in the presence of extraprostatic extension or seminal vesicle invasion in the pathology result of RP (11). The risk of upstaging in low-risk PCa patients is approximately 25% (12). Upstaging increases the risk of biochemical recurrence (12). A meta-analysis investigating the importance of biochemical recurrence showed that the risk of distant metastasis and PCa-related death increased in patients with biochemical recurrence (13). In our study, upstaging was 15.8% in patients who met the active criteria, and a surgical margin positivity rate of 9.8% was observed in the same patient group.

The prostate does not have a true capsule but is surrounded by fibrous and muscular tissues (14). This situation complicates the work of imaging methods and makes local staging of PCa difficult (15). Current European Association of Urology guidelines recommend multiparametric magnetic resonance imaging (mpMRI) before biopsy in patients undergoing biopsy for the first time and systemic and targeted biopsy if a lesion is described on mpMRI (16). The patients in our study did not undergo mpMRI because mpMRI was not expected at that time, and these data were not yet accepted in the guidelines.

Table 1. Comparison of preoperative data and follow-up periods of patients eligible for active surveillance and other patients

	Eligible patients for active surveillance (n=184)	Other patients (n=422)	p-value
Age (years)	61.3±6.3	63.9±6.4	0.462
PSA (ng/mL)	6.1±2.0	9.9±8.6	<0.001
Duration of follow-up (months)	148.2±49.6	118.6±47.0	0.622
PV (mL)	57.3±21.3	50.2±21.3	0.241
PSAD (ng/mL²)	0.11±0.05	0.22±0.21	<0.001
Number of biopsy cores	11.1±1.7	11.7±2.4	0.136
Number of positive biopsy cores	1.35±0.47	3.93±2.50	<0.001

The difference between numerical data was evaluated with the Student's t-test
PSA: Prostate-specific antigen, PV: Prostate volume, PSAD: PSA density (PSA/prostate volume)

Table 2. Comparison of pathology data and follow-up data of patients who met the criteria for active surveillance and other patients

	Eligible patients for active surveillance (n=184)	Other patients (n=422)	Total (n=606)	p-value
Survival status				0.018
Death due to cancer	0	18 (4.3%)	18 (3.0%)	
Death from other causes	33 (17.9%)	72 (17.1%)	105 (17.3%)	
Alive	151 (82.1%)	332 (78.7%)	483 (79.7%)	
Upgrading	77 (41.8%)	117 (27.7%)	194 (32.0%)	<0.001
Upstaging	29 (15.8%)	234 (55.5%)	263 (43.4%)	<0.001
RP pathologies				<0.001
ISUP GRADE-1	107 (58.2%)	53 (12.6%)	160 (26.4%)	
ISUP GRADE-2	72 (39.1%)	264 (62.6%)	336 (55.4%)	
ISUP GRADE-3	4 (2.2%)	60 (14.2%)	64 (10.6%)	
ISUP GRADE-4	1 (0.5%)	19 (4.5%)	20 (3.3%)	
ISUP GRADE-5	0	26 (6.2%)	26 (4.3%)	
T stage				<0.001
T2	155 (84.2%)	188 (44.5%)	343 (56.6%)	
T3A	26 (14.1%)	177 (41.9%)	203 (33.5%)	
T3B	3 (1.6%)	56 (13.5%)	60 (9.9%)	
Positive surgical margin	18 (9.8%)	130 (30.8%)	148 (24.4%)	<0.001
Biochemical recurrence	5 (2.7%)	68 (16.1%)	73 (12.0%)	<0.001

The significance between groups was analyzed by chi-square test
ISUP: International Society of Urological Pathology

Adding mpMRI to AS criteria and surveillance protocols will make AS safer and more successful. In this way, both clinically significant PCa patients will be detected more efficiently, and local staging of the disease will be performed more accurately. We are waiting for the long-term results of ongoing studies using mpMRI. The results of these studies will perhaps make it easier for us to consider ISUP grade 1 as a benign condition (17).

Biomarkers such as prostate cancer antigen 3 or prostate health index used preoperatively are effective in showing the aggressiveness of PCa, but their costs leave question marks in terms of their cost-effectiveness (18). In a study by Gokce et al. (19), the neutrophil-to-lymphocyte ratio was a cheap and reliable method for predicting upgrading and biochemical recurrence. PSAD is also an important predictor used in risk calculations, and recent studies have shown that its combination with mpMRI significantly reduces unnecessary prostate biopsy (22). Although the cut-off value for PSAD is generally accepted as 0.15 ng/mL/cm^3, it is more effective when this value is reduced to 0.10 (20).

In the ProtecT study, 1643 patients were randomized into three groups and received RP, radiotherapy, or surveillance accordingly (21). Although the patients in this study did not fully comply with the current AS monitoring protocols, approximately 90% of the included patients met the current AS inclusion criteria (21). In this study, the 10-year cancer-specific survival rate of patients followed up without treatment was 98.8% vs. 99%, but the probability of metastatic progression was 6% vs. 2.6% (21). It should be kept in mind that metastases although rare, can be observed in AS protocols (4). In the ProtecT study, the authors also reported that 2/3 of AS patients received definitive treatment at the 7-year surveillance (21). Similarly, in the PRIAS study, no difference was found in the cancer-specific survival of patients in the low-risk group compared with those who received curative treatment (22). However, three-fourths of those in the AS group underwent curative treatment in this 10-year study (22). The mean surveillance period in our study was 127 months, indicating a long mean surveillance period of 10 years. During the surveillance period, which can be considered long enough for PCa, no cancer-related deaths occurred in the group of patients who met the criteria for AS.

While cancer-specific survival after RP was 80% in low- and intermediate-risk PCa patients in the pre-PSA era (23), this rate is 99% in the currently screened population (21). In our study, similar to the literature, cancer-specific survival was 100% in patients who met the criteria for AS. These data allow us to predict a high rate of success when low- and intermediate-risk PCa patients are treated with appropriate screening. High-risk PCa patients have a cancer-specific survival rate

of approximately 60% with RP and subsequent multimodal therapies (24). Therefore, it is necessary not to misclassify high-risk patients under AS as low-risk.

Study Limitations

Our study has some limitations, with the retrospective design being main. RP was not performed by a single surgeon, and there may be differences between surgeons' experiences over a 14-year period. In addition, because mpMRI, recommended before biopsy in current guidelines, was not routinely performed during the study, these data were not included in our study.

Conclusion

AS has an important place among the treatment strategies for PCa. Despite being in the low-risk group and meeting the criteria for AS, 41% of patients who underwent RP in our study had upgraded and 15% had upstaging. Patients should be informed about these risks when AS is recommended. In our study, no cancer-related deaths were observed in patients who is eligible for AS but underwent RP. This may suggest that active surveillance criteria are suitable for detecting low-risk prostate cancer patients.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Dokuz Eylül University Faculty of Medicine Institutional Review Board Ethics Committee approval (decision no: 2023/34-02, date: 25.10.2023). The study was performed in accordance with the most recent version of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ş.O., V.Ş., B.T., K.Y., G.A., M.U.M., İ.C., Concept: Ş.O., A.E.S., S.H.B.Y., B.S., S.C., B.T., K.Y., M.U.M., Design: Ş.O., S.H.B.Y., S.C., V.S., B.T., K.Y., M.U.M., Data Collection or Processing: E.S., S.H.B.Y., B.S., Analysis or Interpretation: Ş.O., A.E.S., V.S., Literature Search: Ş.O., S.C., K.Y., M.U.M., Writing: Ş.O., V.Ş.

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References

1. Klotz L. Overdiagnosis in urologic cancer : For World Journal of Urology Symposium on active surveillance in prostate and renal cancer. World J Urol. 2022;40:1-8. [Crossref]
2. Parker C. Active surveillance: an individualized approach to early prostate cancer. BJU Int. 2003;92:2-3. [Crossref]
3. Willemse PM, Davis NF, Grivas N, Zattoni F, Lardas M, Briers E, Cumberbatch MG, De Santis M, Dell'Oglio P, Donaldson JF, Fossati N, Gandaglia G, Gillessen S, Grummet JP, Henry AM, Liew M, MacLennan S, Mason MD, Moris L, Plass K, O'Hanlon S, Omar MI, Oprea-Lager DE, Pang KH, Paterson CC, Ploussard G, Rouvière O, Schoots IG, Tilki D, van den Bergh RCN, Van den Broeck T, van der Kwast TH, van der Poel HG, Wiegel T, Yuan CY, Cornford P, Mottet N, Lam TBL. Systematic Review of Active Surveillance for Clinically Localised Prostate Cancer to Develop Recommendations Regarding Inclusion of Intermediate-risk Disease, Biopsy Characteristics at Inclusion and Monitoring, and Surveillance Repeat Biopsy Strategy. Eur Urol. 2022;81:337-346. [Crossref]
4. Thomsen FB, Brasso K, Klotz LH, Røder MA, Berg KD, Iversen P. Active surveillance for clinically localized prostate cancer--a systematic review. J Surg Oncol. 2014;109:830-835. [Crossref]
5. Carlsson S, Benfante N, Alvim R, Sjoberg DD, Vickers A, Reuter VE, Fine SW, Vargas HA, Wiseman M, Mamoor M, Ehdaie B, Laudone V, Scardino P, Eastham J, Touijer K. Long-Term Outcomes of Active Surveillance for Prostate Cancer: The Memorial Sloan Kettering Cancer Center Experience. J Urol. 2020;203:1122-1127. [Crossref]
6. Alchin DR, Murphy D, Lawrentschuk N. Risk factors for Gleason Score upgrading following radical prostatectomy. Minerva Urol Nefrol. 2017;69:459-465. [Crossref]
7. Jang WS, Koh DH, Kim J, Lee JS, Chung DY, Ham WS, Rha KH, Choi YD. The prognostic impact of downgrading and upgrading from biopsy to radical prostatectomy among men with Gleason score 7 prostate cancer. Prostate. 2019;79:1805-1810. [Crossref]
8. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, Vickers AJ, Parwani AV, Reuter VE, Fine SW, Eastham JA, Wiklund P, Han M, Reddy CA, Ciezki JP, Nyberg T, Klein EA. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol. 2016;69:428-435. [Crossref]
9. Wang Y, Chen X, Liu K, Liu R, Li L, Yin C, Song P. Predictive Factors for Gleason Score Upgrading in Patients with Prostate Cancer after Radical Prostatectomy: A Systematic Review and Meta-Analysis. Urol Int. 2023;107:460-479. [Crossref]
10. De Nunzio C, Pastore AL, Lombardo R, Simone G, Leonardo C, Mastroianni R, Collura D, Muto G, Gallucci M, Carbone A, Fuschi A, Dutto L, Witt JH, De Dominicis C, Tubaro A. The new Epstein gleason score classification significantly reduces upgrading in prostate cancer patients. Eur J Surg Oncol. 2018;44:835-839. [Crossref]
11. Wu S, Jiang Y, Liang Z, Chen S, Sun G, Ma S, Chen K, Liu R. Comprehensive analysis of predictive factors for upstaging in intraprostatic cancer after radical prostatectomy: Different patterns of spread exist in lesions at different locations. Cancer Med. 2023;12:17776-17787. [Crossref]
12. Taggart R, Dutto L, Leung HY, Salji M, Ahmad I. A contemporary analysis of disease upstaging of Gleason 3+3 prostate cancer patients after robot-assisted laparoscopic prostatectomy. Cancer Med. 2023;12:20830-20837. [Crossref]
13. Van den Broeck T, van den Bergh RCN, Arfi N, Gross T, Moris L, Briers E, Cumberbatch M, De Santis M, Tilki D, Fanti S, Fossati N, Gillessen S, Grummet JP, Henry AM, Lardas M, Liew M, Rouvière O, Pecanka J, Mason MD, Schoots IG, van Der Kwast TH, van Der Poel HG, Wiegel T, Willemse PM, Yuan Y, Lam TB, Cornford P, Mottet N. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. Eur Urol. 2019;75:967-987. [Crossref]
14. Ayala AG, Ro JY, Babaian R, Troncoso P, Grignon DJ. The prostatic capsule: does it exist? Its importance in the staging and treatment of prostatic carcinoma. Am J Surg Pathol. 1989;13:21-27. [Crossref]
15. Caglic I, Kovac V, Barrett T. Multiparametric MRI - local staging of prostate cancer and beyond. Radiol Oncol. 2019;53:159-170. [Crossref]

16. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, Fanti S, Fossati N, Gandaglia G, Gillessen S, Grivas N, Grummet J, Henry AM, van der Kwast TH, Lam TB, Lardas M, Liew M, Mason MD, Moris L, Oprea-Lager DE, van der Poel HG, Rouvière O, Schoots IG, Tilki D, Wiegel T, Willemse PM, Cornford P. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2021;79:243-262. [Crossref]

17. Nickel JC, Speakman M. Should we really consider Gleason 6 prostate cancer? BJU Int. 2012;109:645-646. [Crossref]

18. Kornberg Z, Cooperberg MR, Spratt DE, Feng FY. Genomic biomarkers in prostate cancer. Transl Androl Urol. 2018;7:459-471. [Crossref]

19. Gokce MI, Tangal S, Hamidi N, Suer E, Ibis MA, Beduk Y. Role of neutrophil-to-lymphocyte ratio in prediction of Gleason score upgrading and disease upstaging in low-risk prostate cancer patients eligible for active surveillance. Can Urol Assoc J. 2016;10:E383-E387. [Crossref]

20. Falagario UG, Martini A, Wajswol E, Treacy PJ, Ratnani P, Jambor I, Anastos H, Lewis S, Haines K, Cormio L, Carrieri G, Rastinehad AR, Wiklund P, Tewari A. Avoiding Unnecessary Magnetic Resonance Imaging (MRI) and Biopsies: Negative and Positive Predictive Value of MRI According to Prostate-specific Antigen Density, 4Kscore and Risk Calculators. Eur Urol Oncol. 2020;3:700-704. [Crossref]

21. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, Davis M, Peters TJ, Turner EL, Martin RM, Oxley J, Robinson M, Staffurth J, Walsh E, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Neal DE; ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375:1415-1424. [Crossref]

22. Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, Roobol MJ; PRIAS study group. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur Urol. 2016;70:954-960. [Crossref]

23. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, Häggman M, Andersson SO, Andrén O, Steineck G, Adami HO, Johansson JE. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med. 2018;379:2319-2329. [Crossref]

24. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, Nordling S, Häggman M, Andersson SO, Spångberg A, Andrén O, Palmgren J, Steineck G, Adami HO, Johansson JE. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014;370:932-942. [Crossref]