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Expending the Paradigm: Active Surveillance for Intermediate Risk Prostate Cancer

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Abstract

Prostate cancer is the leading male cancer worldwide. There remains a controversy as to which patients have indolent disease and which patients present an aggressive disease needing treatment with intent to cure. Because of quality of life impairment associated with treatment by radiation or surgery, active surveillance (AS) is a valid management option to avoid or differ aggressive treatment. Traditionally, AS was reserved for men with low risk prostate cancer, however intermediate risk patients are more and more found in AS cohorts. The aim of this review is to describe the place of AS in intermediate risk patients and the perspectives offered by such a treatment modality.

Keywords

Prostate Cancer, Active Surveillance, Intermediate Risk

1. Introduction

Prostate cancer is the leading non-cutaneous male cancer in the US with an estimated incidence of 238,590 and a disease related deaths reaching 29,720 in 2013 [1]. These figures—a high incidence and steadily following age-specific mortality—are the consequence of a steady downward stage migration since the approval of the prostate specific antigen (PSA) test by the Food and Drug Administration of the United States in the mid-1990s and its subsequent wide use [2]. In the face of screening, most tumors are diagnosed at an organ-confined stage with excellent long-term survival [1]. In fact, most men with prostate cancer die of other causes like cardiovascular disease and aging related morbidities rather than prostate cancer and a relatively small minority of prostate cancers ultimately prove lethal [3].

Due to the repeated use of PSA testing, prostate cancer has been increasingly diagnosed with early stage, low risk disease as determined by the PSA, Gleason score, and other parameters. A study of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database found that among the 10,385 patients, 4232 (41.6%), 2761 (26.6%), and 3301 (31.8%) had low, intermediate, and high risk prostate cancer at diagnosis, respectively [4]. This finding is consistent with a more recently published paper in a Scandinavian cohort where the very low risk accounted for 46% of the cohort (n = 57,713) [5]. The multiplicity of prostate cancer risk assessment tools, including several intended to identify indolent tumors [6]-[11], reflects a lack of consensus on precisely how to distinguish between aggressive and indolent disease.

This uncertainty, combined with significant rates of upgrading and upstaging among men initially thought to have low-risk disease [12], fuels anxiety which helps drive men toward aggressive management of lower risk tumors [13]. Subsequently, we observe high rates of aggressive treatments of these patients with low-risk, localized disease [14] therefore exposing them to the risks of treatment related morbidity and quality of life impact [15] [16]. In fact, many prostate cancers would never cause any impairment to quality or quantity of life if they remained undetected and are thus said to be over-diagnosed [17]. In 2012, the US Preventive Services Task Force released a recommendation that all PSA-based screening should be ended [18], a policy that would reduce over diagnosis but at the price of dramatic increases in cancer-specific morbidity and mortality [19]. Recently in Sweden, Loeb *et al*. [5] analyzed the contemporary trends of prostate cancer management. Using the National Prostate Cancer Register they found that for the period 2007-2011, 16.1% (n = 13,030) of men with intermediate risk elected to be on Active Surveillance compared to 58.9% (n = 4594) of men with low risk. This finding favor a trend towards a higher utilization of AS and in logistic regression the only factor associated with Active Surveillance in intermediate risk men was never being married while in the low risk group a higher education was associated with Active Surveillance use.

A far better solution to the problems of over diagnosis and overtreatment is selective screening of men with good life expectancy, with the clear understanding that the purpose of screening is the early identification and targeted treatment of higher-risk disease. For the larger numbers of men diagnosed with low-risk tumors, on the other hand, a growing consensus supports deferring immediate treatment in favor of active surveillance (AS) [20]. AS aims at monitoring carefully the patients with serial PSA assessments, repeat biopsies, and other tests intended to identify early signs of progression. If and when such progression is noted, the patient undergoes treatment. Such delayed treatment, when needed, is done within a window of opportunity for cure often measurable in many years, without compromising long term outcomes in carefully selected patients [21] [22] [23].

AS initially was designed for patients with low-risk tumors and based on the

different institutions, the criteria for inclusion in AS cohort varies from the most restrictive (Johns Hopkins definition) [22] to the most permissive (Royal Marsden definition) [24]. Despite the promising role of AS in prostate cancer management, however, its uptake is still low. In fact in the United States, only 10% of patients eligible for AS chose this option [20].

In an effort to evaluate the benefit of active treatment over observation, the Prostate Cancer intervention versus observation trial (PIVOT), an ongoing study is promising and yet has important findings. In this study, patients were randomly assigned to surgery or observation and at 10 years (median) follow-up. In patients with low-risk disease men, there was no significant difference between the two treatment groups in all-cause or prostate cancer-specific mortality overall. Conversely, in the high-risk disease men, there were significantly fewer deaths from prostate cancer or from any cause in the surgery group compared to their observed counterpart [25]. While the PIVOT study provides evidence favoring observation for low risk prostate cancer, there remains uncertainties concerning intermediate risk disease. In this latter group, PIVOT suggests tentatively radical prostatectomy over observation. Further evaluation at 15 or 20 years follow up will provide further evidence [26].

Using data from the Johns Hopkins prostate cancer patient Xia *et al*. [27] found that the absolute difference between prostate cancer mortality under surveillance or immediate radical prostatectomy is likely to be modest which is similar to the PIVOT findings.

2. Disease Progression in AS

An increase in grade is currently considered to be the most reliable indicator of tumor progression, especially late upgrading because this more likely reflects true biologic progression rather than initial undersampling [28] [29] [30]. In fact the clinical implication in terms of management decision-making is the same, whether the Gleason Score upgrade as a result of true disease progression or as a finding of an occult more aggressive cancer site.

Based on the D'Amico risk stratification [4], it appears that the intermediate risk group is very heterogeneous. The Gleason score 7 component comprises 3 + 4 and 4 + 3 irrespective of tumor volume, therefore putting in the same group biologically different men. Similarly, a patient can be at intermediate risk due to a PSA in the 10.1 - 20 ng/ml range while his Gleason is 3 + 3. In this case there can be an overlap between low risk and intermediate risk men. An evaluation by National Comprehensive Cancer Network found that among men classified as intermediate risk, 83.6% met only one Intermediate-risk criterion and 73.8% were in this group because of biopsy Gleason score of 7 while 15.9% and 6.0% had respectively a PSA in the 10.1 - 20 ng/ml range and a clinical stage T2b-T2c as the only criteria [31]. The criteria that put the patients in the intermediate group appear to be important again underlying the mosaic of men in this group. The same study found a trend toward more adverse pathologic outcomes for pa-

tients with a biopsy Gleason score of 7 compared to those with clinical stage T2b-T2c lesions or PSA level of 10 - 20 ng/mL and the 10-year Biochemichal Reccurence-free (BCR-free) survival was significantly greater in men with clinical stage T2b-T2ctumors (88.8%) compared to those with Gleason score 7 (73.6%) or PSA level 10 - 20 ng/ml. Interestingly when considering men meeting only 1 intermediate-risk criterion, no significant difference was found in 10-year BCR-free survival between the low-risk men and the men classified as intermediate risk by clinical stage while the 10-year BCR-free survival was significantly worse for the intermediate risk men with Gleason score 7. Another interesting finding came when comparing men who met only 1 high-risk criterion with intermediate-risk men, no significant difference was seen in 5-year BCR-free survival between the intermediate-risk men and those classified as high risk because of clinical stage. The clinical and pathological variability within the intermediate risk group and the subsequent overlap with low risk and high risk groups may explain in part why the treatment outcomes can be closer to that of high risk patients [32].

There are controversies as to the role of tumor volume in predicting the outcomes after radical prostatectomy (RP). At UCSF, Porten *et al*. [33] studied men with localized prostate cancer who underwent RP as monotherapy with the aim of assessing the prognostic role of tumor volume. When volume was analyzed as a categorized variable, hazard ratios for biochemical progression tended to increase with increasing tumour volume reaching a statistically significant difference for tumour volumes > 4 mL ($P < 0.05$). However after controlling for known independent predictors of prostate cancer recurrence, no tumour volume was an independent predictor of outcome. In addition a subgroup analysis of the low risk men found that tumour volume did not correlate with BCR-free survival on univariate or multivariate analysis. These findings are consistent with other previous studies [34] [35]. Conversely, Nelson *et al*. [36] in a study of 431 patients who underwent RP between 2000 and 2001, found that tumor volume correlates with pathological stage and is independently correlated with biochemical recurrence.

Therefore the ideal intermediate risk candidate ford AS should be men with high-volume GS 3 + 3, low-volume GS 3 + 4 and maybe those with PSA > 10 but otherwise low risk.

3. AS and Intermediate Risk Men

One key question in AS is determining eligibility for surveillance. Indeed, despite the fact that to date AS has been considered primarily designed for low risk patients, several reported AS cohorts include some men with intermediate risk prostate cancer—both men initially diagnosed with intermediate risk disease, and mendiagnosed with low risk who subsequently progress and still opt to remain on surveillance [23] [37] [38] [39].

Generally men with intermediate risk are advised that their risk of progression

is believed to be higher, and to date most men with good life expectancy have been recommended to undergo treatment. If they are strongly motivated to avoid treatment, however, and are willing to accept these risks they are offered a trial of AS. A report from the UCSF cohort, for example, identified 90 men considered to be at intermediate risk [23]. Compared with those with low-risk disease, men with intermediate-risk were older and had higher baseline PSA levels (mean, 10.9 vs. 5.1 ng/mL). They had more rapid PSA kinetics, and among those ultimately undergoing surgery, they were more likely to be upstaged; however neither of these differences were statistically significant. The likelihood of progression did not differ between low risk and intermediate risk men with the caveat that it is easier for a man with low-risk Gleason 3 + 3 to progress to Gleason 3 + 4 than for an intermediate-risk Gleason 3 + 4 tumor to progress to 4 + 3.

Men not meeting strict criteria for low risk prostate cancer were also found in other cohorts like the Johns Hopkins cohort. In that study the rates of progression to active treatment were higher for men not meeting strict criteria for AS (clinical stage T1c, PSAD < 0.15 ng/mL, Gleason ≤ 6, ≤ 2 cores with cancer, and ≤ 50% involvement of any core with cancer) compared to those meeting these criteria (40% vs. 31%; P = 0.03), and the rates of upgrading or increase in tumor volume were also higher in men not meeting the strict criteria for inclusion in AS [37]. One particularity of this study was that 136 men (17.7%) of the cohort did not meet AS criteria due the PSA density while only 30 men (3.9%) failed to meet another very-low-risk disease criterion. Conversely in the UCSF cohort, the major difference between low risk and intermediate risk men was related to the Gleason score with 376 men having Gleason 2 to 6 and CAPRA 0 to 2 (low risk), and 90 men having Gleason 7 and/or CAPRA 3 to 5 (intermediate risk) [23].

In the University of Toronto AS cohort, between 1995 and 1999 the study was offered to all favorable-risk patients (*i.e.*, Gleason 6 or less, PSA 10 ng/ml or less) and to patients older than 70 years with PSA up to 15 ng/ml or Gleason up to 3 + 4. Since January 2000, the study was restricted to favorable-risk patients only. Among 450 patients of the study, there were 85 patients (18.9%) who were intermediate risk at baseline, defined as either PSA > 15 ng/mL, Gleason 7, or stage T3. On those, 49 patients (11%) remained untreated, and 36 patients (8%) were eventually treated. Of the 49 untreated, no patient had disease progression and of the 36 who were treated, only one had experienced progression to metastatic disease and death [38].

The largest AS cohort of intermediate risk men was recently published by Loeb *et al.* [5]. This study was conducted using the unique Swedish prostate cancer registry. The criteria used to define intermediate risk were stage T1-T2, Gleason 7 and/or PSA 10-20). A total of 2104 intermediate risk men were involved accounting for 16% of all intermediate risk from 2007 to 2011. In comparison, this proportion was 59% and 41% for very low risk and of low-risk respectively. While AS and watchful waiting were initially recorded as deferred

treatment in the registry, the distinction was made between these 2 modalities from 2007.

A recent study by Abern *et al*. [40] retrospectively evaluated men who underwent RP between 1988 and 2011 at 5 veterans' affairs (VA) Medical Centers across the US using the Shared Equal Access Regional Cancer Hospital (SEARCH) database. The study compared low and intermediate risk men who underwent a delayed radical prostatectomy after diagnosis and did not find a significant difference in pathological upgrade based on the time to surgery in the 2 groups. On multivariable analysis, there were no associations between interval to RP and pathologic upgrading and ECE in either low or intermediate risk men or the intermediate risk men to the exception that a delay > 9 months was associated with Extra Capsular Extension (OR: 6.68, CI: 1.04 - 42.77, P = 0.045) in the low volume subset of intermediate-risk men. While the interval to RP did not impact the Positive surgical margin (PSM) rate in the low risk group, a delay > 9 months was associated with increased PSM risk (OR: 4.08, P < 0.01) among men with intermediate-risk disease. However, for men with intermediate-risk disease, there was an increased risk of BCR for delays > 9 months (HR: 2.19, P < 0.01), but not for the 3 - 6 or 6 - 9 months intervals. Delays > 9 months remained associated with BCR even in subsets of intermediate-risk patients with Gleason 3 + 4 (HR: 2.51, P < 0.01) and PSA ≤ 6 ng/ml (HR: 2.82, P = 0.06). In the cohort of intermediate-risk men believed to have low volume disease, delays > 9 months (HR: 2.59, P = 0.057) were associated with increased BCR though it did not reach statistical significance. The major limitation of this study was the short follow up before surgery; in fact only 58 out of 1561 had a delay in RP beyond 9 months.

4. Perspectives

More research is needed to better determine the place of active surveillance in well-selected intermediate risk prostate cancer. It is possible that this treatment modality is extended due to a better segregation between indolent and aggressive disease, to the aggressive treatment related quality of life impairment and patient and patient preferring this treatment modality.

5. Conclusion

Active surveillance is a viable option, is a subset of intermediate risk prostate cancer patients. Because there is still a small proportion of intermediate risk prostate cancer patients accounting for this treatment, there is a need for more studies to evaluate the effectiveness of this treatment modality to reduce treatment related quality of life impairment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Siegel, R., Naishadham, D. and Jemal, A. (2013) Cancer Statistics. *CA*: *A Cancer Journal for Clinicians*, **63**, 11-30. https://doi.org/10.3322/caac.21166

[2] Ries, L.A.G., Melbert, D., Krapcho, M., *et al*. (2008) SEER Cancer Statistics Review, 1975-2005. National Cancer Institute, Bethesda, MD.

[3] Lu-Yao, G.L., Albertsen, P.C., Moore, D.F., *et al*. (2009) Outcomes of Localized Prostate Cancer Following Conservative Management. *JAMA*, **302**, 1202-1209. https://doi.org/10.1001/jama.2009.1348

[4] Cooperberg, M.R., Broering, J.M., Kantoff, P.W. and Carroll, P.R. (2007) Contemporary Trends in Low Risk Prostate Cancer: Risk Assessment and Treatment. *Journal of Urology*, **178**, S14-S19. https://doi.org/10.1016/j.juro.2007.03.135

[5] Loeb, S., Berglund, A. and Stattin, P. (2013) Population-Based Study of Utilization and Determinants of Active Surveillance and Watchful Waiting for Low- and Intermediate-Risk Prostate Cancer. *Journal of Urology*, **190**, 1742-1749. https://doi.org/10.1016/j.juro.2013.05.054

[6] D'Amico, A.V. (2002) Combined-Modality Staging in Predicting Prostate-Specific Antigen Outcome after Definitive Local Therapy for Men with Clinically Localized Prostate Cancer. In: *Prostate Cancer*: *Principles & Practice*, Lippincott Williams & Wilkins, Philadelphia, PA, 254-268.

[7] Cooperberg, M.R., Pasta, D.J., Elkin, E.P., Litwin, M.S., Latini, D.M., Du Chane, J. and Carroll, P.R. (2005) The University of California, San Francisco Cancer of the Prostate Risk Assessment Score: A Straightforward and Reliable Preoperative Predictor of Disease Recurrence after Radical Prostatectomy. *Journal of Urology*, **173**, 1938-1942. https://doi.org/10.1097/01.ju.0000158155.33890.e7

[8] Kattan, M.W., Eastham, J.A., Stapleton, A.M., Wheeler, T.M. and Scardino, P.T. (1998) A Preoperative Nomogram for Disease Recurrence Following Radical Prostatectomy for Prostate Cancer. *Journal of the National Cancer Institute*, **90**, 766-771. https://doi.org/10.1093/jnci/90.10.766

[9] Nakanishi, H., Wang, X., Ochiai, A., *et al*. (2007) A Nomogram for Predicting Low-Volume/Low-Grade Prostate Cancer: A Tool in Selecting Patients for Active Surveillance. *Cancer*, **110**, 2441-2447. https://doi.org/10.1002/cncr.23055

[10] Bangma, C.H., Roobol, M.J. and Steyerberg, E.W. (2009) Predictive Models in Diagnosing Indolent Cancer. *Cancer*, **115**, 3100-3106. https://doi.org/10.1002/cncr.24347

[11] Iremashvili, V., Burdick-Will, J. and Soloway, M.S. (2013) Improving Risk Stratification in Patients with Prostate Cancer Managed by Active Surveillance: A Nomogram Predicting the Risk of Biopsy Progression. *BJU International*, **112**, 39-44. https://doi.org/10.1111/bju.12112

[12] Conti, S.L., Dall' ERA, M., Fradet, V., Cowan, J.E., Simko, J. and Carroll, P.R. (2009) Pathological Outcomes of Candidates for Actives Surveillance of Prostate Cancer. *Journal of Urology*, **181**, 1628-1633. https://doi.org/10.1016/j.juro.2008.11.107

[13] Latini, D.M., Hart, S.L., Knight, S.J., Cowan, J.E., Ross, P.L., Duchane, J. and Carroll, P.R. (2007) CaPSURE Investigators: The Relationship between Anxiety and Time to Treatment for Patients with Prostate Cancer on Surveillance. *Journal of Urology*, **178**, 826-831. https://doi.org/10.1016/j.juro.2007.05.039

[14] Cooperberg, M.R., Broering, J.M. and Caroll, P.R. (2010) Time Trends and Local Variation in Primary Treatment of Localized Prostate Cancer. *Journal of Clinical Oncology*, **28**, 1117-1123. https://doi.org/10.1200/JCO.2009.26.0133

[15] Pardo, Y., Guedea, F., Aguilo, F., *et al*. (2010) Quality-of-Life Impact of Primary Treatments for Localized Prostate Cancer in Patients without Hormonal Treatment. *Journal of Clinical Oncology*, **28**, 4687-4696. https://doi.org/10.1200/JCO.2009.25.3245

[16] Sanda, M.G., Dunn, R.L., Michalski, J., *et al*. (2008) Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. *The New England Journal of Medicine*, **358**, 1250-1261. https://doi.org/10.1056/NEJMoa074311

[17] Draisma, G., Etzioni, R., Tsodikov, A., Mariotto, A., Wever, E., Gulati, R., Feuer, E. and de Koning, H. (2009) Lead Time and over Diagnostic in Prostate Specific Antigen Screening: Importance of Methods and Context. *Journal of the National Cancer Institute*, **101**, 374-383. https://doi.org/10.1093/jnci/djp001

[18] Moyer, V.A., *et al*. (2012) Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine*, **157**, 120-134. https://doi.org/10.7326/0003-4819-157-2-201207170-00459

[19] Scosyrev, E., Wu, G., Mohile, S. and Messing, F.M. (2012) Prostate Specific Antigen Screening for Prostate Cancer and Risk of Overt Metastatic Disease at Presentation: Analysis of Trends over Time. *Cancer*, **118**, 5768-5776. https://doi.org/10.1002/cncr.27503

[20] Ganz, P.A., Barry, J.M., Burke, W., *et al*. (2012) National Institutes of Health State-of-the-Science Conference: Role of Active Surveillance in the Management of Men with Localized Prostate Cancer. *Annals of Internal Medicine*, **156**, 591-595. https://doi.org/10.7326/0003-4819-156-8-201204170-00010

[21] Dall'Era, M.A., Cooperberg, M.R., Chan, J.M., *et al*. (2008) Active Surveillance for Early-Stage Prostate Cancer: Review of the Current Literature. *Cancer*, **112**, 1650-1659. https://doi.org/10.1002/cncr.23373

[22] Warlick, C., Trock, B.J., Landis, P., *et al*. (2006) Delayed versus Immediate Surgical Intervention and Prostate Cancer Outcome. *Journal of the National Cancer Institute*, **98**, 355-357. https://doi.org/10.1093/jnci/djj072

[23] Cooperberg, M.R., Cowan, J.E., Hilton, J.F., *et al*. (2011) Outcomes of Active Surveillance for Men with Intermediate-Risk Prostate Cancer. *Journal of Clinical Oncology*, **29**, 228-234. https://doi.org/10.1200/JCO.2010.31.4252

[24] Van As, N.J., Norman, A.R., Thomas, K., *et al*. (2008) Predicting the Probability of Deferred Radical Treatment for Localized Prostate Cancer Managed by Active Surveillance. *European Urology*, **54**, 1297-1305. https://doi.org/10.1016/j.eururo.2008.02.039

[25] Catalona, W.J. (2012) Words of Wisdom. Re: Radical Prostatectomy versus Observation for Localized Prostate Cancer. *European Urology*, **62**, 1195. https://doi.org/10.1016/j.eururo.2012.09.015

[26] Cheng, J.Y. (2013) The Prostate Cancer Intervention versus Observation Trial (PIVOT) in Perspective. *Journal of Clinical Medicine Research*, **5**, 266-268. https://doi.org/10.4021/jocmr1395w

[27] Xia, J., Gulati, R., Au, M., Gore, J.L., Lin, D.W. and Etzioni, R. (2013) Effects of Screening on Radical Prostatectomy Efficacy: The Prostate Cancer Intervention versus Observation Trial. *Journal of the National Cancer Institute*, **105**, 546-550. https://doi.org/10.1093/jnci/djt017

[28] Albertsen, P.C., Hanley, J.A. and Fine, J. (2005) 20-Year Outcomes Following Conservative management of Clinically Localized Prostate Cancer. *JAMA*, **293**, 2095-2101. https://doi.org/10.1001/jama.293.17.2095

[29] Ross, A.E., Loeb, S., Landis, P., *et al*. (2010) Prostate-Specific Antigen Kinetics dur-

ing Follow-Up Are an Unreliable Trigger for Intervention in a Prostate Cancer Surveillance Program. *Journal of Clinical Oncology*, **28**, 2810-2816. https://doi.org/10.1200/JCO.2009.25.7311

[30] Porten, S.P., Whitson, J.M., Cowan, J.E., *et al*. (2011) Changes in Prostate Cancer Grade on Serial Biopsy in Men Undergoing Active Surveillance. *Journal of Clinical Oncology*, **29**, 2795-2800. https://doi.org/10.1200/JCO.2010.33.0134

[31] Reese, A.C., Pierorazio, P.M., Han, M. and Partin, A.W. (2012) Contemporary Evaluation of the National Comprehensive Cancer Network Prostate Cancer Risk Classification System. *Urology*, **80**, 1075-1079. https://doi.org/10.1016/j.urology.2012.07.040

[32] Mitchell, J.A., Cooperberg, M.R., Elkin, E.P., Lubeck, D.P., Mehta, S.S., Kane, C.J. and Carroll, P.R. (2005) Ability of 2 Pretreatment Risk Assessment Methods to Predict Prostate Cancer Recurrence after Radical Prostatectomy: Data from CaPSURE. *Journal of Urology*, **173**, 1126-1131. https://doi.org/10.1097/01.ju.0000155535.25971.de

[33] Porten, S.P., Cooperberg, M.R. and Carroll, P.R. (2010) The Independent Value of Tumour Volume in a Contemporary Cohort of Men Treated with Radical Prostatectomy for Clinically Localized Disease. *BJU International*, **105**, 472-475. https://doi.org/10.1111/j.1464-410X.2009.08774.x

[34] Solomon, K., Levrel, O., Anastasiadis, A.G., *et al*. (2003) Prognostic Significance of Tumor Volume after Radical Prostatectomy: Amultivariate Analysis of Pathological Prognostic Factors. *European Urology*, **43**, 39-44. https://doi.org/10.1016/S0302-2838(02)00493-1

[35] Kikuchi, E., Scardino, P.T., Wheeler, T.M., *et al*. (2004) Is Tumor Volume an Independent Prognostic Factor in Clinically Localized Prostate Cancer? *Journal of Urology*, **172**, 508-511. https://doi.org/10.1097/01.ju.0000130481.04082.1a

[36] Nelson, B.A., Shappell, S.B., Change, S.S., *et al*. (2006) Tumour Volume Is an Independent Predictor of Prostate-Specific Antigen Recurrence in Patients Undergoing Radical Prostatectomy for Clinically Localized Prostate Cancer. *BJU International*, **97**, 1169-1172. https://doi.org/10.1111/j.1464-410X.2006.06148.x

[37] Tosoian, J.J., Trock, B.J., Landis, P., *et al*. (2011) Active Surveillance Program for Prostate Cancer: An Update of the Johns Hopkins Experience. *Journal of Clinical Oncology*, **29**, 2185-2190. https://doi.org/10.1200/JCO.2010.32.8112

[38] Klotz, L., Zhang, L., Lam, A., *et al*. (2010) Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort with Localized Prostate Cancer. *Journal of Clinical Oncology*, **28**, 126-131. https://doi.org/10.1200/JCO.2009.24.2180

[39] Klotz, L. (2012) Active Surveillance: The Canadian Experience. *Current Clinical Urology*, **22**, 222-230. https://doi.org/10.1007/978-1-61779-912-9_8

[40] Abern, M.R., Aronson, W.J., Terris, M.K., Kane, C.J., Presti Jr., J.C., Amling, C.L. and Freedland, S.J. (2013) Delayed Radical Prostatectomy for Intermediate-Risk Prostate Cancer Is Associated with Biochemical Recurrence: Possible Implications for Active Surveillance from the SEARCH Database. *The Prostate*, **73**, 409-417. https://doi.org/10.1002/pros.22582