Pathological outcome for Chinese patients with low-risk prostate cancer eligible for active surveillance and undergoing radical prostatectomy: comparison of six different active surveillance protocols

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ABSTRACT

Introduction: Active surveillance is one of the therapeutic options for the management of patients with low-risk prostate cancer. This study compared the performance of six different active surveillance protocols for prostate cancer in the Chinese population.

Methods: Patients who underwent radical prostatectomy for prostate cancer from January 1998 to December 2012 at a university teaching hospital in Hong Kong were reviewed. Six active surveillance protocols were applied to the cohort. Statistical analyses were performed to compare the probabilities of missing unfavourable pathological outcome. The sensitivity and specificity of each protocol in identifying low-risk disease were compared.

Results: During the study period, 287 patients were included in the cohort. Depending on different active surveillance protocols used, extracapsular extension, seminal vesicle invasion, pathological T3 disease, and upgrading of Gleason score were present on final pathology in 3.3%-17.1%, 0%-3.3%, 3.3%-19.1%, and 20.6%-34.5% of the patients, respectively. The University of Toronto protocol had a higher rate of extracapsular extension at 17.1% and pathological T3 disease at 19.1% on final pathology than the more stringent protocols from John Hopkins (3.3% extracapsular extension, P=0.05 and 3.3% pathological T3 disease, P=0.03) and Prostate Cancer Research International: Active Surveillance (PRIAS; 8.0% pathological T3 disease, P=0.04). The Royal Marsden protocol had a higher rate of upgrading of Gleason score at 34.5% compared with the more stringent protocol of PRIAS at 20.6% (P=0.04). The specificities in identifying localised disease and low-risk histology among different active surveillance protocols were 59%-98% and 58%-94%, respectively. The John Hopkins active surveillance protocol had the highest specificity in both selecting localised disease (98%) and low-risk histology (94%).

Conclusions: Active surveillance protocols based on prostate-specific antigen and Gleason score alone or including Gleason score of 3+4 may miss high-risk disease and should be used cautiously. The John Hopkins and PRIAS protocols are highly specific in identifying localised disease and low-risk histology.

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New knowledge added by this study

- Active surveillance protocols based on prostate-specific antigen (PSA) and Gleason score only may miss high-risk prostate cancer.
- Active surveillance protocols using PSA density as an inclusion criteria were highly specific in identifying localised disease and low-risk pathology.

Implications for clinical practice or policy

- When adopting active surveillance in patients with prostate cancer, protocols with PSA density as an inclusion criteria are preferred.

Introduction

Prostate-specific antigen (PSA) plays a significant role in the early detection of prostate cancer in current practice.[1,2] It is, however, a double-edged sword that leads to overdiagnosis, especially for clinically insignificant prostate cancer.[3,4] Curative

適合積極監察並已接受根治性前列腺切除術的低風險前列腺癌華籍患者：比較六種積極監察方案下患者的病理結果

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引言：積極監察是管理低風險前列腺癌患者的治療方法之一。本研究比較六種前列腺癌積極監察方案應用在華籍患者身上的表現。

方法：研究對象為1998年1月至2012年12月期間於香港一所大學教學醫院內接受根治性前列腺切除術的患者。我們分別利用六種積極監察方案，用統計學分析比較不同方案下可能遺漏的不良病理結果的可能性。亦比較各方案識別低風險患者的敏感性和特異性。

結果：共287名患者被納入研究範圍。視乎不同方案，最終病理結果發現3.3%至17.1%有外囊擴張、0%至3.3%有精囊浸潤、3.3%至19.1%有病理性T3病變，以及20.6%至34.5%的Gleason分數上升。其中University of Toronto方案與較嚴格的John Hopkins方案及PRIAS方案比較，有較高外囊擴張比率（University of Toronto方案17.1%比John Hopkins方案3.3%；P=0.05），亦有較高病理性T3病變比率（University of Toronto方案19.1%比John Hopkins方案3.3%〔P=0.03〕和PRIAS方案8.0%〔P=0.04〕）。而Royal Marsden方案與嚴格的PRIAS方案比較有較高Gleason分數上升（34.5%比20.6%；P=0.04）。不同的積極監察方案下，偵測局部疾病和低風險組織學的特異性分別為59%至98%和58%至94%。John Hopkins方案在偵測局部疾病（98%）和低風險組織學（94%）方面有最高的特異性。

結論：純粹根據前列腺特異性抗原和Gleason分數或者包括Gleason 3 + 4的主動監測方案可能會錯過高風險患者，所以應謹慎使用。John Hopkins方案和PRIAS方案在識別局部疾病和低風險組織學方面有高度特異性。

treatments for low-risk prostate cancer include radical prostatectomy and radiotherapy, both of which are associated with significant morbidities.[5-7] In recent years, the concept of active surveillance (AS) has been adopted with the aim of monitoring clinically insignificant prostate cancer until disease progression, at which point radical prostatectomy or radiotherapy is considered. The ultimate objective is to delay or avoid the morbidities associated with radical treatments without compromising survival.[8-10]

Although AS is an established management option for low-risk prostate cancer, different AS protocols have been adopted.[11-17] The most commonly used include those from the University of Toronto,[11] Royal Marsden,[12] John Hopkins,[13,14] University of California San Francisco (UCSF),[15] Memorial Sloan Kettering Cancer Center (MSKCC),[16] and Prostate Cancer Research International: Active Surveillance (PRIAS).[17] Most AS protocols select prostate cancer with a Gleason score of ≤6, PSA level of ≤10 ng/mL, and clinical stage of ≤T2. Other parameters that are considered by some protocols include PSA density, number of positive biopsy cores, and percentage of core involvement (Table 1[11-17]).

Currently, there is no consensus regarding which AS protocol we should adopt for our patients. In addition, direct comparisons between different AS protocols are few. Before deciding to follow any particular AS protocol, urologists and oncologists should be aware of their individual strengths and limitations. Our study aimed to provide some insight into this issue by performing a head-to-head comparison of six AS protocols.

Methods

Patients who underwent radical prostatectomy for prostate cancer from January 1998 to December 2012 at a university teaching hospital in Hong Kong were reviewed. Indication for radical prostatectomy was localised prostate cancer in patients with a life expectancy exceeding 10 years. All patients underwent clinical assessment including clinical T staging by digital rectal examination, serum PSA level, and transrectal ultrasound-guided prostate biopsy. Sextant biopsies were performed from 1998 to 2002, but changed to 10-core biopsies from 2002 to 2011 and subsequently 12-core biopsies thereafter. Preoperative magnetic resonance imaging of the prostate was routinely performed from 2007. From 1998 to 2007, open or laparoscopic radical prostatectomies were performed. After November

TABLE 1. Inclusion criteria of six active surveillance protocols[11-17]

Inclusion criterion	University of Toronto[11]	Royal Marsden[12]	John Hopkins[13,14]	UCSF[15]	MSKCC[16]	PRIAS[17]
PSA (ng/mL)	≤10	≤15	-	≤10	≤10	≤10
PSA density (ng/mL/mL)	-	-	≤0.15	-	-	<0.2
Clinical T stage	-	T1/T2a	T1	T1/T2	T1/T2	T1/T2
Gleason score	≤3+3	≤3+4	≤6	≤6	≤6	≤6
Positive biopsies	-	≤50%	≤2	<33% (of all biopsies)	≤3	≤2
% Of core involvement	-	-	≤50%	-	≤50%	-

Abbreviations: MSKCC = Memorial Sloan Kettering Cancer Center; PRIAS = Prostate Cancer Research International: Active Surveillance; PSA = prostate-specific antigen; UCSF = University of California San Francisco

2007, all prostatectomies at our institution were performed with the da Vinci robotic surgery system. Pathological assessment of transrectal ultrasound-guided biopsy and radical prostatectomy specimens was performed by a specialist pathologist in our institution. All patients attended a follow-up visit with physical examination 2 weeks after operation, and physical examination with serum PSA level checked every 3 months for the first year, every 6 months for the second year, and then annually thereafter. Data on patient demographics, clinical T stage, serum PSA level, transrectal ultrasound-guided biopsy results, and final pathology of radical prostatectomy specimen were retrospectively retrieved by an independent third party. Pathological assessment of the radical prostatectomy specimen was performed by independent specialist pathologists.

In our current study, we compared six different AS protocols, specifically from the University of Toronto,[11] Royal Marsden,[12] John Hopkins,[13,14] UCSF,[15] MSKCC,[16] and PRIAS[17] (Table 1). The six protocols were retrospectively applied to our cohort and patients were stratified accordingly based on clinical T stage, serum PSA level, PSA density, Gleason score on biopsy, number of positive biopsy cores, and percentage of positive core involvement. Data from the pathological assessment of radical prostatectomy specimens including extracapsular extension, seminal vesicle invasion, upgrading to pathological T3 disease, and upgrading of Gleason score were analysed. The clinical data used in the AS protocols were those available on diagnosis of prostate cancer and operations were performed within 12 weeks of diagnosis.

Statistical analyses to compare the rate of not diagnosing clinically significant prostate cancer—defined as extracapsular extension, seminal vesicle invasion, upgrading to T3 disease, and upgrading of Gleason score in the final prostatectomy specimens—were performed. The sensitivity and specificity of each protocol in selecting localised prostate cancer (defined as pathological stage <T3) and histological low-risk disease (defined as no upgrading of Gleason score on final pathology) were compared.

Statistical analysis was performed using the SPSS (Windows version 20.0; IBM Corp, Armonk [NY], US). Independent sample *t* test and Pearson Chi-squared test were used for continuous and categorical variables, respectively. A P value of <0.05 was considered statistically significant. This study was done in accordance with the principles outlined in the Declaration of Helsinki.

Results

A total of 287 patients were included in the cohort. The mean age was 66 years, mean serum PSA level was 10 ng/mL, mean number of positive cores during biopsy was 3, and mean Gleason sum at biopsy was 6. In the current cohort, 266 (93%) patients had clinical T1c or T2a prostate cancer—198 (69%) had clinical T1c disease and 68 (24%) had clinical T2a disease. Table 2 summarises the basic demographics of all patients.

When the six AS protocols were applied to the cohort, 30 to 152 patients were identified as low-risk; their mean serum PSA level ranged from 5.3 ng/mL to 7.7 ng/mL, and mean PSA density ranged from 0.12 ng/mL/mL to 0.25 ng/mL/mL. All six protocols had a mean biopsy Gleason sum of 6. Table 3 summarises the clinical characteristics of patients stratified according to different AS protocols.

In the analyses of final pathological outcomes in patients stratified into different AS protocols, extracapsular extension rate varied from 3.3% to 17.1%. The incidence of seminal vesicle invasion was low in all six protocols, ranging from 0% to 3.3%. The rate of pathological T3 disease was lowest according to the John Hopkins criteria (3.3%), while the University of Toronto criteria had the highest incidence (19.1%). Regarding the upgrading

TABLE 2. Basic demographics of patients (n=287)

Demographics	Mean (range) or No. (%) of patients*
Age (years)	66 (48-79)
PSA (ng/mL)	10 (1-68)
No. of positive cores	3 (1-10)
Gleason sum at biopsy	6 (6-10)
3+3	229 (80%)
3+4	26 (9%)
4+3	16 (6%)
8-10	16 (6%)
CAPRA score	1-9 (3)
Clinical T stage	
T1a	3 (1%)
T1b	0
T1c	198 (69%)
T2a	68 (24%)
T2b	6 (2%)
T2c	10 (3%)
T3a	2 (1%)
Margin positive rate	35 (12%)
pT2	22 (8%)
pT3	13 (5%)
5-Year biochemical recurrence rate	40 (14%)
Need of adjuvant/salvage therapy in 5 years	35 (12%)

Abbreviations: CAPRA = Cancer of the Prostate Risk Assessment; PSA = prostate-specific antigen

* Because of rounding, not all percentages total 100

of Gleason score in the radical prostatectomy specimens, all six protocols had a relatively high rate ranging from 20.6% to 34.5%. Table 4 summarises the pathological outcomes among the six AS protocols.

Comparative analyses of individual AS protocols against each other were also performed (Table 5). The University of Toronto protocol had a significantly higher rate of extracapsular extension at 17.1% and pathological T3 disease at 19.1% when compared with the more stringent protocol from John Hopkins (3.3% extracapsular extension, P=0.05 and 3.3% pathological T3 disease, P=0.03) and PRIAS (8.0% pathological T3 disease, P=0.04). In addition, the Royal Marsden protocol had a significantly higher rate of upgrading of Gleason score at 34.5% when compared with the more stringent protocol of PRIAS at 20.6% (P=0.04). There was no significant difference in the incidence of seminal vesicle invasion between the six protocols.

In terms of the ability of each protocol to identify pathological localised disease (defined as pathological stage <T3) and histologically low-risk cancer (defined as no upgrading of Gleason score), sensitivity varied from 13%-61% and 14-71%, respectively. The John Hopkins criteria demonstrated highest specificity in identifying pathological localised disease (98%) and histological low-risk cancer (94%). Table 6 illustrates the sensitivity and specificity of identifying localised and histological low-risk disease for the six AS protocols.

Discussion

Prostate cancer screening has always been a controversial issue and evidence of improved survival is awaited.[1,2] Nonetheless, PSA screening has undoubtedly led to overdiagnosis of insignificant prostate cancer.[3,4] Active surveillance, with the purpose to delay or even avoid radical treatments and their associated morbidities, plays an important

TABLE 3. Clinical characteristics of patients stratified according to six active surveillance protocols*

Characteristic	University of Toronto	Royal Marsden	John Hopkins	UCSF	MSKCC	PRIAS
No. of patients	152 (53.0%)	165 (57.5%)	30 (10.5%)	90 (31.4%)	91 (31.7%)	63 (22.0%)
Age (years)	65 (48-79)	66 (48-79)	64 (50-75)	65 (48-79)	66 (48-79)	65 (48-79)
PSA (ng/mL)	6.8 (1.5-10)	7.7 (2.8-15)	5.3 (2.8-8.6)	6.5 (2.8-10)	6.5 (2.8-10)	5.6 (2.8-10)
Prostate volume (mL)	35 (12-97)	36 (11-97)	46 (23-97)	36 (13-97)	36 (13-97)	44 (19-97)
PSA density (ng/mL/mL)	0.22 (0.04-0.83)	0.25 (0.04-1.00)	0.12 (0.05-0.14)	0.21 (0.05-0.64)	0.21 (0.05-0.64)	0.13 (0.04-0.2)
No. of positive cores	2 (1-8)	2 (1-6)	1 (1-2)	2 (1-4)	2 (1-3)	1 (1-2)
Mean Gleason sum	6	6	6	6	6	6
Clinical T stage						
T1a	1 (0.7%)	1 (0.6%)	0	1 (1.1%)	1 (1.1%)	1 (1.6%)
T1b	0	0	0	0	0	0
T1c	123 (80.9%)	134 (81.2%)	30 (100%)	77 (85.6%)	78 (85.7%)	52 (82.5%)
T2a	25 (16.4%)	30 (18.2%)	0	12 (13.3%)	12 (13.2%)	10 (15.9%)
T2b	0	0	0	0	0	0
T2c	3 (2.0%)	0	0	0	0	0
T3a	0	0	0	0	0	0

Abbreviations: MSKCC = Memorial Sloan Kettering Cancer Center; PRIAS = Prostate Cancer Research International: Active Surveillance; PSA = prostate-specific antigen; UCSF = University of California San Francisco

* Results are shown as No. (%) of patients (out of 287), or mean (range)

TABLE 4. Pathological outcomes of six active surveillance protocols

Pathological outcome	University of Toronto	Royal Marsden	John Hopkins	UCSF	MSKCC	PRIAS
Extracapsular extension	17.1%	14.0%	3.3%	14.4%	14.2%	8.0%
Seminal vesicle invasion	2.6%	3.0%	0%	3.3%	3.3%	1.6%
Pathological T3 disease	19.1%	16.3%	3.3%	16.7%	16.7%	8.0%
Upgrading of Gleason score	31.2%	34.5%	26.7%	28.9%	30.0%	20.6%

Abbreviations: MSKCC = Memorial Sloan Kettering Cancer Center; PRIAS = Prostate Cancer Research International: Active Surveillance; UCSF = University of California San Francisco

TABLE 5. Comparative analyses of pathological outcomes of six active surveillance protocols

Pathological outcome	University of Toronto (UT)	John Hopkins (JH)	PRIAS	Royal Marsden (RM)	P value		
					UT vs JH	UT vs PRIAS	RM vs PRIAS
Extracapsular extension	17.1%	3.3%	8.0%	14.0%	0.05	0.08	0.22
Seminal vesicle invasion	2.6%	0%	1.6%	3.0%	0.37	0.64	0.54
Pathological T3 disease	19.1%	3.3%	8.0%	16.3%	0.03*	0.04	0.10
Upgrading of Gleason score	31.2%	26.7%	20.6%	34.5%	0.59	0.11	0.04

Abbreviation: PRIAS = Prostate Cancer Research International: Active Surveillance

* In view of multiple comparison performed, significant P value was adjusted according to Benjamini-Hochberg correction and this P value was insignificant after adjustment

TABLE 6. Sensitivity and specificity of six active surveillance protocols in predicting low-risk prostate cancer

	University of Toronto	Royal Marsden	John Hopkins	UCSF	MSKCC	PRIAS
Pathological stage <T3						
Sensitivity	54%	61%	13%	33%	34%	26%
Specificity	59%	59%	98%	78%	78%	94%
No upgrading of Gleason score						
Sensitivity	68%	71%	14%	43%	43%	33%
Specificity	66%	58%	94%	81%	81%	91%

Abbreviations: MSKCC = Memorial Sloan Kettering Cancer Center; PRIAS = Prostate Cancer Research International: Active Surveillance; UCSF = University of California San Francisco

role in managing these patients. Unfortunately there are different AS protocols with various inclusion criteria, and urologists and oncologists may have difficulty deciding which protocol to adopt. The gold standard to answer this question will be a prospective randomised trial to compare overall survival following the application of different AS protocols. This, however, will require decades to observe low-risk prostate cancer patients before survival endpoints are reached. Our study provides data on pathological outcomes when different AS protocols were compared.

In our cohort, the proportion of patients eligible for active surveillance varied widely from approximately 11% to 58% according to different selection criteria (Table 3). Two recent series showed similar findings of a large discrepancy in the proportion of patients eligible for different AS protocols, varying from 16% to 63% and 28% to 69%.[18,19] We demonstrated that although all AS protocols aim to select low-risk prostate cancer, the heterogeneity between them can be quite large. Clinicians need to be vigilant before adopting any of the AS protocols for their patients when further data from comparative analyses among different protocols are unavailable. The proportion of patients who were eligible for AS protocols in our study was lower than that in previous series.[18,19] This may be because some patients with localised prostate cancer were treated with radiotherapy. The proportion of patients who can be selected in different AS protocols will be affected by the proportion of patients who undergo radiotherapy instead of surgery. In our centre, it is also possible that low-risk patients were selected to undergo a non-operative approach.

When the six protocols were compared after stratifying patients according to different AS criteria, the University of Toronto protocol had a significantly higher rate of extracapsular extension at 17.1% and pathological T3 disease at 19.1% than the John Hopkins protocol (3.3% extracapsular extension, P=0.05 and 3.3% pathological T3 disease, P=0.03) and PRIAS criteria (8.0% pathological T3 disease, P=0.04) [Table 5]. This observation can be explained by the difference in stringency of the two protocols. The University of Toronto criteria selected patients by two factors only: PSA of <10 ng/mL and Gleason score of ≤6; PSA density, number of positive biopsy cores, and percentage of core involvement were not considered. On the contrary, the John Hopkins criteria applied very strict criteria: a PSA density of 0.15 ng/mL/mL. In addition, only patients with T1 disease with at most two positive cores during biopsy and no more than 50% involvement of each core were selected (Table 1). Contrary to our findings, El Hajj et al[19] found no significant difference in the rate of extracapsular extension, upgrading of Gleason score, or unfavourable disease when they

compared the University of Toronto protocol with the John Hopkins protocol. The difference can be explained by the high rate of extracapsular extension (15%) and unfavourable disease (46%) within the John Hopkins criteria in their series, compared with 3% extracapsular extension and 3% pathological T3 disease in our cohort. This also implies that disease heterogeneity among different populations may influence the choice and results of different AS protocols.

In our study, analyses of final pathology revealed that the Royal Marsden protocol had a significantly higher rate of upgrading of Gleason score at 34.5% compared with the PRIAS criteria at 20.6% (P=0.04; Table 5). This result can be explained by the less-stringent selection criteria of the Royal Marsden protocol. First, it is the only protocol that allowed a Gleason score of 3+4 to be selected. Second, PSA level up to 15 ng/mL was permitted. These factors will invariably result in the inclusion of a proportion of patients with higher-risk disease. In the study by El Hajj et al,[19] the Royal Marsden protocol were compared with the John Hopkins protocol and significantly more unfavourable disease was observed in the Royal Marsden group. Klotz et al[11] also demonstrated that inclusion of Gleason score of 4 on biopsy into AS was a risk factor in predicting definitive treatment during active surveillance. These findings illustrate that active surveillance in patients with Gleason score of 3+4 is likely to miss higher-risk disease. It should be used cautiously and preferably not in young patients who are otherwise fit for radical treatments.

We have shown that less pathological T3 disease and Gleason score upgrading were present in the more-stringent John Hopkins and PRIAS protocols compared with the less stringent University of Toronto and Royal Marsden criteria. Nonetheless their sensitivity in identifying low-risk disease may be compromised by the more stringent selection criteria. More low-risk disease may therefore be excluded from surveillance by these stringent criteria. We addressed this issue in the last part of our analyses. The sensitivity and specificity in identifying localised disease (pathological stage <T3) and low-risk histology (no upgrading of Gleason score) among different AS protocols were compared (Table 6). The most stringent protocols of the John Hopkins and PRIAS had the highest specificity when selecting localised disease (94%-98%) and low-risk histology (91%-94%). However, inclusion of less pathological T3 disease and Gleason score upgrading by the more stringent protocols of John Hopkins and PRIAS should be cautious because it will, inevitably, be at the expense of low-risk patients who is excluded from AS and may receive unnecessary aggressive treatments. A recent study by Iremashvili et al[18] showed that the PRIAS criteria had a better balance of sensitivity and specificity compared with the UCSF and MSKCC criteria. From our point of view, we tend to place more emphasis on high specificity since low specificity will include patients with high-risk tumours into active surveillance and thus patient survival may be jeopardised.

The present study had several limitations. First, the number of biopsy cores was not consistent throughout the study period. A proportion of patients had six-core biopsies in the early period of the cohort versus the current more recent standard of 10-12–core biopsies. Second, the sample size was relatively small due to the low incidence of prostate cancer in our population. Third, the tumour volume in prostatectomy specimens that might predict low-risk prostate cancer was not assessed. Lastly, the final prostatectomy pathology in this study was from patients who were operated on soon after diagnosis and not after a period of post-diagnosis surveillance. As a note of caution, it would be expected that the final pathology would show even worse pathological features if the patients were put on AS and operated on later. This should be noted when interpreting the results of the current study and counselling patients.

In conclusion, there is a wide range of variation in the selection criteria of different AS protocols. Active surveillance protocols based on PSA and Gleason score alone or including Gleason score of 3+4 may miss higher-risk disease and should be applied cautiously. The more stringent criteria of John Hopkins protocol and the PRIAS protocol were highly specific in identifying localised disease and low-risk histology.

Declaration

All authors have disclosed no conflicts of interest

References

1. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
2. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310-9.
3. Ploussard G, Epstein JI, Montironi R, et al. The contemporary concept of significant versus insignificant prostate cancer. Eur Urol 2011;60:291-303.
4. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst 2002;94:981-90.
5. Novara G, Ficarra V, Rosen RC, et al. Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol 2012;62:431-52.
6. Boorjian SA, Eastham JA, Graefen M, et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. Eur Urol 2012;61:664-75.

7. Zaorsky NG, Harrison AS, Trabulsi EJ, et al. Evolution of advanced technologies in prostate cancer radiotherapy. Nat Rev Urol 2013;10:565-79.
8. Bastian PJ, Carter BH, Bjartell A, et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. Eur Urol 2009;55:1321-30.
9. Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. J Clin Oncol 2011;29:3669-76.
10. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976-83.
11. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010;28:126-31.
12. van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008;54:1297-305.
13. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol 2007;178:2359-64.
14. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011;29:2185-90.
15. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. Cancer 2008;112:2664-70.
16. Berglund RK, Masterson TA, Vora KC, Eggener SE, Eastham JA, Guillonneau BD. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for active surveillance. J Urol 2008;180:1964-7.
17. van den Bergh RC, Roemeling S, Roobol MJ, Roobol W, Schröder FH, Bangma CH. Prospective validation of active surveillance in prostate cancer: the PRIAS study. Eur Urol 2007;52:1560-3.
18. Iremashvili V, Pelaez L, Manoharan M, Jorda M, Rosenberg DL, Soloway MS. Pathologic prostate cancer characteristics in patients eligible for active surveillance: a head-to-head comparison of contemporary protocols. Eur Urol 2012;62:462-8.
19. El Hajj A, Ploussard G, de la Taille A, et al. Patient selection and pathological outcomes using currently available active surveillance criteria. BJU Int 2013;112:471-7.