A validation study of new decision algorithms for interpretation of cancer significance on prostate systematic biopsy

Gerald O. Ogola, PhD,[1] Nicolas Delongchamps, MD,[2,3] Robert Serfling, PhD[4]

[1]Center for Clinical Effectiveness, Office of the Chief Quality Officer, Baylor Scott and White Health, Dallas, Texas, USA

[2]Department of Urology, Cochin Hospital, Paris Descartes University, Paris, France

[3]Inserm 1151, INEM, Paris Descartes University, Paris, France

[4]Department of Mathematical Sciences, University of Texas at Dallas, Richardson, Texas, USA

OGOLA GO, DELONGCHAMPS N, SERFLING R. A validation study of new decision algorithms for interpretation of cancer significance on prostate systematic biopsy. *Can J Urol* 2017;24(2):8721-8727.

Introduction: *To test with actual data a new decision algorithm derived by probability modeling of the number of positive cores, for deciding insignificant versus significant prostate cancer, based on prostate volume, Gleason score, tumor length on biopsy cores, and number of positive cores.*

Materials and methods: *A dataset of 59 cancer-involved autopsied prostate glands from patients aged 42 to 92 years with prostate volumes of 22 cc to 95 cc was used. An 18 core-systematic biopsy was performed on the first 47 patients, and saturation biopsy protocol of 36 cores was performed on the remainder. Clinically insignificant prostate cancer was defined on whole-mount prostates as Gleason score < 7, total tumor volume ≤ 0.5 cc. Separate counts of "significant" versus "insignificant" prostate cancer by both the model-based decision algorithm and the actual data were obtained. These yielded specificity (SP), sensitivity (SE), and concordance values for evaluation of the efficacy of the decision algorithm.*

Results: *The model-based decision algorithm yielded SP from 83% to 100%, SE from 62% to 100%, and concordance from 78% to 100%. These findings compared favorably with those of currently used study-based algorithms and their individually fitted SP and SE derived from their corresponding studies.*

Conclusions: *The model-based decision algorithm performed well with this dataset of autopsied prostates for patients with Gleason score 6 or lower, confirming its practical feasibility and its potential to help reduce over- and under-treatment, especially with marginally positive biopsy cases, by taking prostate volume properly into account. However, additional validation studies with other datasets including higher prostate volumes are needed for further calibration and improvement of the model-based decision algorithm.*

Key Words: validation, specificity, sensitivity, biopsy, prostate cancer, decision algorithm

Introduction

Planning for effective prostate cancer biopsy sessions and interpreting marginally positive biopsy results is highly challenging. With millions of prostate cancer biopsies performed annually, avoiding over-treatment poses a world-wide dilemma of large scale.[1-3] To avoid over-treatment, one needs to distinguish between insignificant and significant prostate cancer with sufficiently high specificity (SP), and this requires assigning some marginally positive cases to "active surveillance".[4-6] How to select such candidates? To avoid under-treatment, decision-making with sufficiently high sensitivity (SE) is required, and this entails increasing the number of biopsy cores as prostate volume increases, keeping in mind the increasing burden on the patient. In what manner should this increase proceed?

To address these questions, a probability model[7] for the number of positive cores in a biopsy session,

Accepted for publication December 2016

Acknowledgment
The authors gratefully thank Dr. Gabriel Haas, and Dr. G. L. Thompson, for very helpful remarks and encouragement.

Address correspondence to Dr. Gerald O. Ogola, Center for Clinical Effectiveness, Office of the Chief Quality Officer, Baylor Scott and White Health, Dallas, TX 75206 USA

as a function of given prostate gland volume, tumor foci volume, and number of biopsy cores, was recently developed. The model was applied to construct favorable prostate-volume-specific decision algorithms for insignificant versus significant prostate cancer on the basis of high SP, high SE and number of positive cores. By "favorable", we mean the best trade-off between SP, SE and number of biopsy cores, while prioritizing high SP over high SE within available options, and at the same time seeking to minimize patient burden in terms of the number of biopsy cores. This is consistent with prostate cancer screening, where most efforts are directed towards increasing SP, because it is highly unlikely that men will be tested only once in their lifetime, but will undergo serial tests, perhaps annually, and hence a false negative test is less likely to be serious.[8] Enhancing the model-based decision algorithm, the Gleason score and the tumor lengths in the positive biopsy cores were incorporated as additional data, to develop a comprehensive decision algorithm for distinguishing significant versus insignificant prostate cancer on the basis of results from a prostate biopsy session. Since Gleason scores 7 or higher already indicate intermediate to high grade prostate cancer, the model-based decision algorithm that we propose is intended for application just to patients with Gleason score 6 or lower, whose cancer is lower grade and less likely to be aggressive, presenting greater uncertainty regarding best treatment options. Thus it comes into play after preliminary review of Gleason score and tumor lengths. Our model-based decision algorithm is especially of interest for interpretation of the challenging case of marginally positive biopsy outcomes.

The present study validates the comprehensive decision algorithm introduced above, using data collected from a cancer-involved autopsied prostate glands dataset. While the cohort used for validation is relatively small, this study is the first of its kind. It is understood that in practice any such algorithm-based guideline will be considered only within a fuller context including all other findings that may be available such as DRE and MRI information.

Materials and methods

Probability model, specificity and sensitivity

We developed a probability model[7] for the number of positive cores in a biopsy session, as a function of prostate gland volume, number of tumor nodules and their volumes, and number of cores. For prostate volumes 10 cc through 200 cc and number of cores 6, 12, 18, and 24, we evaluated model-based SP and SE for decision algorithms of the form "decide insignificant prostate cancer if $D \leq x_0$", for specified x_0 and with D the number of positive cores. Initially, we set aside Gleason score and tumor lengths in cores and defined "insignificant prostate cancer" simply as "total tumor volume T ≤ 0.5 cc". For this purpose, we defined model-based SP and SE, respectively, as the conditional probability of deciding "insignificant prostate cancer" when prostate cancer is truly insignificant, and the conditional probability of deciding "significant prostate cancer" when prostate cancer is truly significant. For SP we chose a total tumor volume T below the commonly adopted clinically significant threshold of 0.5 cc. In particular we used T = 0.25 cc, and defined

$$SP(x_0|n,V) = P(D \leq x_0|n,V,T = 0.25\ cc) = \sum_{x=0}^{x_0} P(D = x|n,V,T = 0.25\ cc).$$

For SE we chose T above 0.5 cc, in particular using T = 2.0 cc and defining

$$SE(x_0|n,V) = P(D > x_0|n,V,T = 2.0\ cc) = \sum_{x=x_0+1}^{\min\{k,n\}} P(D = x|n,V,T = 2.0\ cc).$$

Based on the derivations of (SP, SE) from,[7] we obtained favorable choices of n and x_0.

Since biopsy results also yield Gleason score and tumor lengths (or percentages of prostate cancer) in the positive cores, we incorporated this information with our model-based decision algorithm to develop a comprehensive decision algorithm, as follows. For Gleason sum 7 or higher, immediately conclude "significant prostate cancer". Otherwise, consider tumor lengths and if the percentages of prostate cancer are sufficiently large in sufficiently many cores, then again conclude "significant prostate cancer". Otherwise, finally, apply the appropriate model-based decision algorithm to decide insignificant versus significant prostate cancer.

Validation data

The validation dataset was collected from consecutive prostate glands from deceased men, and was provided by the University Hospital and the Onondaga County Medical Examiner, Syracuse, NY, USA and by the National Disease Research Interchange, Philadelphia, PA, USA. Informed consent was obtained by tissue suppliers from the next of kin. All samples were de-identified to protect the identity of the individual. Age, race and cause of death were recorded. The men had no known history of prostate cancer.[9]

The validation dataset consisted of 59 patients aged 42 to 92 years with prostate volumes ranging from 22 cc to 95 cc. Biopsy data on 47 patients was from an 18-core biopsy scheme and on 12 patients was from a saturated 36-core scheme.

The following data elements were provided in the validation dataset: prostate volume, number of

biopsy cores, number of positive cores, positive core locations, core lengths, tumor lengths, percent of tumor involvement in cores, tumor volumes (index and total), and Gleason scores.

A biopsy protocol diagram of the prostate labeled with locations of biopsy core was provided with the validation dataset. The biopsy locations were labeled 1-36, with 6-core systematic biopsy represented by locations labeled 1-6; 12-core systematic biopsy represented by locations labeled 1-6 and 13-18; and 18-core systematic biopsy represented by locations 1-18, Figure 1.

Although our model-based algorithm also included the case of 24-core biopsies, and we could have extracted 24-core biopsies from the 36-core biopsies, the algorithm under study recommends 24 cores only as a possibility for prostate volumes above 100 cc, which were lacking in the present dataset. Due to small numbers of cases for some volumes, we combined into groups as needed, resulting in the prostate volume groups and number of cores subgroups 20 cc-30 cc (with 6 cores), 40 cc (with 6, 12, and 18 cores), 50 cc (with 6, 12, and 18 cores), 60 cc-70 cc (with 12 and 18 cores), and 80 cc-100 cc (with 12 and 18 cores).

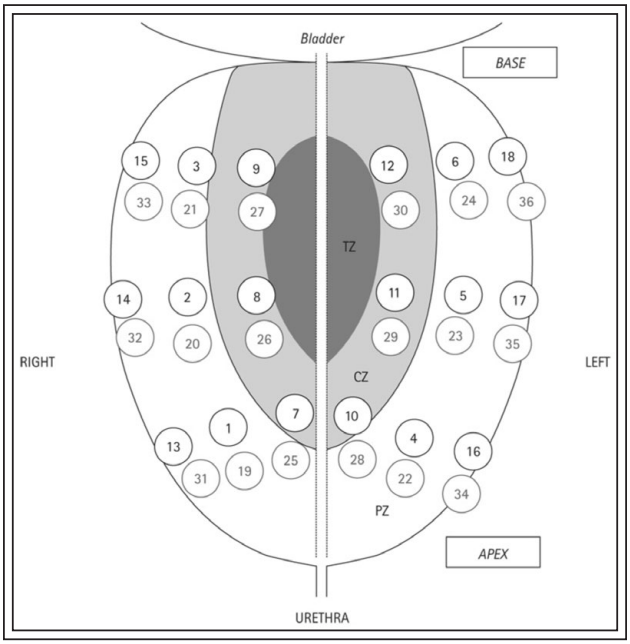

Figure 1. The saturation biopsy scheme: cores 1-18, extended biopsy protocol; cores 1-6, mid peripheral zone (MPZ); cores 7-12, lateral peripheral zone (LPZ); cores 13-18, central zone (CZ); cores 19-36 are additional cores; 19-24, MPZ; 25-30, LPZ; 31-36, CZ. Reprinted with permission from John Wiley & Sons.[9]

Using the dataset, we validated the comprehensive decision algorithm for prostate volumes 10 cc through 90 cc and numbers of biopsy cores 6, 12, and 18, by extracting 6-core and 12-core biopsies from the actual 18- and 36-core biopsies, and also using the 18-core biopsies as is. We obtained SP, SE, and concordance for our comprehensive decision algorithm, by prostate volume and number of biopsy cores. Also, as a matter of interest, we obtained SP, SE, and concordance for just the model-based decision algorithm.

Validation approach

Separately by available prostate volumes and numbers of cores, we determined the empirical SP, SE, and concordance of both the comprehensive algorithm and the model-based components. In particular, for each combination of prostate volume and number of biopsy cores, we classified the corresponding validation data into a two-by-two contingency table and calculated SP, SE, and concordance values of the decision algorithm against actual findings with the dataset of cancer-involved autopsied prostate glands. High values of SP, SE, and concordance reflected strong performance of the decision algorithm.

Results

Figure 1 displays the biopsy protocol diagram labeling the biopsy needle locations.[9]

Table 1 summarizes the model based decision algorithm to be validated.[10] The comprehensive decision algorithm, incorporating tumor length and Gleason score is exhibited in Table 2.

Table 3 provides the SP, SE, and concordance values for both the comprehensive decision algorithm and the component using the number of positive cores only, for each combination of prostate volume (or prostate volume range) and number of biopsy cores. For example, for 40 cc prostate volume, this table gives for the comprehensive decision algorithm: (SP, SE, concordance) = (100%, 86%, 90%), (100%, 100%, 100%), and (100%, 100%, 100%) for number of cores = 6, 12, and 18, respectively. The corresponding values for the component using only the number of positive cores exhibits comparable SP but lower SE and lower concordance.

It is seen that the SP values range from 83% (a singular low) to 100%, the SE values from 0% (a singular low) to 50%, and the concordance values from 78% to 100%. Also, as an overall summary, Table 3 provides (SP, SE, concordance) for the group of 6-core biopsies combining the counts for the separate prostate volumes, and likewise for the 12- and 18-core biopsies.

TABLE 1. **Model-based specificity (SP) and sensitivity (SE) for selected insignificant prostate cancer thresholds (x_0), by prostate volume (V) and number of biopsy cores (n). Favorable cases in bold prioritize on high SP and offer n versus SE trade-offs.**

				n				
	6		**12**		**18**		**24**	
V (cc)	x_0	(SP, SE)	x_0	(SP, SE)	x_0	(SP, SE)	x_0	(SP, SE)
10	1	(67, 93)	2	(58, 93)				
	2	(95, 53)	3	(91, 63)				
20	0	(47, 100)	1	(62, 98)				
	1	(89, 73)	2	(92, 75)				
30	0	(61, 91)	1	(80, 91)				
	1	(95, 45)	2	(97, 52)				
40	0	(69, 80)	0	(47, 100)	1	(75, 97)		
	1	(97, 29)	1	(88, 81)	2	(96, 68)		
50	0	(75, 71)	0	(55, 96)	1	(82, 90)		
	1	(98, 21)	1	(92, 65)	2	(98, 51)		
60			0	(61, 91)	1	(87, 83)		
			1	(94, 51)	2	(99, 39)		
70			0	(66, 85)	0	(52,98)		
			1	(96, 41)	1	(90, 72)		
80			0	(69, 80)	0	(57, 95)		
			1	(97, 34)	1	(92, 62)		
90			0	(72, 75)	0	(61, 91)		
			1	(97, 28)	1	(94, 53)		
100			0	(75, 71)	0	(64, 87)		
			1	(98, 24)	1	(95, 46)		
110					0	(67, 84)	0	(58, 94)
					1	(96, 40)	1	(92, 61)
120					0	(69, 80)	0	(61, 91)
					1	(96, 35)	1	(94, 54)
130					0	(72, 77)	0	(64, 88)
					1	(97, 31)	1	(94, 49)
140					0	(73, 74)	0	(66, 85)
					1	(97, 28)	1	(95, 44)
150					0	(75, 71)	0	(68, 83)
					1	(98, 25)	1	(96, 40)
160					0	(76, 68)	0	(69, 80)
					1	(98, 22)	1	(96, 36)
170					0	(78, 65)	0	(71, 78)
					1	(98, 20)	1	(97, 33)
180					0	(79, 63)	0	(72, 75)
					1	(98, 18)	1	(97, 30)
190					0	(80, 60)	0	(74, 73)
					1	(98, 17)	1	(97, 28)
200					0	(81, 58)	0	(75, 71)
					1	(99, 15)	1	(98, 26)

TABLE 2. **Comprehensive decision algorithm for insignificant versus significant prostate cancer**

Check Gleason sum. If 7 or higher, conclude significant prostate cancer. Otherwise proceed to next step.

Check tumor lengths in the positive biopsy cores. If

At least 1 core contains ≥ 1.0 cm tumor (or 67%),

Or at least 2 cores each contain ≥ 0.8 cm tumor (or 53%),

Or at least 3 cores each contain ≥ 0.7 cm tumor (or 47%),

Or at least 4 cores each contain ≥ 0.65 cm tumor (or 43%),

conclude significant prostate cancer. Otherwise proceed to next step.

Apply model-based decision algorithm based on number of positive cores, for given prostate volume and number of biopsy cores. Conclude either significant prostate cancer or insignificant prostate cancer.

TABLE 3. **Validation results for comprehensive decision algorithm [for model-based component only]**

Prostate volume (cc)	Number of cores	Algorithm decision	Prostatectomy result - n		(SP, SE) %	Concordance %
			Significant	Insignificant		
20-30	6	Significant	3 [1]	0 [0]	(100, 75)	
		Insignificant	1 [3]	8 [8]	[(100, 25)]	92 [75]
40	6	Significant	6 [0]	0 [0]	(100, 86)	
		Insignificant	1 [7]	3 [3]	[(100, 0)]	90 [30]
	12	Significant	7 [2]	0 [0]	(100, 100)	
		Insignificant	0 [5]	3 [3]	[(100, 27)]	100 [50]
	18	Significant	7 [1]	0 [0]	(100, 100)	
		Insignificant	0 [6]	3 [3]	[(100, 14)]	100 [40]
50	6	Significant	7 [3]	0 [0]	(100, 87)	
		Insignificant	1 [5]	6 [6]	[(100, 37)]	93 [64]
	12	Significant	8 [4]	1 [1]	(83, 100)	
		Insignificant	0 [4]	5 [5]	[(83, 50)]	93 [64]
	18	Significant	8 [4]	0 [0]	(100, 100)	
		Insignificant	0 [4]	6 [6]	[(100, 50)]	100 [71]
60-70	12	Significant	5 [4]	1 [1]	(90, 62)	
		Insignificant	3 [4]	9 [9]	[(90, 50)]	78 [72]
	18	Significant	5 [4]	0 [0]	(100, 62)	
		Insignificant	3 [4]	10 [10]	[(100, 50)]	83 [78]
80-100	12	Significant	2 [1]	0 [0]	(100,100)	
		Insignificant	0 [1]	3 [3]	[(100, 50)]	100 [80]
	18	Significant	2 [1]	0 [0]	(100,100)	
		Insignificant	0 [1]	3 [3]	[(100, 50)]	100 [80]
All	6	Significant	16 [4]	0 [0]	(100, 84)	
		Insignificant	3 [15]	17 [17]	[(100, 21)]	92 [58]
	12	Significant	22 [11]	2 [2]	(91, 88)	
		Insignificant	3 [14]	20 [20]	[(91, 44)]	89 [66]
	18	Significant	22 [10]	0 [0]	(100, 88)	
		Insignificant	3 [15]	22 [22]	[(100, 40)]	94 [68]

These (SP, SE, concordance) values are (100%, 84%, 92%), (91%, 88%, 89%), and (100%, 88%, 94%), respectively.

The results show that the SP and SE of our comprehensive decision algorithm with this particular data set are highly competitive with those of various study-based algorithms in current practice. Also, the results are consistent with those of the model-based component provided in Table 1. These findings confirm with this data set that the comprehensive decision algorithm incorporating the component based on probability modeling has practical potential to be effective in lessening both over- and under-treatment.

Discussion

The findings here show that the comprehensive decision algorithm with a model-based component performs very well with the present prostatectomy dataset. For the 6-core biopsies, which were used only for prostate volumes 20 cc-50 cc, the SP is 100% in all cases and the SE ranged from 75% to 87%. For the 12-core biopsies, used for volumes 40 cc-100 cc, the SP ranged from 83% to 100% and the SE was 100% in all cases except for one (60 cc-70 cc with SE = 62%). For the 18-core biopsies, used for volumes 40 cc-100 cc, the SP is 100% in all cases and the SE is 100% in all cases except for one (60 cc-70 cc with SE = 62%). Looking at all cases together for the 6-core, 12-core, and 18-core biopsies, the corresponding (SP, SE) values are (100%, 84%), (91%, 88%), and (100%, 88%), respectively. This favorable finding supports the fundamental design of our comprehensive decision algorithm, which prioritizes on SP in order to avoid over-treatment, uses more cores with larger prostates to obtain reasonable SE in order to avoid under-treatment, uses fewer cores with smaller prostates, and includes a component based on the number of positive cores as data. It is also seen from Table 3 that by itself the latter component is similar in SP but lower in SE, as expected.

Being derived using a probability model, rather than from a particular dataset, our decision algorithm possesses generality of potential application. It is reassuring to see that it performs well with this particular data set, the only one investigated to date, and this suggests going forward with validation studies using other available data sets, hopefully including prostate volumes 110 cc-200 cc.

For comparison with other methods in current practice, a review of leading methods[11] indicates (SP, SE) such as (100%, 14%), **(99%, 70%)**, (99%, 34%), (98%, 53%), (98%, 52%), (98%, 23%), **(97%, 67%)**, (96%, 50%), (96%, 27%), (95%, 56%), (89%, 33%), (78%, 71%), and (75%, 77%), with the two in bold including prostate volume as an input in the statistical model. These were derived, typically, by fitting logistic regression models to particular data sets, the different "optimal" fitted models differing across the different data sets of patients, thus making it problematic to decide which to use with a given new patient. Also, these concern a range of only 6 to 12 biopsy cores. In contrast, the proposed comprehensive algorithm not only compares well in (SP, SE) but also, very importantly, properly adjusts for prostate volume.

The following guideline follows from Table 1: For prostate volume 10 cc-30 cc, 6 biopsy cores are recommended; for prostate volume 40 cc-50 cc, 6, 12 or 18 biopsy cores are recommended; for prostate volume 60 cc-100 cc, 12 or 18 biopsy cores are recommended; and for prostate volume 110 cc-200 cc, 18 or 24 biopsy cores are recommended.

Regarding the recommendation of performing only 6 cores for prostate volume 10 cc-30 cc, we recognize that this number would seem too low for many clinicians. However, strong justification follows from Table 1, which shows that using 12 cores instead of 6 for this prostate volume range increases significantly the burden to patients without actually improving the best SP-SE trade-off. Specifically, the (SP, SE) values for 12 cores versus 6 are (91%, 63%) versus (95%, 53%) for volume 10 cc, (92%, 75%) versus (89%, 73%) for volume 20 cc, and (97%, 52%) versus (95%, 45%) for volume 30 cc. It is thus important for clinicians to at least consider this guideline and its implications, in each individual clinical context. Also, with the development of pre-biopsy MRI, a 12-core systematic biopsy may not be appropriate for all patients. In patients with small prostate, normal DRE and non-suspicious pre-biopsy MRI, 6-core systematic biopsy may be sufficient, as proposed in this algorithm. For future research, the performance for other numbers of cores between 6 and 12, for this prostate volume range, can be investigated.

The particular choices of total tumor volume, T = 0.25 cc and T = 2.0 cc to obtain specificity and sensitivity, respectively, indeed may be considered arbitrary in the derivation of the proposed model-based decision algorithm in this work. However, in the development of this work, we also considered other total tumor volume values $T < 0.5$ for SP and > 1.0 for SE, and arrived at generally similar recommendations. For practical purposes, the choices T = 0.25 cc and T = 2.0 cc, respectively, may be taken as judicious options. In comparison with study-based guidelines with somewhat vague underpinnings, a model-based guideline with the underlying premises explicitly known offers a more precise orientation for the user of the guideline.

We recognize that biopsy protocols used for primary diagnosis of prostate cancer have changed over the last few years due to the development of MRI, which enables

detection of most high grade and large tumors.[12-22] Image fusion software currently available allows biopsy cores to be targeted within specific suspicious areas detected solely by MRI, whatever the gland volume. Studies have reported that MRI targeted biopsies significantly outperform conventional systematic biopsies in the detection of significant prostate cancer.[18,22] However, some studies have also recommended that systematic biopsies should not be omitted for optimal staging of disease, as long as negative predictive value for MRI is still imperfect.[18] Despite MRI having high diagnostic accuracy (about 95%) for diagnosing clinically significant prostate cancer, the MRI fusion targeted biopsy cannot replace systematic biopsy as confirmatory biopsy for men enrolled in active surveillance protocol.[17] We have reviewed the checklists for Standard of Reporting for MRI-targeted Biopsy Studies (START) criteria,[12] and it would be interesting to compare results from such studies with our findings. However, from some published studies, it is clear that fewer total number of cores are used in MRI-targeted biopsy protocols.[13]

Despite the evolution of biopsy protocols through the increased use of targeted MRI, the findings in this work are still applicable with patients who are potential candidates for active surveillance. Patients having normal prostate MRI and low risk cancer usually undergo systematic biopsies at 6 months. Also, many urologists still perform sole systematic biopsies without pre-biopsy MRI. In general, our results apply generally whenever a prostate cancer biopsy is to be undertaken, for whatever reason.

The model-based decision algorithm performs very well when validated with this actual prostatectomy data and is consistent with model-based expectations. This suggests its value in judicious practical application, particularly for patients with Gleason 6 or lower, and especially for interpretation of the challenging case of marginally positive biopsy outcomes. Also, the findings establish that additional modeling and additional validation studies, for possible further calibration and improvement of the decision algorithm, would be worthwhile. While the cohort is small relative to larger studies, this study examines a completely new decision algorithm not examined in any previous study. □

References

1. Bostwick DG, Qian J. High-grade prostatic intraepithelial neoplasia. *Mod Pathol* 2004;17(3):360-379.
2. Klotz L. Prostate cancer overdiagnosis and overtreatment. *Curr Opin Endocrinol Diabetes Obes* 2013;20(3):204-209.
3. Loeb S, Bjurlin MA, Nicholson J et al. Overdiagnosis and overtreatment of prostate cancer. *Eur Urol* 2014;65(6):1046-1055.
4. Chodak GW, Warren KS. Watchful waiting for prostate cancer: a review article. *Prostate Cancer Prostatic Dis* 2006;9(1):25-29.
5. Dahabreh IJ, Chung M, Balk EM et al. Active surveillance in men with localized prostate cancer: a systematic review. *Ann Intern Med* 2012;156(8):582-590.
6. Bill-Axelson A, Holmberg L, Garmo H, Rider JR et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014;370(10):932-942.
7. Serfling R, Ogola G. Probability modeling of the number of positive cores in a prostate cancer biopsy session, with applications. *Stat Med* 2016;35(3):424-454.
8. Mould RF. Introductory Medical Statistics. 3 ed. Bristol and Philadelphia: Institute of Physics Publishing; 1998.
9. Delongchamps NB, de la Roza G, Jones R, Jumbelic M, Haas GP. Saturation biopsies on autopsied prostates for detecting and characterizing prostate cancer. *BJU Int* 2009;103(1):49-54.
10. Serfling R, Shulman M, Thompson GL et al. Quantifying the impact of prostate volumes, number of biopsy cores and 5alpha-reductase inhibitor therapy on the probability of prostate cancer detection using mathematical modeling. *J Urol* 2007;177(6):2352-2356.
11. Anast JW, Andriole GL, Bismar TA, Yan Y, Humphrey PA. Relating biopsy and clinical variables to radical prostatectomy findings: can insignificant and advanced prostate cancer be predicted in a screening population? *Urology* 2004;64(3):544-550.
12. Moore CM, Kasivisvanathan V, Eggener S et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. *Eur Urol* 2013;64(4):544-552.
13. Robertson NL, Emberton M, Moore CM. MRI-targeted prostate biopsy: a review of technique and results. *Nat Rev Urol* 2013; 10(10):589-597.
14. Hu JC, Chang E, Natarajan S et al. Targeted prostate biopsy in select men for active surveillance: do the Epstein criteria still apply? *J Urol* 2014;192(2):385-390.
15. Grenabo Bergdahl A, Wilderang U, Aus G et al. Role of magnetic resonance imaging in prostate cancer screening: a pilot study within the Goteborg randomised screening trial. *Eur Urol* 2016; 70(4):566-573.
16. Peltier A, Aoun F, Lemort M, Kwizera F, Paesmans M, Van Velthoven R. MRI-targeted biopsies versus systematic transrectal ultrasound guided biopsies for the diagnosis of localized prostate cancer in biopsy naive men. *Biomed Res Int* 2015;2015:571708.
17. Pepe P, Garufi A, Priolo G, Pennisi M. Can MRI/TRUS fusion targeted biopsy replace saturation prostate biopsy in the re-evaluation of men in active surveillance? *World J Urol* 2016;34(9):1249-1253.
18. Radtke JP, Teber D, Hohenfellner M, Hadaschik BA. The current and future role of magnetic resonance imaging in prostate cancer detection and management. *Transl Androl Urol* 2015;4(3):326-341.
19. Toner L, Weerakoon M, Bolton DM, Ryan A, Katelaris N, Lawrentschuk N. Magnetic resonance imaging for prostate cancer: Comparative studies including radical prostatectomy specimens and template transperineal biopsy. *Prostate Int* 2015;3(4):107-114.
20. Turkbey B, Brown AM, Sankineni S, Wood BJ, Pinto PA, Choyke PL. Multiparametric prostate magnetic resonance imaging in the evaluation of prostate cancer. *CA Cancer J Clin* 2016;66(4):326-336.
21. Valerio M, McCartan N, Freeman A, Punwani S, Emberton M, Ahmed HU. Visually directed vs. software-based targeted biopsy compared to transperineal template mapping biopsy in the detection of clinically significant prostate cancer. *Urol Oncol* 2015;33(10):424.e9-e16.
22. Radtke JP, Schwab C, Wolf MB et al. Multiparametric magnetic resonance imaging (MRI) and MRI-transrectal ultrasound fusion biopsy for index tumor detection: correlation with radical prostatectomy specimen. *Eur Urol* 2016;70(5):846-853.