Evaluation of a Novel High-Resolution Diffusion-Weighted MRI Sequence

[redacted]

[redacted]

Biostatistician: [redacted]

Study Intervention: High-resolution MRI

Funding Source: NIH

Amended version: **4/7/2020**

Initial version: 1/8/2017

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

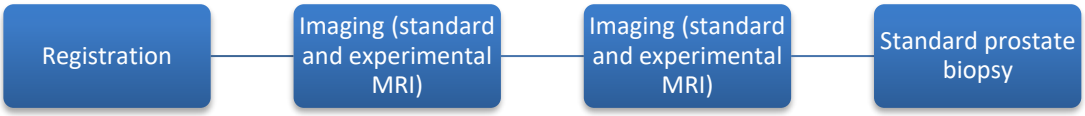
Date: _____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADC	Apparent diffusion coefficient
AS	Active surveillance
AUC	Area under the curve
DCE	Dynamic contrast enhanced
DWI	Diffusion-weighted imaging
EPI	Echo-planar imaging
hrMRI	High resolution MRI
mpMRI	Multiparametric MRI
MRI	Magnetic resonance imaging
PI-RADS	Prostate Imaging-Reporting and Data System
ROI	Region of interest
TRUS	Transrectal ultrasound

STUDY SCHEMA



STUDY SUMMARY

Title	Evaluation of a Novel High-Resolution MRI Sequence
Short Title	High resolution MRI
Protocol Number	
Phase	Not applicable
Methodology	Single arm, paired imaging
Study Duration	3 years
Study Center(s)	Cedars Sinai Medical Center
Objectives	To determine if enhanced prostate imaging (high resolution MRI) will detect prostate lesions not seen on standard MRI.
Number of Subjects	80 Study Subjects

Diagnosis and Main Inclusion Criteria	Inclusion Criteria:
	• Age over 18 years
	• Patients diagnosed with clinically localized prostate cancer
	• Low or Low-intermediate Risk Prostate cancer[1] defined as:
	  ○ Pre-operative PSA ≤ 20.0 ng/ml
	  ○ Clinical stage cT1 or cT2
	  ○ Gleason score 3+3 or 3+4
	• Patients choosing AS or already on AS as primary management strategy
	• No previous treatment for prostate cancer with radiotherapy, chemotherapy, or hormonal therapy
	• No contraindications for gadolinium enhanced MRI

Study Imaging	Standard multiparametric prostate MRI with high resolution diffusion weighted imaging
Control Imaging	Standard multiparametric prostate MRI
Reference standard	Evidence of disease progression on standard 12-core ultrasound-guided prostate biopsy.
Statistical analysis	Our hypothesis is that changes in tumor size or apparent diffusion coefficient (ADC) on high resolution MRI will predict presence of biopsy criteria for disease progression. 59 patients achieve 91% power to detect a 0.285 cm^3 difference (between patients progressing and patients not progressing) in the mean change in tumor volume at the two-sided two-sample t-test with a 0.05 level of significance. With respect to change in ADC, 59 patients achieve 80% power to detect a difference in the mean change ADC around 0.07 at the two-sided two-sample t-test with a 0.05 level of significance. This corresponds to about a 50% increase in ADC between the two groups of patients.

1.0 STUDY ABSTRACT

We developed 3D magnetization-prepared high resolution diffusion weighted imaging (DWI) to overcome the major problems associated with 2D conventional single-shot echo-planar imaging (EPI) technique for prostate imaging. Major technical novelties are:

- Magnetization-prepared DWI was optimized to improve image quality. Standard DWI uses single-shot EPI acquisition, which inherently results in relatively poor image quality with apparent image artifacts, such as streaking (high image intensity bands) and geometric distortion (round objects may appear oval)[2], which may hinder the detection of small lesions. Magnetization-prepared DWI allows separate diffusion-preparation and data acquisition, which in turn allows segmented/multi-shot (vs single-shot) data acquisition and more robust acquisition techniques such as steady-state free precession (SSFP) or turbo-spin-echo (TSE) (vs EPI), which **eliminate typical image artifacts** associated with single-shot EPI.[2] An optimized **first-order motion-compensated diffusion preparation scheme** was developed to minimize the diffusion preparation time, which reduced T2 decay and minimize signal loss due to motion.
- 3D DWI was developed to achieve high and isotropic spatial resolution: While single-shot EPI acquisition is limited to 2D imaging with low in-plane resolution and thick slices (2.1x2.1x3.5 mm^3), segmented/mult-shot SSFP or TSE acquisitions allow for contiguous slices of the entire prostate in one scan volume with isotropic resolution of 1.2x1.2x1.2 mm^3, represents a **9-fold increase** over the conventional protocol. 3D DWI with high and isotropic spatial resolution is critically important for accurate measurement of lesion size and reducing partial voluming for **more accurate ADC quantification**.
- Hybrid Cartesian-radial readout and real-time-feedback self-gating **minimized the effects of motion**: Radial sampling was used to provide inherent motion robustness of images and allow for additional accelerated data acquisition through iterative non-Cartesian reconstruction. A self-gating signal was acquired to keep track of patient motion and data acquired during apparent motion was excluded from image reconstruction prospectively and the data was immediately reacquired.

This high resolution MRI (hrMRI), along with stand MRI (sMRI) will be obtained at baseline and again in approximately 1 year in patients on prostate cancer active surveillance. Changes in lesion size and ADC values will be assessed on the serial studies. This study evaluates the hypothesis that hrMRI will detect changes that sMRI cannot detect and that these changes will correlate with prostate cancer progression as determined on prostate biopsy.

2.0 BACKGROUND AND RATIONALE

Multiparametric MRI

Multiparametric MRI combining T2-weighted, diffusion-weighted, and dynamic contrast enhanced (DCE) images is commonly employed for detection and localization of prostate lesions.[3, 4] Diffusion-weighted imaging (DWI) is sensitive to the diffusion of water molecules interacting with surrounding macromolecules. DWI, which provides a quantitative biological parameter called apparent diffusion coefficient (ADC) value, is a robust MRI parameter for differentiating benign and malignant prostate tissue.[5, 6] In fact, the latest version of the Prostate Imaging-Reporting and Data System (PI-RADS) scoring system relies almost exclusively on DWI to identify tumors in the peripheral zone, which is where the vast majority of prostate cancers form. Findings on T2 images are not used to identify cancer, and DCE images are only used to differentiate between some PI-RADS 3 and 4 lesions. In a pilot study of prostate cancer AS, DW-MRI was useful for detecting progression of Gleason score based on changes in ADC value.[7] Tumor size is another important clinical criterion for defining low risk prostate cancer, and tumor size based on DWI has been shown to crudely predict low risk prostate cancer.[8] **However, conventional DWI using single-shot echo-planar imaging is unable to detect small tumors[9], low grade tumors, or small changes in tumor size on serial imaging.** Approximately 20% of small, low grade tumors found in men on AS are detected on modern prostate MRI. [10]

High Resolution MRI

We introduce a new three-dimensional (3D) high-resolution diffusion-weighted imaging sequence (HR-DWI), which improves image quality while conferring at least a 5-fold improvement in resolution when compared to standard two-dimensional (2D) DWI (S-DWI). This novel 3D DWI technique has been developed by our team and can be applied on existing 1.5T or 3T MRI systems. S-DWI suffers from two important limitations. a) It uses single-shot echo-planar imaging (EPI) for data acquisition, which produces magnetic susceptibility induced streaking artifacts and geometric distortions so that round objects may appear oval. b) The relatively low signal-to-noise ratio and 2D image acquisition with S-DWI limit spatial resolution, which is defined by the minimum distance between two objects required to resolve them uniquely. Our HR-DWI overcomes these limitations by using magnetization prepared, multi-shot, turbo-spin-echo acquisition, which improves signal-to-noise ratio (SNR), spatial resolution, and image quality, and eliminates geometric distortions and streaking artifacts associated with EPI.

Preliminary studies

In preliminary studies assessing the performance of our HR-DWI in a prospective pilot trial of prostate cancer AS patients, the technique could detect tumors not seen on S-DWI and measure ADC, which correlates with grade.[2, 11] This is important because the long-term natural history of small prostate cancers invisible to S-DWI has never been prospectively defined, in part due to lack of adequate imaging technology. In the era of molecular diagnostics and next-generation sequencing, an important step in understanding the biology of these lesions is to develop technologies to image and characterize these lesions. Importance of HR-DWI includes:

- Better imaging will allow these lesions to be monitored serially and **targeted for biopsy**, providing tissue for both histologic and molecular characterization.
- Higher resolution imaging will **better delineate tumor boundaries**, which can improve tumor staging and identify margins during partial-gland ablation by cryotherapy or high intensity focused ultrasound (HIFU), which was approved in 2015 by the U.S. FDA.

- Improved imaging resolution will allow for **more accurate measurement of tumor size and ADC, and detection of small changes in size or grade over time**. Standard prostate DWI has poor resolution; therefore, tumor growth kinetics have never been accepted as clinical criteria for cancer progression while on AS. If tumor growth kinetics or changes in grade determined by ADC prove prognostic, AS can rely less on serial transrectal biopsies, which can lead to serious complications.

Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men and the second leading cause of cancer death in US men.[12] In the US, there are more than 200,000 newly diagnosed cases and nearly 40,000 deaths from prostate cancer annually. The lifetime risk of developing prostate cancer is one in seven men.[13] The vast majority of men diagnosed with prostate cancer do not die of their disease even when curative therapy is not administered.[14, 15] However, historically approximately 90% of men diagnosed with localized prostate cancer elect therapies such as radical prostatectomy or radiotherapy.[16] The problem is that definitive therapies for prostate cancer can negatively impact quality-of-life by producing side-effects such as permanent urinary incontinence (7-14% post-treatment) and erectile dysfunction (44-51% post-treatment).[17] Therefore overtreatment of prostate cancer has broad impact on quality of life and health care costs. The U.S. Preventive Services Task Force (USPSTF) recommends against PSA-based screening for all U.S. men; they argue that screening provides little to no benefit for most men while harming many men.[18] On the other hand, the American Urologic Association (AUA) maintains that prostate cancer screening and risk assessment should be offered to asymptomatic men 55-69 years of age.[19]

Both opponents and advocates of PSA-based screening acknowledge that screening increases the detection of prostate cancer. An important assumption underlying the USPSTF recommendation against screening is that men with indolent cancer will continue to receive unnecessary treatment. An important assumption underlying the AUA recommendation for screening is that patients and physicians will be able to uncouple the diagnosis of prostate cancer from treatment. For example, men at highest risk for death from prostate cancer will receive treatment. All other men will undergo a period of active surveillance (AS). During followup on AS, men with evidence of high risk disease or cancer progression are offered definitive local therapy; however, men who continue to have low risk cancer can delay or completely avoid treatment. A barrier to AS is that clinical tools for risk-stratifying and monitoring men with newly diagnosed prostate cancer have limited accuracy. Prostate cancers are multifocal and biopsies are vulnerable to sampling error. Transrectal ultrasound-guided (TRUS) biopsy remains the gold standard for diagnosing prostate cancer and monitoring patients on AS. However, the standard prostate biopsy may miss clinically significant disease. TRUS biopsy undergrades and understages the cancer in approximately a third of patients.[20, 21] Furthermore, TRUS biopsy is accompanied by complications such as systemic infection, bleeding, and transient erectile dysfunction.[22] **There is a clear need for innovations to reduce the clinical burden of diagnosing and monitoring prostate cancer.**

3.0 STUDY DESIGN:

A. Overview

Prostate cancer is the rare malignancy where there is no imaging strategy to serially monitor the tumor. MRI, which is the best tool we have for imaging the prostate, cannot detect most tumors and does not have the resolution to detect subtle changes in tumor size or tumor characteristic. Therefore, followup during AS relies on serial transrectal biopsies. An effective imaging strategy will decrease the clinical burden of AS. This prospective trial will compare the effectiveness of high resolution MRI (hrMRI) and standard MRI (sMRI) for serially monitoring prostate tumors for clinical progression, which is an indication for definitive local therapies such as radical prostatectomy and external beam radiotherapy. **We test the hypothesis that hrMRI may detect changes in tumor size or ADC value, which will predict clinical progression as defined by biopsy criteria.**

B. Study Population

The study population for recruitment will be patients at Cedars-Sinai Medical Center with prostate cancer on active surveillance.

C. Inclusion/Exclusion Criteria

Inclusion Criteria:

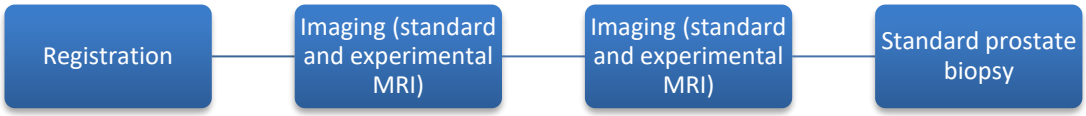
- Age over 18 years
- Patients diagnosed with clinically localized prostate cancer
- Low or Low-intermediate Risk Prostate cancer[1] defined as:
  - Pre-operative PSA $\leq$ 20.0 ng/ml
  - Clinical stage cT1 or cT2
  - Gleason score 3+3 or 3+4
- Patients choosing AS or already on AS as primary management strategy
- No previous treatment for prostate cancer with radiotherapy, chemotherapy, or hormonal therapy
- No contraindications for gadolinium enhanced MRI

D. Study endpoints

Primary Endpoint: evidence of disease progression as defined by any of the following:

- Increase in Gleason score from 3 + 3 to Gleason sum 7 on biopsy
- Gleason score 4+3 on biopsy
- Gleason sum 8-10 on biopsy
- $\geq$ 3 Increase in number of positive cores
- Progression to nodal or bone involvement

E. Study Design



The study enrolls patients with low and low-intermediate risk prostate cancer. The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer list AS as an option for these patients.[1] There is no proven standard for monitoring patients on AS. The NCCN recommends a standard 12-core prostate biopsy every 1-2 years, at the discretion of the treating physicians depending on risk category and length of stable followup on AS. All Patients enrolling on the study will undergo standard (control) MRI (sMRI) and experimental High-Resolution MRI (hrMRI) at the time of study enrollment and again in 12 months (+/-2 months). The patients then undergo a standard ultrasound guided 12-core prostate biopsy, where prostate ultrasound is used to sample 2 cores from the left and right lobes at the base, midgland and apex. At the discretion of the treating physician, the 2nd MRI and biopsy may be performed early if disease progression is suspected due to increasing PSA or adverse change in prostate exam. These for-cause MRI and biopsies will be used for the final analysis if the interval between MRIs is at least 5 months.

All MRI images will be read according to PI-RADS (version 2). All lesions with PI-RADS greater than or equal to 3 will be considered suspicious for cancer. A region of interest (ROI) application will be used. The circumference of a suspicious lesion will be drawn on each individual MRI slice. The lesion volume and average ADC will be calculated from the ROI's. At the discretion of the treating physician, the MRI images may be used to perform a MRI-ultrasound fusion biopsy of suspicious lesions, however, only the standard 12-core biopsy will be used for the statistical analysis.

Study calendar

Study Calendar	
Registration/consenting	
Standard and experimental MRI	
Standard and experimental MRI*	12 months after first MRI (+/- 2 months)
Prostate biopsy*	within 3 months of the 2nd MRI

* At the discretion of the treating physician, the 2nd MRI and biopsy may be performed early if disease progression is suspected due to increasing PSA or adverse change in prostate exam.

F. Study Risks

All agents administered to patients in this study are approved by the U.S. Food and Drug Administration. This study investigates a novel software-based MRI imaging protocol that improves image resolution.

Magnetic Resonance Imaging (MRI)

MRI imaging is among the least invasive of all imaging modalities. The U.S. Food and Drug Administration has labeled MR systems of up to 4.0 Tesla as having “non-significant risk” and currently there is no evidence that MR imaging causes any long-term or irreversible effects in human beings. However, there are certain risks, which are detailed below.

MRI imaging utilizes magnetic fields and radiofrequency fields, both of which can be harmful in certain situations. Magnetic fields can cause ferromagnetic implants or ferromagnetic foreign bodies, such as intracranial aneurysm clips, shrapnel, and intraocular metal chips to become dislodged and tear the surrounding soft tissue. Therefore, MRI imaging is contraindicated in persons with ferromagnetic implants or ferromagnetic foreign bodies. It is also contraindicated in persons with electrically, magnetically or mechanically activated implants because the magnetic field can cause these to function erratically. In addition, persons wearing metallic objects may be at danger for them becoming dangerous projectiles, due to them inadvertently becoming introduced into the magnetic field. All subjects will be prescreened carefully and all scanners are used in accordance with guidelines set by the Bureau of Radiological Health.

Gadolinium contrast (Gadavist

The intravenous contrast agent to be used in this study is gadolinium-based. The intravenous contrast has an excellent safety profile and is commonly used in MR studies. Allergic reactions are extremely rare, but may be more common in persons with a history of allergic reactions to iodinated contrast. Studies support a rate of serious allergy reactions of 1 in 20,000.

The most common side effect is bruising at the site of vein puncture, inflammation of the vein and infection; care will be taken to avoid these complications. Rare side effects are headache (5%), a coldness feeling on your arm where the needle was placed (2.8%), nausea (2.5%), dizziness (less than 2%), and vomiting (less than 1%). The use of gadolinium-based contrast agents in patients who already have serious kidney problems or who have a liver transplant may lead to a possibly fatal disease involving the skin, muscle and internal organs. This possibly fatal disease is called nephrogenic systemic fibrosis (NSF). Prior to giving a gadolinium-based contrast agent, we will ask about any history of kidney problems or liver transplant, and will test the health of the participant’s kidneys by a blood test. If there are known risk factors for developing this disease, the participant will not be eligible to receive contrast.

Cedars Sinai conducted a research study looking for gadolinium deposits in the brain of 119 patients who underwent at least 7 contrast enhanced scans. Approximately half the patients had all their scans performed with a contrast agent categorized as a macrocyclic molecule and the remainder of the patients had all their scans performed with a contrast agent categorized as a linear agent. Patients who received the linear agent had contrast agents in their brain but none of the patients who received the macrocyclic agent had brain deposits. All patients in this study will receive the macrocyclic contrast agent for the MRI studies.

Hypersensitivity to Medications - Occasionally, people have allergic reactions when taking any medication. Subjects may receive medications such as contrast. Hypersensitivity reactions may include symptoms such as shortness of breath, wheezing,

flushing, nasal congestion and skin rash. In most cases, initial symptoms occur within minutes of drug administration and quickly reverse themselves or resolve with prompt medical treatment.

In general, allergic reactions to medicines are more likely to occur in people who have allergies to other drugs, foods, or things in the environment. Subjects will be asked about any pre-existing allergies before administering any medications during the study.

Incidental Findings

Only noted clinically significant incidental findings will be communicated to the subject, per CSMC IRB and Legal Department approved policy, as a result of agreeing to undergo a research MRI scan. No reports or images will be provided to subjects and their medical records.

G. Statistical Analysis

Power. The progression rate used for the power calculations comes from the REDEEM trial, which was a phase III trial conducted at 65 academic medical centers to assess the role of a 5-alpha reductase inhibitor to decrease progression during AS.[23] The REDEEM trial followed patient for a total of 3 years. In the placebo group, the progression rate for patients already on active surveillance undergoing their 2nd surveillance biopsy was 20%. This is expected to be a conservative estimate for progression since the REDEEM trial only included low risk patients while our study allows for low intermediate risk patients, who have a higher risk of progression. The patients at 20% risk for progression drive our power calculation.

Preliminary data from 13 patients with a total of 14 Gleason score 6 lesions show a mean of 0.19 cm^3 and standard deviation of 0.19 cm^3. We expect to detect at least a 50% increase in tumor volume in the group who progress compared to the group of patients that do not progress relative to baseline. Assuming that the standard deviation at the biopsy/MRI is similar to the baseline biopsy/MRI, group sample sizes of 12 patients who progressed and 47 patients that do not progress achieve 91% power to detect a difference in the mean change tumor volume around 0.285 cm^3 at the two-sided two-sample t-test with a 0.05 level of significance. The estimate standard deviation of the difference in tumor size in each group (SDdiff) was estimated assuming the correlation coefficient measurements is 0. Since this correlation coefficient is likely to be positive, this power calculation is very conservative and much smaller mean change tumor volume can be detected. In fact, if this correlation coefficient equals to 0.6, then we can achieve 90% power to detect a mean change tumor volume around 0.18 cm^3. With respect to change in ADC, preliminary data show that the mean and SD of ADC are 0.2 and 0.05, respectively. Under similar assumptions for the correlation coefficient between the first and second measurements (corr = 0), group sample sizes of 12 patients who progressed and 47 patients that do not progress achieve 80% power to detect a difference in the mean change ADC around 0.07 at the two-sided two-sample t-test with a 0.05 level of significance. This corresponds to about a 50% increase in ADC between the two groups of patients.

Multivariable logistic regression model will be used to study the association between change in tumor size and ADC from the first and the second biopsy as assessed by imaging and disease progression adjusting for potential baseline characteristics such as PSA level, clinical stage, NCCN risk category, and size of prostate nodule. Tumor size

and ADC is measured by averaging the volumes or ADCs of all detectable lesions (PI-RADS 3 - 5). Secondary analyses include studying this association by considering changes of single lesions. Automatic variable selection methods such as backward and stepwise selection will be used as a guideline to identify sets of important predictors of progression. More rigorous approach based on a 4-step procedure outlined in Collett[24] will be employed. Several model checking diagnostics will be employed to ensure that the logistic model is appropriate.[25]

4.0 REFERENCES

1. National Comprehensive Cancer Network: Prostate Cancer (Version 1.2015). Accessed: May, 2015.

2. Nguyen, C., Sharif-Afshar, A. R., Fan, Z. et al.: 3D high-resolution diffusion-weighted MRI at 3T: Preliminary application in prostate cancer patients undergoing active surveillance protocol for low-risk prostate cancer. Magn Reson Med, **75:** 616, 2016

3. Lawrence, E. M., Gnanapragasam, V. J., Priest, A. N. et al.: The emerging role of diffusion-weighted MRI in prostate cancer management. Nat Rev Urol, **9:** 94, 2012

4. Outwater, E. K., Montilla-Soler, J. L.: Imaging of prostate carcinoma. Cancer Control, **20:** 161, 2013

5. Boesen, L., Chabanova, E., Logager, V. et al.: Apparent diffusion coefficient ratio correlates significantly with prostate cancer gleason score at final pathology. J Magn Reson Imaging, 2014

6. Jie, C., Rongbo, L., Ping, T.: The value of diffusion-weighted imaging in the detection of prostate cancer: a meta-analysis. Eur Radiol, **24:** 1929, 2014

7. Morgan, V. A., Riches, S. F., Thomas, K. et al.: Diffusion-weighted magnetic resonance imaging for monitoring prostate cancer progression in patients managed by active surveillance. Br J Radiol, **84:** 31, 2011

8. Lee, D. H., Koo, K. C., Lee, S. H. et al.: Tumor lesion diameter on diffusion weighted magnetic resonance imaging could help predict insignificant prostate cancer in patients eligible for active surveillance: preliminary analysis. J Urol, **190:** 1213, 2013

9. van As, N. J., de Souza, N. M., Riches, S. F. et al.: A study of diffusion-weighted magnetic resonance imaging in men with untreated localised prostate cancer on active surveillance. Eur Urol, **56:** 981, 2009

10. Le, J. D., Tan, N., Shkolyar, E. et al.: Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol, **67:** 569, 2015

11. Sharif-Afshar, A. R., Nguyen, C., Feng, T. S. et al.: Prospective Pilot Trial to Evaluate a High Resolution Diffusion-Weighted MRI in Prostate Cancer Patients. EBioMedicine, **7:** 80, 2016

12. Siegel, R. L., Miller, K. D., Jemal, A.: Cancer statistics, 2015. CA Cancer J Clin, **65:** 5, 2015

13. American Cancer Society: Cancer Facts & Figures. Atlanta, GA, American Cancer Society http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. Accessed: March 15, 2015.

14. Albertsen, P. C., Hanley, J. A., Fine, J.: 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA, **293:** 2095, 2005

15. Bill-Axelson, A., Holmberg, L., Ruutu, M. et al.: Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med, **364:** 1708, 2011

16. Ip, S., Dahabreh, I. J., Chung, M. et al.: An Evidence Review of Active Surveillance in Men With Localized Prostate Cancer. Rockville, MD: Agency for Healthcare Research and Quality, 2011

17. Sanda, M. G., Dunn, R. L., Michalski, J. et al.: Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med, **358:** 1250, 2008

18. Screening for Prostate Cancer. http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm, U.S. Preventive Services Task Force http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm. Accessed: May 22, 2012.

19. Carter, H. B., Albertsen, P. C., Barry, M. J. et al.: Early detection of prostate cancer: AUA Guideline. J Urol, **190:** 419, 2013

20. Cohen, M. S., Hanley, R. S., Kurteva, T. et al.: Comparing the Gleason prostate biopsy and Gleason prostatectomy grading system: the Lahey Clinic Medical Center experience and an international meta-analysis. Eur Urol, **54:** 371, 2008

21. Kawachi, M. H., Bahnson, R. R., Barry, M. et al.: NCCN clinical practice guidelines in oncology: prostate cancer early detection. J Natl Compr Canc Netw, **8:** 240, 2010

22. Loeb, S., Vellekoop, A., Ahmed, H. U. et al.: Systematic review of complications of prostate biopsy. Eur Urol, **64:** 876, 2013

23. Fleshner, N. E., Lucia, M. S., Egerdie, B. et al.: Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. Lancet, **379:** 1103, 2012

24. Collett, D.: Modeling survival data in medical research: Chapman and Hall, 2003

25. Hosmer, D. W., Lemeshow, S.: Applied Logistic Regression, 2nd ed. New York, NY: Wiley, 2000

26. Kromrey ML, Liedtke KR, et al. "Intravenous injection of gadobutrol in an epidemiological study group did not lead to a difference in relative signal intensities of certain brain structures after 5 years." European Radiology. 2016 May 24.

27. Radbruch A, Weberling LD, et al. "High-signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evaluation of the macrocyclic gadolinium-based contrast agent gadobutrol."