MRI of the Prostate: Recommendations on Patient Preparation and Scanning Protocol

MRT der Prostata: Empfehlungen zur Vorbereitung und Durchführung

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ABSTRACT
The Working Group Uroradiology and Urogenital Diagnosis of the German Roentgen Society has developed uniform recommendations for the preparation and implementation of prostate MRI. In the first part detailed recommendations are given in tabular form regarding 1. anamnestic data before prostate MRI, 2. termination of examinations and preparation of examinations, 3. examination protocol and 4. MRI-guided in-bore biopsy. In the second part, the recommendations are discussed in detail and relevant background information is provided.

Key Points:
- Uniform recommendations for prostate MRI has been developed from the Working Group Uroradiology and Urogenital Diagnosis of the German Roentgen Society.
- Necessary anamnestic data, recommendations for termination of examinations and preparation of examinations, examination protocol and MRI guided in-bore biopsy are detailed expressed and documented.

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ZUSAMMENFASSUNG

Introduction
MRI of the prostate has become an established part of routine diagnostic radiology at hospitals and private practices in Germany. Rapid technical and scientific development in this area requires constant updating and adjustment of radiological procedures. Therefore, at the German Congress of Radiology in 2015, the Uroradiology and Urogenital Diagnosis Working Group of the German Roentgen Society set the goal of formulating standardized recommendations for preparing and performing MRI examination of the prostate based on the latest technical and scientific data. All centers clinically and scientifically active in this area were invited to participate in the general assembly. A total of 9 centers par-

A questionnaire was created in a first step and was revised by the participating centers and served as a basis for discussion. During 8 90-minute teleconferences and multiple discussions at conventions and per e-mail, the following recommendations were formulated in consensus under consideration of the current literature (see background information). The examination parameters were intentionally restricted to slice thickness, in-plane resolution and a few additional parameters that are important for examination quality.

It should be emphasized at this point that the recommendations are provided for general orientation purposes and must be adapted to the individual conditions (Table 1).

### Background information

#### Anamnestic information prior to MRI of the prostate PSA

Determination of the serum prostate-specific antigen (PSA) value is an established method for the early detection of prostate cancer. It is recommended in the S3 guidelines for men starting at age 45. The probability of the presence of prostate cancer increases as the PSA value increases. The PSA value, possibly also the ratio between the free and total PSA value and, if available, information regarding the PSA curve and PSA doubling time should be specified for every MRI examination [1].

#### Previous biopsies

A biopsy results in hemorrhage in the parenchyma. This has low signal intensity on the T2w image and high signal intensity on

### Table 1

<table>
<thead>
<tr>
<th>Detailed recommendations to anamnestic data before prostate MRI, termination of examinations and preparation of examinations, examination protocol and MRI-guided in-bore biopsy.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Anamnestic information prior to MRI of the prostate</strong></td>
</tr>
<tr>
<td><strong>1.1. PSA</strong></td>
</tr>
<tr>
<td><strong>1.2. Previous biopsies</strong></td>
</tr>
<tr>
<td><strong>1.3. Histological results</strong></td>
</tr>
<tr>
<td><strong>1.4. Additional information</strong></td>
</tr>
<tr>
<td><strong>1.5. Creatinine and eGFR</strong></td>
</tr>
<tr>
<td><strong>2. Examination scheduling and preparation</strong></td>
</tr>
<tr>
<td><strong>2.1. Time of examination</strong></td>
</tr>
<tr>
<td><strong>2.2. Antispasmodic</strong></td>
</tr>
<tr>
<td><strong>2.3. Emptying the rectum</strong></td>
</tr>
<tr>
<td><strong>2.4. Abstinence</strong></td>
</tr>
<tr>
<td><strong>3. Examination protocol</strong></td>
</tr>
<tr>
<td><strong>For detection, staging, active monitoring, diagnosis of recurrence after radiotherapy and prostatectomy, an identical standardized current protocol both for 1.5 T and 3 T should be used. There are differences when using an endorectal coil. To ensure consistently high image quality, the sequence parameters should be adapted according to the design of the endorectal coil. Note: Protocols are to be adapted as needed to the requirements of the Associations of Statutory Health Insurance Physicians</strong></td>
</tr>
<tr>
<td><strong>3.1. Morphological T2w TSE/ FSE sequences</strong></td>
</tr>
<tr>
<td>• Axial: SD 3 mm, in-plane resolution ≤ 0.5 × 0.5 mm</td>
</tr>
<tr>
<td>• Sagittal: SD 3 mm, in-plane resolution ≤ 0.7 × 0.7 mm</td>
</tr>
<tr>
<td>• Coronal: SD 3 mm, in-plane resolution ≤ 0.7 × 0.7 mm</td>
</tr>
</tbody>
</table>
### 3.2. DWI, DCE-MRI, 1H-MRS

To increase diagnostic accuracy, diffusion-weighted imaging (DWI) and at least one additional functional sequence should be included in the protocol. The currently established methods are dynamic contrast-enhanced MRI (DCE-MRI) and 1H-MR spectroscopy (1H-MRS).

**DWI**
- DWI should be acquired axially:
  - SD 3 mm, in-plane resolution ≤ 2.0 × 2.0 mm
- At least 2 different b-values should be measured. A b-value should be between 50 – 200 mm/s² and another value between 800 – 1000 mm/s². In addition, a higher b-value ≥ 1400 mm/s² can be measured or calculated.

**DCE-MRI**
- DCE-MRI should be acquired axially:
  - SD 3 mm, in-plane resolution ≤ 2.0 × 2.0 mm
- The temporal resolution should be at least 9 s, preferably ≤ 6 s. The flow of contrast agent and the subsequent NaCl bolus should be ≥ 2.0 ml/s.
- With the SI-t curves of DCE-MRI, calculated pharmacokinetic parameter maps can be used for diagnosis provided that the technical requirements are met and the necessary expertise is available.

**1H-MRS**
- 1H-MRS should be acquired as a 3 D spin echo sequence. The entire peripheral zone should be included in the region of interest (ROI) and the volume of interest (VOI) should be significantly larger than the ROI. The 3 D acquisition matrix should be at least
  - 8 × 8 × 8 voxels (interpolation to up to 16 × 16 × 16 voxels should be targeted).
- The influence of tissues outside the prostate should be minimized by outer volume suppression (OVS). Signal contributions of water and lipids should be minimized.
- The following repetition times (TR) and echo times (TE) have proven particularly useful depending on the field strength:
  - 1.5 T: TR 1000 ms and TE 130 ms
  - 3.0 T: TR up to 1000 ms and TE 145 ms

### 3.3. T1w TSE/FSE sequence

To evaluate bone, lymph node, and the prostate with respect to the presence of bleeding, for example, a T1w-TSE sequence should be acquired axially and the entire pelvis from the aortic bifurcation to the pelvic floor should be visualized.
- SD ≤ 5 mm, in-plane resolution ≤ 0.8 × 0.8 mm
- To increase sensitivity, a diffusion-weighted sequence or an axial fat-saturated T1w-GE sequence can additionally be performed after contrast administration.

### 3.4. Endorectal coil

At 1.5 T, the combined endorectal body phased-array coil increases the signal-to-noise ratio while using an identical technique and identical sequence structure. If no endorectal coil is used/can be used, the parameters of the sequence should be adapted so that the same image quality is achieved. It must be taken into consideration that there are differences in image quality depending on the MRI unit and coils that are used with similar to identical sequence parameters.
- At 3.0 T, a combined endorectal body phased-array coil can be used when the goal is to improve image quality for the evaluation of extracapsular growth and for the characterization of prostate carcinomas.
- When using an endorectal coil, it should be filled with air.

For the diagnosis of recurrence after prostatectomy, no endorectal coil should be used since the region of anastomosis as a site of frequent relapse cannot be reliably evaluated due to susceptibility artifacts.

### 3.5. Further sequences

**T2w-3D multiecho sequences with variable small refocusing flip angles**

The contrast properties of this sequence have not been sufficiently examined for diagnosis compared to 2D-T2w-TSE sequences. Therefore and due to the increased susceptibility to motion artifacts, this sequence should not be used for diagnosis. Due to the isotropic voxels, this sequence can however be advantageous for fusion with other imaging methods (e.g. ultrasound).

**Diffusion tensor imaging and diffusion kurtosis imaging**

Higher diffusion models are the object of research and have not yet been sufficiently evaluated. The present data does not show a significant advantage of these models compared to the models used in the clinical routine. Therefore, they should not be used for diagnosis.

### 4. MRI-guided in-bore biopsy

#### 4.1. Laboratory

Prior to MRI (in-bore) biopsy, the bleeding history should be recorded in a standardized manner. Current laboratory parameters (INR, pTT and thrombocytes per volume unit) can be determined.

**Prior to biopsy, the patient should be questioned with regard to “burning during urination”.

#### 4.2. Anticoagulants

ASS at a dose of 100 mg p. o. per day can continue to be taken. A pause in Marcumar therapy is recommended but is not absolutely necessary and should be evaluated on an interdisciplinary manner.

#### 4.3. Antibiotics

Transrectal biopsy should be performed under antibiotic therapy.

#### 4.4. Miscellaneous

Biopsy should be performed under anesthesia (e.g. local anesthesia with lidocaine gel).
the T1w image. A hemorrhage thus changes the initial images of dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted imaging (DWI). The changes can be detectable many months after biopsy and can complicate tumor detection. Therefore, the time at which the biopsy was performed should be indicated [2]. Moreover, the number of biopsy specimens and the biopsy site, if available, should be specified [1].

**Histological results**

With a previously negative prostate biopsy, the probability of a tumor diagnosis in a new systematic biopsy decreases. Prostate MRI for tumor detection in combination with a targeted biopsy can increase the detection rate in these cases. Therefore, prostate MRI is particularly useful after a previous negative biopsy. In the case of a positive biopsy, the number of positive core biopsies, the location of the positive core biopsies, the Gleason grade of the tumor, and, if available, the size/infiltration of the tumor in the core biopsy specimen should be specified. Therefore, a correlation with the MRI finding is possible. On the one hand, the presence of additional tumor foci can be detected and on the other hand it can be determined whether the present biopsy was representative.

**Additional information**

Hormone therapy: The prostate is an androgen-sensitive organ. Hormone therapy results in decreased activity of the gland function. MRI shows a reduction in prostate volume and signal reduction of the gland on the T2w image. Delineation of the prostate zones is more difficult or impossible. The effects of hormone therapy complicate tumor detection on the T2w image and in DWI. Tumors are typically significantly smaller under hormone therapy. The effects of hormone therapy on the prostate and also on prostate cancer are typically noticeable after only 4 weeks of treatment [3].

Therapy with 5-alpha reductase inhibitors: During treatment with 5-alpha reductase inhibitors, the volume of the prostate decreases with a volume reduction of the peripheral zone and the transitional zone [4].

Radiotherapy: After radiotherapy, zonal structuring is eliminated and the peripheral zone has low signal intensity. A volume reduction often occurs over the course. The contour and the neovascular bundle can be emphasized and the bladder wall and rectal wall can be thickened [5, 6].

Hematospermia: The changes correspond to those in hemorrhage after biopsy but are less diffuse and are often also detectable in the seminal vesicle [7].

Clinical prostatitis and information regarding the treatment of prostatitis: Prostatitis can show similar changes as in carcinoma of the prostate on MRI and can therefore be difficult to differentiate from carcinoma. Prostatitis often shows extensive changes without the displacement of structures and can be detected on the basis of a band-like, wedge-shaped, diffuse rather than focal appearance. There are also overlaps in the evaluation of DWI, DCE-MRI and 1H-MR spectroscopy (1H-MRS). Prostatitis typically shows low diffusion restriction, a low signal amplitude, and no rapid decrease in signal enhancement after peak enhancement in DCE-MRI [8].

Previous operations in the small pelvis: Transurethral resection (TUR-P) of benign prostate hyperplasia (BPH) leaves a typical defect in the central zone. The remaining peripheral zone usually has mildly reduced signal intensity. Since BPH nodules occasionally develop again in the periphery, the time at which TUR-P was performed and information regarding treatment success, if available, is helpful. Rectal resection and rectal amputation as well as extensive repeat local treatment of bladder tumors can change the prostate and the tissue surrounding the prostate.

**Creatinine and eGFR**

When using gadolinium-containing contrast agent in DCE-MRI, factors concerning the patient and properties of the contrast agent must be taken into consideration. The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) evaluated the risk for gadolinium-containing contrast agents and the occurrence of nephrogenic systemic fibrosis (NSF). This evaluation provides the basis for the application recommendations of the European Society for Urogenital Radiology (ESUR). The following risk classes for gadolinium-containing contrast agents and patients were defined [9]: high risk: gadodiamide, gadopentetate dimeglumine and generics, gadoversetamide; medium risk: gadobenate dimeglumine, gadofosveset trisodium, gadoxetate disodium; low risk: gadobutrol, gadoteridol, gadoterate-meglumine. High-risk contrast agents are contra-indicated in patients with a GFR < 30 ml/min and in patients requiring dialysis. Determination of the serum creatinine (eGFR) and a clinical evaluation, possibly via questionnaire, are absolutely necessary [9]. Substances with an average or low risk should only be used with caution in patients with an eGFR < 30 ml/min. It is not absolutely necessary to determine renal function. If the serum creatinine was not determined, renal function should be recorded on the questionnaire. The administered contrast agent dose should never be higher than 0.1 mmol/kg body weight per examination and patient [9].

**Examination scheduling and preparation**

**Time of examination**

Bleeding into the prostate after a preceding biopsy can be detected for months in the MRI examination and affects the ability to evaluate the examination. In the case of MRI with the indication for tumor detection or active monitoring, a minimum time of 6 weeks with respect to biopsy should be observed. In the case of MRI for local tumor staging in histologically verified carcinoma, examination can be performed sooner in order to provide the patient with definitive therapy as quickly as possible. MRI to search for tumors can be performed at any time.

**Antispasmodic**

To improve image quality and to reduce artifacts caused by bowel movement, one to two ampoules of butylscopolamine (20–40 mg) can be applied in fractionated doses if not contraindicated. Alternatively, intravenous administration of one ampoule of glucagon (1 mg) under consideration of the contraindications is possible. However, there are no guidelines or studies verifying a clear improvement in the image quality and diagnostic accuracy...
of prostate MRI as a result of the administration of an antispasmodic [10–12].

Emptying the rectum

Air in the rectum can result in artifacts, particularly in the case of DWI. To reduce these artifacts, patients should be required to empty the rectum and bladder prior to examination. If significant air in the rectum is detected in the planning sequences, decompression of the rectum via a rectal tube can be advantageous [12]. Enemas or laxatives should not be administered since these increase intestinal peristalsis and can intensify artifacts.

Abstinence

Sexual abstinence on the part of the patient for 3–5 days can ensure greater filling and thus better delineation of the seminal vesicle particularly in T2w sequences. A clear advantage of a defined period of abstinence prior to MRI regarding the detection, localization, and staging of prostate cancer has not yet been shown.

Examination protocol

The goal of the protocol should be the reliable detection and localization of significant carcinomas of the prostate with a volume ≥ 0.5 ml and the detection of extracapsular growth incl. infiltration of the seminal vesicle. For detection, MRI of the prostate is useful both in the primary and the secondary indication since it was able to be shown that targeted biopsy maximizes the detection rate of areas suspicious for carcinoma on MRI in addition to systematic TRUS-guided biopsy [13–15].

A standardized protocol ensures comparability (e.g. during active monitoring) and avoids unnecessary duplicate examinations. A combination of T2w imaging, DWI, and DCE-MRI provides the highest diagnostic accuracy [16]. Studies that were not able to show a statistically significant advantage for the use of DCE-MRI for detection were recently published [17, 18]. Since the available data is still insufficient in our opinion, DCE-MRI should continue to be used. For the diagnosis of local relapse after radiotherapy, MRI seems more suitable than nuclear medicine methods for the detection of a recurrence near the bladder.

Morphological T2w TSE/FSE sequences

T2w imaging via high-resolution T2w turbo spin echo (TSE) or fast spin echo (FSE) sequences provides the basis for MRI of the prostate [19]. The sensitivity regarding prostate cancer detection varies in the literature between 32% and 95% which primarily depends on the cohort that was examined. To evaluate the diagnostic quality of T2w imaging as a function of tumor size, it was shown in a study with histological large-area sections that morphological T2w imaging alone is not able to reliably rule out carcinoma foci smaller than 10 mm [20]. Therefore, morphological MRI must be supplemented by functional techniques. Carcinomas are hypointense in T2w imaging. The differentiation between prostatitis and prostate cancer can be difficult in the peripheral zone. In the transitional zone differentiation particularly with respect to stromal hyperplasia, which is also hypointense, is difficult. Nevertheless, T2w imaging is the most important sequence for detecting carcinomas in the transitional zone. The differentiation criterion here is primarily the architectural distortion followed by size [12]. Morphological T2w sequences are decisive for determining the location of focal lesions. A targeted biopsy can be performed on this basis in the next step. In the case of non-cognitive fusion techniques, the transverse T2w DICOM dataset can be used for automatic fusion [21].

DWI, DCE-MRI, 1H-MRS

DWI: Carcinomas of the prostate with increased cell density decrease the size of the interstitial space and displace, compress, or destroy the glandular ducts. This limits the free particle mobility that can be detected with DWI [22].

DWI is typically comprised of images with single-shot-echo-planar-imaging (SSEPI) sequences with a low diffusion-weighted gradient (b-value between 0 and 150 s/mm²) and at least one high diffusion-weighted gradient (b-value between 800 and 1500 s/mm²). Higher b-values have been used with varied results. With a mono-exponential function, the so-called apparent diffusion coefficient (ADC) can be determined using the particular image datasets with the low and the high b-value for each image point and the numerical value can be shown with color coding [22].

In DWI, healthy prostate tissue shows a high signal at low b-values and significant signal reduction at high b-values. The ADC values qualitatively show the signal intensity difference. Carcinomas of the prostate with a low percentage of water and limited particle mobility show a low signal at a low b-value and a constant to significantly increasing signal at a high b-value. The ADC values qualitatively show the minimal signal difference. A low ADC value is quantitatively present. There is a correlation between the increasing biological aggressiveness of carcinomas of the prostate and the decreasing ADC value in DWI [23].

The sensitivity and specificity of DWI alone for the detection of carcinoma of the prostate are specified in a current meta-analysis including a total of 1204 patients as 62 % and 90 %, respectively [24]. In a meta-analysis including a total of 698 patients with a previous negative prostate biopsy, the average sensitivity of DWI for detecting a carcinoma of the prostate is 38 % and the average specificity is 95 % [25]. The test quality parameters are slightly better for the combination of T2w images with DWI than for T2w images alone [26].

Under external radiotherapy of the prostate, the ADC value in carcinomas of the prostate increases significantly but does not change substantially in healthy prostate tissue [27].

DCE-MRI: DCE-MRI includes the fast acquisition of T1w sequences after bolus application of a gadolinium-containing contrast agent and is established in clinical oncology as a biomarker [28]. DCE-MRI should always be interpreted in combination with DWI and T2w imaging which is facilitated by the use of the same slice thicknesses. DCE-MRI significantly increases the accuracy of tumor detection and lesion evaluation and DCE-MRI increases the sensitivity for tumor detection particularly in the peripheral zone [29, 30]. A high temporal resolution (at least 9 seconds) is a requirement for being able to measure the rapid enhancement of contrast agent in the prostate [31]. DCE-MRI is essential particularly for diagnosing recurrence after prostatectomy or radiotherapy [32].

1H-MRS: Three-dimensional 1H-MRS can localize carcinomas of the prostate as part of MRI examination [33]. Results of T1w/T2w
imaging and $^1$H-MRS that are consistently suspicious for prostate cancer indicate the presence of cancerous prostate tissue with a probability of approximately 50% (positive predictive value) with the important differential diagnosis of focal circumscribed prostatitis. Conversely, results of T1w/T2w imaging and $^1$H-MRS that are consistently negative indicate the presence of healthy prostate tissue with a probability of approximately 95% (negative predictive value) with the differential diagnosis of diffuse prostatitis [34]. The sensitivity and specificity of $^1$H-MRS combined with individual MRI sequences were 58% and 93%, respectively, for the detection of carcinoma of the prostate in a current meta-analysis of 14 studies including a total of 698 patients with a previous negative prostate biopsy [25]. The ability to differentiate between healthy and cancerous prostate tissue is fundamentally maintained with $^1$H-MRS even after treatment of the prostate (e.g., hormone therapy, radiotherapy, cryotherapy) [33].

**T1w TSE/FSE sequence**

The T1w sequence is used to evaluate bone and lymph nodes. For morphological detection of pathological lymph nodes, it is useful to visualize the entire pelvis from the aortic bifurcation to the pelvic floor. Bone marrow metastases of prostate cancer are hypointense and focal in T1w sequences. It is important to observe that spin-echo or fast spin-echo and TSE or FSE sequences are used since gradient echo sequences distort the bone marrow signal and can thus mask bone marrow metastases. For the prostate, a T1w sequence is also useful for detecting post-biopsy or inflammatory bleeding. This has a hyperintense appearance in T1w sequences and can thus be effectively delimited from the surrounding tissue [2].

**Endorectal coil**

In MRI examinations with a field strength of 1.5 T, the application of a combined endorectal body phased-array coil is superior to the exclusive use of a phased-array coil without an endorectal coil with respect to image quality and local staging [26]. By using a combined endorectal body phased-array coil, the sensitivity and the positive predictive value for the detection of prostate cancer could be increased in individual studies even in 3 T MRI examinations [27]. The sole use of a body phased-array coil at 3 T as widely used in practice is justified by the good detection of significant tumors [28]. Use of the combined endorectal body phased-array coil at 3 T can improve local staging, particularly the evaluation of extracapsular growth [35]. When using an endorectal coil, it should be filled with air. To reduce susceptibility artifacts, the balloon for spectroscopy can be filled with distilled water or Fomblin Med 08 (Solvay, Brussels, Belgium) as an alternative to air. However, using Fomblin for this purpose in Germany represents an off-label use.

**Further sequences**

The contrast properties of T2w 3D-TSE/FSE sequences (multiecho sequences with variable flip angles) for the detection of prostate cancer compared to T2w 2D-TSE sequences have not been sufficiently studied. However, a study with a low case number could not show inferiority of the 3 D sequence compared to the classic 2 D sequence for the detection and the staging of a carcinoma of the prostate in the peripheral zone [36]. Therefore and due to the increased susceptibility to motion artifacts, this sequence should not be used to detect prostate cancer. A higher diagnostic accuracy of the 3 D sequence regarding extracapsular extension could be shown in a further study regarding local staging also with a low number of cases [37]. Due to the isotropic voxels, the 3 D sequence can however be advantageous for fusion with other imaging methods (in particular ultrasound).

Complex techniques of diffusion-weighted imaging take into consideration the microstructural complexity of prostate cancer [38]. Intravoxel incoherent motion imaging (IVIM) takes into consideration the multieponential behavior of the diffusion signal at different b-values and the influence of the perfusion components of the signal at low b-values. Diffusion kurtosis imaging (DKI) takes into consideration the kurtosis of the tissue which refers to the deviation from the Gaussian distribution [39]. These complex diffusion models are a current topic of research. The currently available data do not show a significant advantage of these methods compared to classic diffusion weighting and should therefore not be used for diagnosis at this time [39].

Further techniques, such as diffusion tensor imaging, BOLD imaging, MR elastography and T2 mapping, are also currently under development and should therefore not be used outside of studies.

**MRI-guided in-bore biopsy**

The most accurate MRI-guided biopsy method for histological confirmation of MRI lesions is targeted biopsy in the MRI tube [40]. Possible accesses described in the literature are transrectal, transperineal, and transgluteal. MRI (in-bore) biopsy should be performed under local anesthesia. The use of a gel anesthesia was associated in a transrectal setting with a low level of pain (VAS 1–2 in 297/297 patients) [40].

Studies show high detection rates both for patients without a previous biopsy and with a negative prior biopsy [14, 41, 42]. MRI (in-bore) biopsy can be performed alternatively to MRI/US fusion biopsy in the secondary indication [41]. As an alternative to MRI-guided biopsy methods, MRI/US fusion biopsy and cognitive ultrasound biopsy can be used. MRI (in-bore) and fusion-based biopsy methods tend to be superior to simple cognitive biopsy [43]. However, valid prospective comparison data is not currently available [44].

**Laboratory**

Conventional coagulation testing with International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), and thrombocyte number is a poor predictor of the intraoperative bleeding risk and is not capable of detecting the most common blood coagulation disorders (von Willebrand factor deficiency and thrombocyte dysfunction) [45]. A standardized questionnaire for recording bleeding history, prior operations and traumas, familial bleeding diathesis, and coagulation-inhibiting medication is therefore essential. Coagulation testing is mandatory in the case of the suspicion of a coagulation disorder given a positive bleeding history or if the patient is taking oral anticoagulants.

A biopsy in the case of clinical signs of an acute urinary tract infection, such as burning during urination, should be avoided.
Anticoagulants
The taking of acetylsalicylic acid (ASS) during a surgical intervention increases the risk of a bleeding complication by the factor of 1.5 without increasing the fatality rate [46]. The current guidelines of the European Society of Cardiology recommend continued periprocedural administration of ASS at a dose of 100 mg p. o. [47]. In patients with implanted coronary stents, a prostate biopsy – as an elective intervention – should only take place after dual thromboocyte aggregation inhibition (ASS + ADP antagonist (clopidogrel)) has ended and monotherapy with ASS has begun [48].

A prostate biopsy under vitamin K antagonists (Marcumar) requires interdisciplinary consideration. It is recommended to discontinue anticoagulation therapy if possible. A subtherapeutic INR is achieved between four and seven days after discontinuation [48]. In principle, a biopsy of the prostate can however also be performed while taking a vitamin K antagonist.

Antibiotics
Based on the recommendations of the S3 guidelines for transrectal ultrasound-guided biopsy in carcinoma of the prostate, it is recommended to perform transrectal MRI biopsy with antibiotic prophylaxis. It was able to be shown that antibiotic prophylaxis significantly lowers the rate of bacteriuria after core biopsy as a possible surrogate parameter for an infection [49]. The typically lower number of core biopsy specimens in MRI biopsy may also contribute to a lower infection rate. Quinolones are the antibiotic of choice in transrectal biopsy [50]. In recent years an increase in infectious complications after prostate biopsy has been described [51].

References


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