Dissertation

Real-world interobserver agreement and risk stratification of PI-RADS v2 after combining 4-core targeted MRI-TRUS fusion and systematic 12-core TRUS prostate biopsy for the diagnosis of prostate cancer

submitted by

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ao. Univ.-Prof. Dr. Herbert AUGUSTIN (Department of Urology)

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Guidelines of the Medical University of Graz on Good Scientific Practice".

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Disclosures

a. Publication that is based on the thesis:

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Foreword

This work is the result of tremendous efforts taken by the department of urology and radiology of the Medical University of Graz to improve the diagnostic accuracy and treatment of men under suspicion for prostate cancer. I would like to thank my supervisors, especially Prof. Dr. Herbert Augustin who maintained this project at any point with great interest and expertise. Most importantly, sincere thanks are given to my family who encouraged me in every situation of my life. Their love and endorsement as well as the support of my friends were the impetus for all of my achievements.

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Abbreviations and Definitions

ADC	Apparent-diffusion coefficient
ADT	Androgen Deprivation Therapy
ARFI	Acoustic radiation force impulse
AS	Active surveillance
AUC	Area under the curve
BI-RADS	Breast imaging reporting and data system
Bb	Biparametric
BPH	Benign prostatic hyperplasia
CAP	Cluster Randomized Trial of PSA Testing for PC
CEUS	Contrast-enhanced ultrasound
CI	Confidence interval
CS	Clinically significant
CTB	Conventional systematic transrectal ultrasound guided prostate biopsy
C-TRUS	Computer-assisted ultrasound
CZ	Central zone
DWI	Diffusion-weighted imaging
DRE	Digital rectal examination
DCE	Dynamic contrast-enhanced
EAU	European Association of Urology
EDP	Earlier diagnosed prostate cancer due to prior prostatic biopsy
EORTC	European Organisation for Research and Treatment of Cancer
ERSPC	European Randomized study of Screening for PCA
ESUR	European Society of Urogenital Radiology
FNB	Former negative prostate biopsy
GRADE	Grades of Recommendation Assessment, Development, and Evaluation
HS	Histo-scanning
Is	Insignificant
ISUP	International Society of Urological Pathology
K	kappa coefficient
LDB	mpMRI/TRUS-fusion lesion directed prostate-biopsy
LDB&CTB	mpMRI/TRUS-fusion lesion directed prostate-biopsy and conventional systematic transrectal ultrasound guided prostate biopsy
mp	Multiparametric
MRI	Magnetic Resonance Imaging
MUG	Medical University of Graz

NPV	Negative predictive value
OS	Overall survival
PCa	Prostate cancer
PI-RADS	Prostate imaging reporting and data system
PLCO	Prostate, Lung, Colorectal, and Ovarian screening trial
PMP	Primary PI-RADS v2 radiologist report
PPV	Positive predictive value
RCTs	Randomized controlled trials
ROC	Receiver operating characteristic
RP	Radical prostatectomy
RPS	Radical prostatectomy specimen RR Relative risk
PRI-MUS	Prostate Risk Identification using Micro-ultrasound
PSA	Prostate specific antigen
PSAD	Prostate specific antigen density
PZ	Peripheral zone
SMC	Smooth muscle cells
T1	T1-weighted pulse sequences
T2	T2-weighted pulse sequences
TPR	Target defining and PI-RADS v2 evaluating radiologist report
TRSE	Transrektal sonoelastography
TRUS	Transrektal ultrasonography
TZ	Transition zone
UB	Unbiopsied
UGM	Urogenital sinus mesenchyme
UICC	Union for International Cancer Control
US	
USPSTF	US Preventive Services Task Force
v1	Version 1
v2	Version 2

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Abstrakt

Hintergund: Der Einfluss der unverblindeten Re-evaluation der multiparametrischen (mp) Magnetresonanztomographie (MRT) der Prostata auf die Untersucher-Variabilität des Prostate Imaging Reporting and Data System Version 2 (PI-RADS) bei Biopsie-naiven Patienten (UB) verglichen mit negativ vorbiopsierten Patienten (FNB) bleibt unklar. In FNB-Kohorten mit Verdacht auf ein Prostatakarzinom (PCa) wird häufig die alleinige Strategie der fusionierten mpMRT Läsions gezielten Prostatabiopsie (LDB) für PI-RADS ≥ 3 Läsionen empfohlen, obwohl bisher die klinisch relevante (cs) PCa Detektion von unterschiedlichen Biopsiestrategien zwischen UB und FNB Patienten nicht direkt untereinander verglichen und dann mit dem Prostatektomiepräparat (RPS) als idealer Referenzstandard korreliert wurden.

Material und Methoden: Es wurden 813 mpMRI-Bilder/Befunde intramural re-evaluiert und suspekte Areale für die Biopsie markiert. Hiernach wurden in Abhängigkeit vom PI-RADS Score die durch die LDB-, systematische Biopsie- (CTB) oder Kombinationsmethode (LDB&CTB) nachgewiesenen PCa-Detektionsraten von UB Männern den FNB Patienten gegenübergestellt. Abschließend wurde die histopathologische Variabilität des PCa-Aggressivitätsgrades zwischen dem RPS und der Biopsiestanze bewertet. Der PSA-Dichte (PSAD)-Cutoff >0,15 ng/ml/cm3 wurde ebenso in die Analysen miteinbezogen.

Ergebnisse: Wir beobachteten eine UB- vs. FNB-PI-RADS 2-5 Übereinstimmung, Höher- und Abstufung bei 83% vs. 71% ($p < 0,0001$), 9% vs. 16% ($p = 0,006$) und 8% vs. 13% ($p=0,01$). Der Untersucher-Koeffizient war für UB-Patienten substantiell (0,73; 95 % CI: 0,68-0,78) und moderat für FNB-Männer (0,57; 95 % CI: 0,49-0,64). Beim Vergleich von UB (n= 499) vs. FNB (n=314) Personen wurde ein csPCa häufiger bei UB Personen bzw. mit der LDB&CTB-Technik (62 vs. 43 %) entdeckt als mit der LDB (54 vs. 34 %) oder CTB (57 vs. 34 %) alleine (alle $p<0,0001$). Die csPCa-Detektion mittels der LDB und LDB&CTB Strategie war bei re-evaluierten PI-RADS-5 Läsionen, UB-Männer mit einer PSAD> 0,15 ng/ml/cm3 vergleichbar. Beim Nachweis eines csPCa hatten FNB-Patienten mehr falsch-negative Ergebnisse mit der LDB-Methode (UB 11 % vs. FNB 19 %; $p=0,02$). Der LDB&CTB-Ansatz zeigte eine größere „Biopsie-RPS“-Übereinstimmung in der gesamten und UB-Patientenkohorte, sowie generell eine wesentlich geringere Höherstufung.

Zusammenfassung: Die PI-RADS-Interobserver-Übereinstimmung ist in UB-Situationen genauer. Sowohl bei PI-RADS 3-, 4- oder 5-Läsionen von UB- als auch FNB-Männern konnten durch die LDB&CTB-Methode mehr csPCa entdeckt werden. Die LDB Methode sollte das csPCa bei UB-Patienten mit re-evaluiertem PI-RADS 5 und einer PSAD > 0,15 ng/ml/cm3 suffizient abklären. Der LDB&CTB-Ansatz zeigte in der Gesamt- und UB-Patientenkohorten die beste Vorhersage des RPS-Aggressivitätsgrades sowie allgemein die niedrigste Höherstufung. Generell sollte das LDB&CTB-Verfahren auch zur Abklärung des csPCa Verdachts bei FNB-Patienten vorgeschlagen werden.

Abstract

Purpose: The necessity of multiparametric (mp) magnetic resonance imaging (MRI) unblinded re-read in unbiopsied (UB) versus former negative prostate biopsy (FNB) patients on the interobserver variability of the Prostate Imaging Reporting and Data System version 2 (PI-RADS) remains unclear. In FNB cohorts with a suspicion of prostate cancer (PCa), the 'mpMRI/TRUS-fusion lesion directed prostate biopsy' (LDB) alone strategy for PI-RADS ≥3 lesions is frequently recommended, lacking evidence of the direct comparison of biopsy performances in UB versus FNB patients or assessment of the biopsy to radical prostatectomy specimen (RPS) correlation as ideal reference standard.

Materials and Methods: PI-RADS reports and mpMRI-images generated in 15 qualified radiology institutes were intramurally reviewed for assessment of agreement and biopsy planning. We investigated the corresponding UB- and FNB PCa detection rates of the PI-RADS score substratified by the LDB, conventional systematic transrectal ultrasound guided prostate biopsy (CTB), or combination method (LDB&CTB). In addition, we evaluated the RPS to biopsy core histopathological PCa grade variability. The PSA density (PSAD) cut-off >0.15 ng/ml/cm^3 was incorporated.

Results: We observed UB- vs. FNB-PI-RADS 2-5 agreement, up- and downgrading in 83% vs. 71% ($p<0.0001$), 9% vs. 16% ($p=0.006$) and 8% vs. 13% ($p=0.01$), respectively. The inter-rater-coefficient was substantial for UB-patients (0.73; 95% CI: 0.68-0.78) and moderate for FNB men (0.57; 95% CI: 0.49-0.64). After comparing UB (n=499) vs. FNB (n=314) individuals significant (cs) PCa was discovered more frequently in UB patients with the LDB&CTB technique (62 vs. 43%) than with the LDB (54 vs. 34%) or CTB (57 vs. 34%) alone (all $p<0.0001$). We observed no difference for the rate of csPCa found by LDB and LDB&CTB according to reevaluated UB-PI-RADS-5 patients with a PSAD>0.15 ng/ml/cm^3 (n=79 vs. n=81; $p=0.2$). When diagnosing csPCa, FNB patients had a higher rate of false-negative results using the LDB method (UB 11% vs. FNB 19%; $p=0.02$). The LDB&CTB approach showed a greater "biopsy-RPS" agreement in the entire and UB patient cohort but generally demonstrated substantially less upgrading.

Conclusions: The PIRADS interobserver agreement is more accurate in UB situations. Both in PI-RADS 3, 4 or 5 lesions of UB and FNB males, the LDB&CTB method appears to discover a considerably larger number of csPCa. In addition, reevaluated UB-PI-RADS 5 patients with a PSAD >0.15 ng/ml/cm^3 may be advised to omit a concurrent CTB without compromising the csPCa diagnostic accuracy. The exclusion of a concomitant CTB in FNB-men produces significantly more false negative targets among those patients who were csPCa positive. In the total- and UB patient cohorts, the LDB&CTB approach demonstrated the best RPS-grade prediction and consistently displayed the lowest upgrading rates. In general the LDB&CTB process should also be suggested to clarify the csPCa suspicion in FNB patients.

1 Introduction

1.1 The Prostate

1.1.1 Morphological aspects

The prostate represents the dominant supplementary gland of the masculine genital system, which is built by ducts with an internal film of epithelial cells and the prostatic stroma as surrounding matrix.(1)The prostate is found in most mammals but the gross structure differs considerably between species.(2) In humans, the normal prostate gland measures approximately a volume of 20-25 ml and is located between the bladder neck and the urogenital diaphragm.(3) Three zones make up the human prostate gland's anatomy: the central zone, the transition zone, and the peripheral zone.(1)
In rats, the prostate is tiny at birth and only has a small number of immature buds. In addition, postnatally, these cells multiply, primarily at the tips.(4) Hereafter, they go through a canalization process from the urethra towards the tips (proximal to distal). At the same time, the epithelial cells separate into basal and luminal phenotypes.(5) The prostatic basal cells, at least in rodents, are intricate structures with processes that encircle the ducts; this characteristic is not apparent from conventional histologic sections.(6, 7) The urogenital sinus mesenchyme (UGM) multiplies and differentiates into prostatic smooth muscle and interfascicular fibroblasts concurrently with epithelial development.(8) After birth, under the influence of androgens, the epithelial cells go through differentiation, including the development of androgen receptors, and start to produce a variety of secretory products that are lobe- and species-specific.(9) Interestingly, in humans, between birth and puberty, when growth starts in response to increasing androgen levels, the prostate does not expand much, but hereafter tends to increase in size during lifetime. Contrary to popular belief, androgens not only promote the growth and development of the prostate but also serve a critical role in restraining the growth of the adult prostate. Intriguingly, prostatic hyperplasia and prostate cancer (PCa) are not common in young adult males, in whom androgen levels are at their lifetime maximum; rather, these conditions are linked to aging and a decline in serum androgen titers. Anyhow, the benign prostatic hyperplasia, prostatitis and PCa are the three main morbidity-causing diseases of the prostate.(10)

The glandular or epithelial component and the fibromuscular stroma are the two histological fractions of the human prostate.(11, 12) In reaction to androgenic hormones, differentiation factors or growth stimulators of the prostatic stroma and epithelium, the prostate evolves its

structural integrity.(13-16) Based on investigations of human embryos, Lowsley et al. initially postulated the separation of the prostate into five lobes: an anterior, a posterior, two lateral and one middle lobe.(17)

Since the 1960's and throughout time, McNeal further refined this idea and proposed the segmentation of the prostate into the peripheral zone (PZ), the central zone (CZ), and the transition zone (TZ). These anatomical regions were physiologically and histologically different.(12, 18, 19)

The PZ represents about 70% of the prostate, and its ducts emerge laterally from the postero-lateral recesses of the urethral wall.(20) The system is made up of tiny, straightforward acinar structures that range in shape from round to oval and empty into long, narrow ducts. A stroma of haphazardly placed and randomly linked muscle bundles surrounds the system. Simple columnar epithelium covers the interior of ducts and acini, prostatitis and PCa are primarily found in this region.(10)

One quarter of the prostate is described as CZ with even larger polyhedral acini and ducts of unusual shape running proximally next to the ejaculatory ducts. In comparison to the peripheral zone, the muscle stroma is substantially more compact and is less associated with prostatic disease.(10)

Last, the urethra is surrounded by the TZ, which makes up to 5% of the prostate and lies between the bladder and the verumontanum. From the pathophysiologic point of view this area is of interest, due to possible compression of the urethra by nodular enlargement also described as benign prostatic hyperplasia (BPH).(10, 18, 20)

The functional and molecular mechanisms underlying prostatic diseases are insufficiently investigated. Intensive research has been made to determine the causes of BPH and/or PCa, as both illnesses are more likely to manifest in men older than 40. It seems that the increased rate of cell turnover observed in the transition and peripheral zones is linked with the higher prevalence of proliferative illnesses there.(21) In addition, collagen fibers do not substantially differ between the CZ and the PZ but it remains unclear if this regional similarity correlates with PCa development. (20, 22) Nevertheless, CZ carcinomas are an uncommon but extremely aggressive subtype of PCa, whereas the seminal vesicles and ejaculatory ducts were frequent routes to escape from the gland with more extracapsular expansion and positive surgical margins.(23)

The onset and course of prostatitis, BPH and PCa heavily involve muscle fibers. Smooth muscle cells (SMC) may contribute to the pathophysiology of inflammatory diseases such as prostatitis, by modifying the epithelial-stromal interactions.(24) A higher abundance of SMC has been observed in BPH, probably due to stromal cell proliferation and myo-differentiation. Every zone of the prostate contains SMC, myofibroblasts, fibroblasts or collagen fibers. Elastic fibers can be readily seen in the transition zone, and SMC appear

to be the primary stromal component. With respect to the pathophysiology of PCa, these SMC drastically decline and undergo a transformation into fibroblasts and myofibroblasts, indicating that PCa occurs most frequently in locations with sparse muscle fibres, with the highest incidence in the PZ.(20, 24, 25)

The filaments of the stromal matrix play a substantial part in BPH since the netlike fibres exhibited a relevant increment in the BPH samples.(26) There is less information on how elastic filaments and its receptors contribute to PCa progression, however they appear to be unsystematic in the stroma of PCa specimens.(27) Alves et al. showed that the TZ had the most elastic system fibers, which may have been released by the muscle cells that were also more abundant in this area of the prostate. In addition, less innervation of the TZ than PZ was observed and supposed that the PZ's increased nerve density may contribute to the development of cancer.(20, 28) The CZ and the PZ have identical features regarding epithelial height and both zones share the same physical characteristics that favor PCa growth.(20)

The collaboration between epithelial and stromal sections promotes the development of a milieu that is beneficial for tumor enlargement and invasion, mainly under the stimulation of androgens.(27)

1.1.2 Prostate function

The main reproductive gland that affects male fertility is the prostate. The composition of the prostatic mucus as a part of the ejaculate is generated by the epithelial layer of the prostate and directly influences the susceptible balance between liquefaction and clotting of sperm, supporting all the biological functions required to reach and fertilize the egg.(1) Nevertheless, the precise functions of prostatic fluid in semen are insufficiently understood, but it is most likely needed to sustain the spermatozoa's preservation, activity, and metabolism during fertilization.(29)

The testis, epididymis, and male accessory glands such as the seminal vesicles, prostate, and bulbourethral (Cowper's) gland provide the fluids that make up human seminal plasma. All spermatozoa provided by the testicles account for 2-5% of the total volume of the ejaculate.(30)

The secretion of proteins is one of the accessory glands' relevant functions and one relevant liquid found in human seminal plasma is the prostatic secretion from the prostate epithelium (25% of the ejaculate), which is enriched in the trace element Zn^{2+}, citrate, kallikreins, phosphatases or polyamines (spermine). The two main proteins that make up the human semen coagulum to prevent sperm capacitation are semenogelin I and the less common

semenogelin II. Both are produced by seminal vesicles (accounting for about 70% of the whole ejaculate) and are quickly broken down, mostly by the prostate specific antigen (PSA), a kalllikreins.(31) Additionally, the male accessory glands supply growth factors, and hormones generated by Leydig cells, such as testosterone and insulin-like 3 protein. Last, the bulbourethral glands normalizes the acetous milieu of the urethra or vagina, produces galactose, sialic acid, and the glycoprotein mucin released as lubrication during sexual arousal.(1, 32)

The main area involved in producing prostatic secretion is the peripheral zone with zinc and citrate concentrations within the fluid being 500 and 1000 times higher than in blood plasma, respectively. In addition, zinc levels of the prostatic fluid are 10-20 times and citrate levels 30-80 fold greater than in other soft tissues. It's interesting to note that zinc and citrate levels are both significantly reduced in PCa as a result of downregulation of ZIP1 to stop zinc cytotoxicity in the malignant cells, which is described as a crucial early step in prostate oncogenesis. Due to their metabolic and functional connection in the human prostate peripheral zone, zinc and citrate have these similarities.(29)

1.2 Epidemiology of prostate cancer

Worldwide the most commonly diagnosed cancers in 2020 were female breast cancer, lung and PCa s with 2.26, 2.21 and 1.41 million cases, respectively. Nevertheless, PCa is the most diagnosed cancer type in men worldwide and after lung cancer represents the second most frequent cause of death in the male population globally.(33)

The age standardized incidence (per 100.000 men) of PCa diagnosis varies widely between different geographical areas, being highest in Australia/New Zealand, Northern America, Western and Northern Europe (111.6, 97.2, 94.9 and 85, respectively). Reasons for that are mainly the use of PSA testing and the aging population.(34)

In contrast a very low but rising incidence has been observed in Eastern and South-Central Asia showing a standardized incidence rate per 100.000 of 10.5 and 4.5, respectively.(35) Interestingly, there is relatively less variation in mortality rates worldwide, although rates are generally high in populations whose origin is the African continent.(34, 36)

1.3 Most relevant risk factors and etiology of prostate cancer

According to a comprehensive assessment of autopsy studies, the prevalence of PCa increased from 5% at age 30 years to 59% by age > 79 years, with an odds ratio of 1.7 each decade.(37) In the past risk factors for the development of PCa have intensively been investigated especially with respect to ethnical diversity showing a low prevalence in Asian men but higher risk for men of African descent.(38)

Nevertheless, environmental factors also seem to have a highly relevant influence. Breslow et al. showed that Japanese men who move from Japan to California develop a PCa risk comparable to men who originate from America.(39)

Furthermore, PCa is associated with heredity of genetic risk factors. Men are more likely to suffer from PCa if there is a positive history of the disease within the family-tree, especially if a first-degree relative received a PCa diagnose before the age of 65.(40-42) In addition, men with a positive family anamnesis for women with breast cancer have a higher risk for PCa.(43) Recently Beebe-Dimmer et al. published a large American population based study with 619,630 men (aged at least 40 years or older), who were members of a pedigree that included at least 3 consecutive generations. They could show that the family history of hereditary PCa conveyed the greatest relative risk for all PCa subtypes combined (RR, 2.30; 95% CI, 2.22 to 2.40), followed by hereditary breast and ovarian cancer and lynch syndrome. Furthermore, hereditary PCa was associated with a high risk for early onset PCa disease in all pedigree types, consistent with the contribution of genetic factors to disease occurrence.(44)

Genomic alterations with a potential involvement in PCa include somatic mutations, gene deletions or amplifications and chromosomal rearrangements. In the natural history of PCa these alterations are probably accumulated over a period of several decades.(45) Somatic copy number alterations (CNA) have been found in approximately 75% of localized PCa. Losses were found to be five times more common than gains and most often involved 8p (32%), 13q (32%), 6q (22%), 16q (19%), 18q (19%) and 9p (16%). Furthermore, early genome-wide studies also suggested that the pattern of CNA changes with disease progression (i.e. gains of 7, 8q and X were more often observed in the castration resistent PCa state).(46)

Several germline mutations in DNA damage repair genes (BRCA1, BRCA2, CHEK2, ATM and PALB2) and in DNA mismatch repair genes (MLH1, MSH2, MSH6 and PMS2) influence the development of PCa.(47)

Giri et al. evaluated clinical genetic data from 1328 men with PCa unselected for metastatic disease undergoing multigene testing across the USA. The overall germline pathogenic variant rate was 15.6%, of those 10.9% could be found in DNA repair genes. Mutations of

BRCA2 (4.5%), CHEK2 (2.2%), ATM (1.8%), and BRCA1 (1.1%) were most commonly detected. Breast cancer family history was significantly associated with pathogenic germline DNA repair (OR 1.89, [95%CI 1.33, 2.68], P = 0.003). In addition, patients with intermediate or high risk PCa were related with pathogenic DNA repair either (OR 1.85 [95%CI 1.22, 2.80], p = 0.004).(48)

In line, Page et al. reported interim-results of the IMPACT study which investigated 3027 patients (919 BRCA1 carriers, 709 BRCA1 noncarriers, 902 BRCA2 carriers, and 497 BRCA2 noncarriers). After 3 years of screening, compared with noncarriers, BRCA2 mutation carriers were associated with a higher incidence of any PCa, csPCa and younger age at diagnosis. It was concluded that systematic PSA screening is indicated for men with a BRCA2 mutation.(49)

1.4 Local prostate cancer staging and defining clinically significant prostate cancer

Despite established imaging modalities such as TRUS and mpMRI the local clinical tumor stage (cT) is based on the digital rectal examination (DRE) only. The pathological tumor staging (pTNM) correlates the tumor size and location of pathological PCa tissue with the prostate gland, seminal vesicles and adjacent organs. Clinical and pathological staging describe the same with exception for clinical T1 and T2 substages, which do not truly exist histopathologically. The current Union for International Cancer Control (UICC) no longer recognizes pT2 substages whereas pathological stage pT2 may be reported for whole-mount pathology specimens after radical prostatectomy (RP) with PCa confined to the prostate gland.(50)

Donald Gleason and the Veterans Administration Cooperative Urologic Research Group created the current PCa grading system between 1966 and 1974.(51) The Gleason score has been the most accurate indicator for PCa prognosis and identifies the most and second-most frequent pattern from 1 through 5. These patterns are added together resulting in a Gleason score ranging from 2 to 10. Consecutively, 25 potential scores are possible (eg, 1 + 1, 1 + 2, 1 + 3, 1 + 4, 1 + 5, 2 + 1 and so on).

The histologic and clinical diagnosis of PCa, as well as its therapy, have changed throughout the course of the last decades, prompting updates to the Gleason system, published in 2005 and more recently in 2014.(52, 53) Gleason scores 2 to 5 declined from 27% in 1998 to 1% in 2011, whereas Gleason scores 7 accounted for 38% of cases in 2011 emphasizing that the Gleason system demonstrated certain serious flaws influencing patients' treatment.(54)

Current Gleason scores of 6 have a better prognosis than historical Gleason score 6 tumors since sum scores of 2, 3, 4 or 5 are no longer assigned and several patterns that Gleason described as a score of 6 are now rated as 7. The choice of PCa therapy on the basis of a single, simplified Gleason score of 7 failed to acknowledge the significant prognostic differences between sum scores of 3 + 4 and 4 + 3. Furthermore, the fact that the lowest score in the Gleason system is now given a 6, despite being in the midst of the range from 2 to 10, is another significant fault in the system. Due to the low malignant potential a Gleason score of 6 has already been recommended to obtain the terminology "indolent lesion of epithelial origin".(55) Epstein et al. demonstrated a validated alternative to the Gleason Score that accurately generated fewer grades with a tremendous prognostic difference. The hazard ratios relative to Gleason score 6 were 1.9, 5.1, 8.0, and 11.7 for Gleason scores 3 + 4, 4 + 3, 8, and 9–10, respectively. In addition, the discrepancy between Gleason scores 2 + 2, 2 + 3, and 3 + 2 became meaningless after the grade group 1 was defined.

Metastases are seldomly associated with the grade group 2 of 5 (as opposed to Gleason score 7 of 10) and therefore represents a very favourable prognostic group. Compared to Gleason score 7, which comprised Gleason scores 3 + 4 and 4 + 3, Grade group 3 of 5 has a noticeably poorer prognosis than Grade 2. In contrast to Gleason scores 8–10, grade group 4 of 5 is not regarded as the highest grade and has a considerably better prognosis than grade group 5 (Gleason scores 9–10). Finally, there is no longer a need to differentiate between Gleason scores of 4 + 5, 5 + 4, and 5 + 5 for grade group 5.(53)

Different criteria have been published in the past to distinguish between csPCa requiring further treatment and isPCa, suitable for active surveillance (AS), but no consensus has been reached yet. In this regard, some authors categorized high-volume Gleason score 6 as clinically significant, whilst others defined it as PCa with Gleason pattern 4 or 5.(56)

Various authors influenced current prostate biopsy guideline recommendations and reported inconsistent csPCa definitions (53, 57-66):

- Gleason score ≥ 7.
- International society of urological pathology (ISUP) grade group 2 or higher tumors.
- Grade group 1 tumors with MCCL of 6 mm or longer.
- Primary Gleason grade (GG) 4 or greater and cancer core length predictive for the presence of lesions ≥0.5 mL.
- Large GG 1 (GS 3 + 3).
- GG ≥2 or GG ≥ 3.

However, to differentiate between csPCa and isPCa, D'Amico et al. showed that pre-therapy PSA, local tumor extension examined by DRE and biopsy Gleason score were independent predictors of time to post-therapy PSA failure in patients managed with either

RP or radiation therapy (RT).(67) The definition of csPCa by D'Amico et al. includes intermediate and high risk PCa situations and may be more representative as risk stratification for the impact of localized PCa disease after curative treatment. Therefore, both the American Urological Association and the European Association of Urology Guidelines utilize the risk categorization approach developed by D'Amico et al.(68)

1.5 Established pathways for prostate cancer detection with focus on our study perspectives

1.5.1 PSA

Flocks conducted the first studies on prostate antigens in 1960, and Ablin discovered precipitation antigens in the prostate ten years later.(69, 70) In 1966, Hara and colleagues looked for proteins specific to human semen to utilize as forensic evidence in rape cases. These research activities led to gamma-seminoprotein, a distinct protein (similar to PSA) in the fluid of the semen.(71) In the early seventies Li and Beling discovered the protein E1 (has subsequently been shown to be equal to PSA) from human semen, hoping to provide a novel method for fertility management.(72) In 1978 Sensabaugh discovered the semen-specific protein p30, originating from the prostate as well. It is comparable to protein E1.(73) The tissue-specific prostate antigen was isolated by Wang one year later. In 1980, Papsidero conducted the first quantitative assessment of PSA in the blood.(74, 75) The original research on PSA's application in clinical settings as a PCa marker was done by Stamey and colleagues.(64)

In the same year, Kuriyama et al. created an assay for detecting PSA in human serum.(76) PSA is the most widely utilized tumor marker for PCa, a 33-kd glycoprotein with 240 amino acids produced almost exclusively by the epithelial component of the prostate gland.(77, 78) It is a serine protease secreted into the semen, for the lysis of the seminal coagulum.(78) There are three different types of PSA seen in blood: free PSA, alpha-1-antichymotrypsin complexed PSA, and beta-2-macroglobulin complexed PSA.(79)

Men with any kind of prostatic illness may have high serum PSA levels caused by increased PSA production and structural deformities in the gland facilitating PSA access to the blood.(77) Therefore, PSA may be elevated in benign prostatic hypertrophy, prostatitis and other non-malignant conditions (after sexual intercourse, cycling), confirming that PSA is organ but not PCa specific.(80) However, ejaculation may result in a brief less than 1.0 ng/ml elevation in PSA levels, usually gone within 48 hours. In contrast a DRE does not

appear to have any clinically significant effects.(81, 82) The commercial availability of PSA tests from the middle to the late 1980s led to an intensive testing for early PCa detection and rapidly increasing incidence rates.(83)

To date PSA still remains the most used test to detect PCa. Harvey et al. published a systematic review of total-PSA measurements from a European population between 1998 and 2008 and histological confirmation of the diagnosis for all participants. In 10 studies including 5373 patients the diagnostic accuracy of total (t) PSA demonstrated a sensitivity between 0.78 and 1.00 and specificity from 0.06 to 0.66. Therefore tPSA has a role to play beside abnormal DRE to indicate prostate biopsy but its limited test performance may lead to unnecessary biopsies, morbidity and overtreatment.(84)

There is disagreement about potential differences between PSA test kits of various manufacturers'. However, in all patients with altered PSA levels a changeover from one test kit to another should be considered. Furthermore, uncertainty exists concerning the PSA test's sensitivity, specificity, and the threshold at which a biopsy has to be taken.

Prostate biopsies are often regarded as the gold standard for determining the sensitivity and specificity of the PSA test.

However they are typically carried out only when the results of a DRE or PSA test raises suspicion or a false negative result is assumed due to the number of cores and the prostate volume.(77, 85) This results in a workup bias of the PSA test's sensitivity in particular.(84)

In the Physicians' Health Study, Gann and colleagues evaluated in a group of males (mean age 63 years) the relationship between PSA levels at study entry and the eventual clinical diagnosis of PCa that will develop after 10 years. They demonstrated that a cutoff value of 4.0 ng of PSA per milliliter at baseline had a sensitivity of 46%. The cohort's specificity was 91%, and varied with age and the underlying likelihood of benign prostatic hyperplasia.(86)

The specificity of the PSA test with a cutoff value of 4.0 ng per milliliter was observed to be as low as 54% in older men with benign prostatic hyperplasia.(87) However, 12-23% of men who had inconspicuous DRE results and PSA levels between 2.5 and 4.0 ng per milliliter were associated with PCa after biopsy.(88, 89) Nevertheless, some of these PCas would have never become clinically relevant. Hence, some specialists have recommended to reduce the threshold for biopsy.(90) In contrast, other authors pointed out that repeated testing within the recommended threshold might reduce an overdetection of tumors which unlikely lead to clinical problems, but identifies PCa which will be still treatable despite biochemical progression.(91)

In the past, 75% of men who underwent a prostate biopsy owing to PSA values between 4.0 and 10.0 ng/ml never had PCa. This demonstrates the poor PSA test specificity.(92)

The use of age-specific reference ranges has been criticized because of the decreased sensitivities associated with the lower threshold for biopsy in younger men (proposed cutoff

values of 2.5 ng/ml for men 40 to 49 years of age, 3.5 ng/ml for men 50 to 59 years of age) and higher thresholds for older men (proposed cutoff values of 4.5 ng/ml for men 60 to 69 years of age and 6.5 ng/ml for men 70 to 79 years of age.(77)

Irrespective of the threshold employed, the test should be performed repeatedly in patients with moderately elevated levels, maybe with the prescription of sexual abstinence for 48 hours prior to the test, to confirm that the results are reliable.

PSA circulates both alone and in complexes with other macromolecules, which showed a correlation regarding PCa diagnosis. The likelihood of diagnosing PCa, with a systematic prostate biopsy (CTB) among men with a suspicious PSA value (4-10 ng/ml) and normal DRE was 10 and 56 % with a ratio of free PSA to total PSA of 25 and ≤10 %, respectively. In conclusion, percentage of free PSA could reduce unnecessary biopsies in patients undergoing evaluation for PCa.(93)

1.5.2 Prostate cancer screening using Prostate specific Antigen

PSA Screening has been debated intensively due to diverse results found in the Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial (94) and the European Randomized study of Screening for PCa (ERSPC) study.(95) The PLCO summed up that PCa screening provided no reduction in death rates at 7 years and that no indication of a benefit appeared with 67% of the subjects having completed 10 years of follow-up.

In contrast, ERSPC demonstrated a relative risk reduction of 21% in favor of screening in the intention-to-screen analysis after a follow up of 11 years but no effect of screening on all-cause mortality was seen. In addition, the ERSPC study had less prescreening and crossover events than the PLCO trial.

Furthermore, the Cluster Randomized Trial of PSA Testing for PCa (CAP) included 419 582 men aged 50 to 69 years who were randomized to a single PSA screening intervention vs standard practice without screening between 2001 and 2009. There was no significant difference in PCa mortality after a median follow-up of 10 years but the detection of low-risk PCa cases increased. These findings did not support single PSA testing for population-based screening.(96)

Therefore, PCa screening remained controversial because potential mortality or quality-of-life benefits may be outweighed by harms from overdetection and overtreatment. The use of PSA screening decreased significantly following the US Preventive Services Task Force (USPSTF) recommendation against PSA- screening in 2012 leading to a significant reduction of prostate biopsies and RPs.(97)

However, there is also evidence, supported by the EORTC, suggesting that the number of metastases decreases in 3 out of 1000 men with PSA screening after a median follow-up

of 12 years (RR, 0.70 [95% CI, 0.60-0.82]. The AS strategy to mitigate harms of treatment and a small net benefit for screening in men between 55 to 69 years led to the reevaluation of the fundamental USPSTF recommendation. They concluded that the “right” approach would not be a screening of all men for PCa but the screening should be discussed based on each man’s values and preferences after a detailed information process.(98)

In conclusion, in 2014 a review of evidence showed that PSA screening was associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65) and detection of more localized disease (RR: 1.79; 95% CI: 1.19-2.70). From the results of 5 randomized controlled trials (more than 341,000 men) no PCa-specific survival benefit was observed (RR: 1.00, 95% CI: 0.86-1.17). Additionally, the results of four available RCTs, showed that a survival benefit (OS) cannot be expected (RR: 1.00, 95% CI: 0.96-1.03).(99)

A more recent meta-analysis focusing on the performance of PSA screening enrolled 721 718 men of five randomized controlled trials and observed a small effect on prostate-specific mortality (RR 0.79, 0.69 to 0.91; moderate certainty) over a ten-year period but no impact on overall mortality (RR 1.0, 0.98 to 1.02; moderate certainty). For every 1000 males tested, this translates to one less PCa death over a ten-year period. Additionally, comparisons of biopsies and treatment-related side effects from the included studies 1, 3, and 25 men would report erectile dysfunction, pads usage caused by urinary incontinence and hospitalization due to sepsis, respectively.(100)

1.5.3 PSA density

PSA density (PSAD), is measured in nanograms per milliliter per gram (ng/ml/cm^3) of tissue, and calculated by dividing the quantity of blood PSA by the volume of the prostate.(101, 102)

The density of the prostate is similar to that of water and the weight of the prostate is often approximated using volumetric measurements taken on TRUS using the formula Prostatic Length X Width X Height X (π/6), which equals the volume of an ellipse.

Epstein and colleagues divided the PSA value by the gland volume obtained at the time of RP to calculate PSA density. The correlation between the estimated and real PSA densities delivered excellent results.(57) In the past a PSAD value of 0.1 ng/mL/gram was recommended to differentiate between prostates with and without cancer.(101)

Since the mpMRI prostate biopsy pathway has been established a PSAD associated csPCa odds ratio of 1.3 per increase of 0.05 ng/mL/cc has been described. In addition to the mpMRI grade for PCa suspicion, Filson et al. confirmed PSA density as an important risk factor for the presence of csPCA on fusion biopsy.(58) As a result, increased PSAD is often

used as an enrollment exclusion criteria in AS procedures.(103) In addition patients with incidental PCa after surgery for benign prostatic hyperplasia who had a PSAD less than 0.08 ng/ml/cm^3 following surgery and an undetectable cancer lesion on multiparametric (mp) magnetic resonance imaging (MRI) should be considered for AS.(104)

In line, Distler et al. demonstrated that on receiver operating characteristic (ROC) curve analysis (n=1040 men), the predictive value for csPCa was greater for PSAD than that of prostate imaging reporting and data system (PI-RADS) alone (0.79 vs 0.75, p 0.001), harboring csPCa (Gleason score 3+4) in 43%.

When the PSAD was 0.15 ng/ml/cm^3 or below, the negative predictive value for substantial PCa increased in males with unsuspicious MRI from 79% to 89%.

The negative predictive value of csPCa rose from 83% to 93% in the repeat biopsy situation. In the total cohort, the negative predictive value for having high grade PCa increased from 92% to 98%. Consecutively, the negative predictive value of the PI-RADS score was enhanced by employing PSAD in conjunction with mpMRI.(105)

Recently, Stevens et al. reported a csPCa (Gleason score 3+4=7 or ISUP-2) detection rate of 32% and 36%, in the initial diagnosis group of 526 PCa-negative men and 133 patients under active monitoring with ISUP 1 PCa, respectively. All patients had MRI-guided and/or CTB. It could be demonstrated that, in men without a history of PCa, the inclusion of PSAD enhanced the prediction efficacy of the PI-RADS. Men with a PI-RADS score of ≤3 and a PSAD threshold of 0.15 ng/ml/cm^3 had a reduced frequency of missed csPCa cases. In patients with a negative PCA history or AS, negative or ambiguous MRI results and a PSAD of ≥0.15 ng/ml/cm^3 were shown to have a significantly greater percentage of csPCa than those with a PSAD of <0.15 ng/ml/cm^3.

In contrast, greater percentages of csPCa were seen in both groups of individuals with positive MRI findings, even at extremely low PSAD values (0.10 ng/ml/cm^3).

In order to prevent missing csPCa in these individuals, biopsy should be considered regardless of PSAD. Due to the fact that PI-RADS categories are equally predictive in glands of all sizes, this observation suggests that a high PI-RADS category is a better measure of tumor biology than PSAD.(106) These findings were in agreement with a number of previous studies that looked at the predictive usefulness of PSAD in addition to MRI findings.(105, 107-112)

1.5.4 Digital rectal examination

The DRE is a procedure that should be done either with the patient in a standing slightly bent over or a lateral lying knee-chest position. While standing next to the examination

bed, thigs should be leant against the bed and feet should be placed 50cm apart.
Hereafter, the patient should bend over and rest on his hands or forearm.
A glove should be worn to protect the hand before the examination and a gel for lubrication of the index finger is recommended. The anus must be examined first once the buttocks are separated. The investigator should be aware of hemorrhoids, anal cancer or even melanoma.
Hereafter, the index finger is gently inserted into the anus, to give time for relaxation of the patient in order to be able to reach the total prostate gland. A flaccid or spastic anal sphincter predicts comparable alterations in the urinary sphincter and may be a hint to for a neurogenic disease. Determining the anal sphincter's tone is relevant to anticipate if the rectal sonographic probe may be inserted for further diagnostic steps.
The standard size of the prostate equals the size of a chestnut and its texture resembles the ball of the thumb, when it is opposed i.e. to the middle finger. Prostate cancer may be suspected if the consistency of the prostate gland increases and is very high when the prostatic examination is comparable to touching the bone of the metacarpophalangeal joint of the thumb.
Besides the inspection of the prostate the index finger should circumferentially examine the entire rectum, as deep as possible to be able to detect stenosis, exophytic lesions or induration, probably associated with rectal carcinoma. (113)
After controlling for chance agreement, it was discovered that inter-rater reliability among urologists was only "fair" (kappa= 0.22, p =.009) in classifying the DRE of the prostate as suspicious for PCa.(114) It is predicted that non-urologists will do even worse in this regard. Currently, Neji et al. published a systematic review and meta-analysis mentioning ‘Quality Assessment of Diagnostic Accuracy Studies 2’ and ‘Grades of Recommendation Assessment, Development, and Evaluation’ (GRADE) guidelines to evaluate the diagnostic accuracy of DRE in screening for PCa in primary care settings. They included 7 trials with 9,241 patients after the screening procedure. DRE conducted by primary care practitioners had a pooled sensitivity of 0.51 (95% CI, 0.36-0.67; I2 = 98.4%) and a pooled specificity of 0.59 (95% CI, 0.41-0.76; I2 = 99.4%). Both the pooled PPV and the pooled NPV were 0.41 (95% CI, 0.31-0.52; I2 = 97.2%) and 0.64 (95% CI, 0.58-0.70; I2 = 95.0%), respectively. The evidence's quality, as measured by GRADE, was quite poor. In addition, the accuracy may have been underestimated because only individuals with a positive DRE or increased PSA level got a biopsy. On the basis of a poor test performance and effectiveness the authors were unable to advocate routine DRE screening for PCa in the primary care environment in order to decrease unnecessary diagnostic testing, overdiagnosis, and overtreatment.(115)

In 2003 Mistry et al. published a meta-analysis regarding the screening test performance of PSA and DRE to detect PCa based on a positive biopsy. In total, 13 articles were chosen and most studies included asymptomatic men older than 50 years from various countries with 10.1% of the population being positive for PSA > 4 ng/mL (range 4.3-17.2 ng/mL) and 5.0% of the population had abnormal findings on DRE (range 4.2%-19.3%). However, a prostate biopsy was only performed on men who met these cut-off levels. Due to the invasive nature of this test, there were no biopsy data available for individuals with normal PSA levels and DRE findings.

In these mass screenings they demonstrated an overall PCa detection rate of 1.8% (range of 0.6% to 3.9%) whereas 83.4% (range of 64.4% to 90.0%) of PCas were localized. Therefore, these screening tests were associated with the potential for detecting early-stage PCa. The pooled sensitivity, specificity, and positive predictive value for PSA were 72.1%, 93.2% and 25.1%, respectively. For the DRE they were 53.2%, 83.6% and 17.8%, respectively.(78)

Anyhow, prostate biopsy techniques have been refined especially after the introduction of transrectal ultrasound and prostate mpMRI. Therefore, the real diagnostic performance of DRE approved by fusion biopsy as the current gold-standard for PCa detection remains elusive and has to be clarified in future studies.

1.5.5 Transrektal Ultrasound

The transrektal ultrasonography (TRUS) was invented in the early 1970s and represented the only profound imaging platform for PCa diagnosis made by needle biopsy for a few decades.(116) For many urologists, it offers an affordable, convenient, and easy way to perform prostate biopsy in an ambulatory setting. The image quality available in today's TRUS probes allows urologists to precisely define prostate borders and prostate zonal structure initially leading to an increase in office-based prostate biopsies until the invention of mpMRI.(117)

In the 1990’s Oesterling et al recommended that patients should be followed with annual TRUS evaluations in case of PSA levels less than or equal to the age-specific reference range and normal DRE. In addition, TRUS should be carried out if the serum PSA levels exceeded the age-specific reference range and the DRE was benign.

Any apparent lesions were supposed to be biopsied once the gland's echogenicity had been evaluated and a thorough sextant biopsy of the residual prostatic tissue with additional focus on the prostate's anterior region was also recommended to sample the gland entirely.

In general, regardless of the serum PSA value, patients should have had TRUS done if the DRE was abnormal and any palpable anomalies and any hypoechoic lesions should have received TRUS guided and additional sextant biopsies. Regarding these recommendations urologist should have been able to identify more csPCas at an early, potentially curable stage.(118)

1.5.5.1 Conventional B-mode TRUS

Conventional B-mode TRUS, was unable to consistently find lesions that were positive on biopsy. Although the lack of such lesions does not rule out PCa, it is possible for the disease to infrequently show up as a hypoechoic lesion on grayscale TRUS.(119)

In a cross-sectional study involving 3912 patients, it was shown that PCa was found in a quarter of cases with and without hypoechoic lesions, respectively. As a result, collecting biopsies from hypoechoic lesions did not always lead to a higher identification of PCa compared to isoechoic lesions.(120) In the last twenty years, a false-negative rate of 30 to 40% and inaccurate grade assessment in up to 30% was seen to negatively impact TRUS biopsy performance overall.(121, 122) Overdiagnosis and overtreatment of PCa have been caused by combining the poor diagnostic capabilities of TRUS prostate imaging with the test features of blood PSA.(123)

Contrast-enhanced ultrasound (CEUS), computer-assisted ultrasound (C-TRUS), elastography, and HistoScanning^{TM} were attempts to increase the diagnostic performance of TRUS.(124)

A consensus panel held in 2012 determined that standard TRUS without biopsy was ineffective for identifying and staging PCa. Despite being a cheap and easy operation, it should only be used to locate the prostate, guide biopsies, and determine the volume of the gland as well as any anatomical differences (such as a large median lobe). Furthermore, the panel recommended that the whole gland should be imaged sagittally and axially, with anatomical differences, hypoechoic lesions, the volume of the gland and transition zone noted. In addition, the Doppler TRUS technique may be used showing a color based on the direction of blood flow in relation to the transducer that is receiving the signal. Increased and asymmetrical regional blood flow brought on by increased tumor vasculature could facilitate the identification of PCa.(119) Although, for its own this method produced inconsistent results but in combination with grayscale TRUS, the diagnostic performance could be enhanced.(125)

1.5.5.2 Contrast-enhanced ultrasound

CEUS is an additional variant of ultrasound that has been invented. This technique is characterized by a contrast agent made up of microbubbles enclosed in lipid shells.(126) The medium is injected intravenously and enables visualization of the perfused prostate microvasculature using real time ultrasound.(126, 127)

According to Wink et al., up to 78% of PCa cases can be seen and localized. A better visualization of the tumor combined with focused biopsies resulted in less biopsies per session without a significant restriction of the detection rate. The best rate resulted from a mixed CEUS strategy.(128)

The meta-analysis of 16 studies (n=2624 men) in which CEUS was used as a diagnostic technique to detect PCa, showed a sensitivity, specificity, and the diagnostic odds ratio of 0.70, 0.74, and 9.09, respectively. Sensitivity was superior in positive patient trials compared to those using positive biopsy cores (0.78 vs. 0.64). The authors concluded that CEUS would be a promising tool for the detection of PCa, but could not replace the CTB completely due to missing standardized imaging techniques and diagnostic criteria. Therefore, prospective trials have to be conducted to assess its true clinical impact.(129)

1.5.5.3 Sonoelastography

Transrektal sonoelastography (TRSE) bases on the observation that malignant prostatic tissue is often stiffer than benign and normal tissues. Consequently, pictures taken during compression and decompression are compared to determine the tissue's elasticity.(130)

The meta-analysis performed by Teng et al. to assess the overall accuracy of TRSE targeted biopsy in PCa detection found a pooled sensitivity, specificity , AUC, positive likelihood ratio and negative likelihood ratio for TRSE of 62 (confidential intervals 95% (CI): 55–68), 79% (CI: 74–84%), 0.7696, 2.92 (CI:2.28–3.74) and 0.49 (CI:0.41–0.59).(131)

A different technique, applies an acoustic radiation force impulse (ARFI), on the basis of the Young's modulus to create a shear wave whose speed is measured. High quality delineation of PCa and other prostate tissue is possible with this ultrasonic, elasticity-based imaging technique.(132-134) Regions of hard tissue, which are indicative of prostate cancer, may be distinguished on the elastography picture from those of soft tissue.(119)

ARFI imaging, according to preliminary research, offers quick acquisition times, is inexpensive, and is portable, making it an option for usage in outpatient clinical settings to direct TRSE targeted biopsies.(135) Recently, a systematic review and meta-analysis (including 1380 patients) assessed the value of shear wave elastography for diagnosis of

primary PCa and indicated a high degree of diagnostic security with a pooled sensitivity, specificity and AUC of 86% (95% CI:0.75–0.92), 89% (95% CI:0.82–0.93) and 94% (95% CI:0.91–0.95), respectively.(136)

1.5.5.4 Histoscanning

Another ultrasound-based tool called "histoscanning" (HS) measures tissue disorganization due to cancerous processes using computer-aided analysis.(137) Sonohistology is based on spectrum analysis of radiofrequency ultrasonic echo data along with assessments of textural, contextual, morphological, and clinical aspects in a multiparameter approach.(138) Lately, a review of trials ranging from 13 to 282 patients, compared the sextant and patient-based HS PCa detection rate with RP pathology. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported, with values ranging from 16 to 100%, 45 to 82%, and 52 to 100%, respectively.(117) Probably on the basis of a larger study cohort of 148 males, who had HS prior to RP, Schiffmann et al. observed no association between HS measured tumor volume and RP associated tumor volume.(139) Porres et al. reported on the examination of HS before RP in 282 males (second largest trial) and discovered that HS tumor volume did not match RP tumor volume or correctly predicted disease location on a sextant basis.(140) Finally, Simmons et al. included 249 patients into the prospective, paired-cohort validating trial and assessed the diagnostic accuracy of HS with transperineal template prostate mapping biopsy in men under significant PCa risk after previous biopsy. HS classified 70% of patients as suspicious. Sensitivity, NPV, specificity and PPV were 70.3% (95% CI:59.8-79.5), 41.3% (95% CI:27.0-56.8), 14.7% (95% CI:9.1-22.0) and 36.8% (95% CI:29.6-44.4), respectively.(141) Consecutively, it has been shown that HS did not considerably enhance the diagnosis of PCa and did not represent a useful test in men seeking risk stratification following initial prostate biopsy.(117, 141) These conclusions are underlined by the fact that mpMRI outperformed HS for disease evaluation.(142, 143)

1.5.5.5 Microultrasound

The latest progress in the field of TRUS imaging was the development of 29 MHz high-resolution micro-ultrasound to increase prostate biopsy diagnostic precision while preserving the accessibility and practicality of ultrasound. When compared to conventional

ultrasound devices, which use frequencies of 6–9 MHz, micro-ultrasound works at 29 MHz.(144)

Due to the 90µm crystal spacing the lateral resolution is also enhanced and the axial resolution of micro-ultrasound is increased from 200µm with conventional ultrasound to <70µm. This magnification represents the width of the prostatic ducts, and opens up the possibility to see the ductal architecture changes caused by cancer.

Two methods combined within this approach detect the alterations linked to high-grade malignancy. First, to measure the random Brownian motion of water molecules within a tissue voxel, a technique known as diffusion-weighted imaging (DWI) is used. Second, lower diffusion coefficients can be seen in highly cellular tissues. Therefore, it is possible to perform a real-time targeted biopsy after diagnostic evaluation within one procedure.(145)

Micro-ultrasound images have been categorized based on the likelihood of csPCa using a categorial risk stratification called “Prostate Risk Identification using Micro-ultrasound (PRI-MUS)”. It was developed according to the PI-RADS used for the csPCa risk classification of mpMRI prostate images of men, suspected of having PCa.(146)

Klotz et al. performed a multicenter, prospective registry including 1040 patients from 11 centers located in in North America and Europe. Patients had elevated PSA level and/or worrisome DRE results, and a prior mpMRI. The authors compared the frequencies of PCa detection by mpMRI and microultrasound in all individuals who had either a positive (83%) or negative mpMRI. Using a variety of mpMRI target sampling techniques, biopsies were obtained from both mpMRI targets (PI-RADS >3) and micro-ultrasound targets (PRIMUS >3). Additionally, CTB (maximum of 14 cores) was carried out. But there were differences across sites in the number of cores, the diagnostic approach, the blinding to MRI data, and the experience.

In total, 39.5% of the study cohort received a csPCa diagnosis. The sensitivity of micro-ultrasound and mpMRI were 94% and 90%, respectively (p=0.03).Their corresponding NPVs were 85% and 77%. PPV (44% vs. 43%) and specificities (both 22%) of MRI and micro-ultrasound were fairly equal. In conclusion the comparison of mpMRI to micro-ultrasound demonstrated comparable specificity and better sensitivity for csPCa detection when using the micro-ultrasound.(145)

1.5.6 Multi-Parametric Magnetic Resonance Imaging

Since the 1980s, noninvasive MRI has been utilized to evaluate the prostate gland and its surrounding tissues. Initially, locoregional staging in patients with biopsy-proven cancer was the primary indication of prostate MRI, which was entirely based on morphologic evaluation

utilizing T1-weighted (T1) and T2-weighted (T2) pulse sequences. The mpMRI combines anatomic T2 with functional and physiologic assessment and has been developed as a result of technological advances. It includes diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) MRI embedding the advancement of the apparent-diffusion coefficient (ADC) maps. In addition to locoregional staging, image guidance for biopsy, surgery, focal therapy, and radiation therapy of the prostate has been added to the list of clinical uses for prostate MRI. Others included tumor localization, characterization, risk stratification, surveillance, and assessment of suspected recurrence. The International Prostate MRI Working Group was established by the AdMeTech Foundation in 2007 as it became clear that MRI was playing an increasingly significant role in the diagnosis of PCa. Notable authorities from both academic research and business were brought together. It was concluded, that for multi-center clinical assessments a higher degree of uniformity and consistency was absolutely necessary.(146)

The detection of abnormal lesions within the gland is the main purpose of the mpMRI interpretation procedure. The diagnosis of csPCa depends on various criteria in the PZ, TZ and AS of the prostate gland the reading must be done systematically and should evaluate each compartment individually.(147) A quicker evaluation of the whole gland is possible with this approach. When the multi-parametric procedure is followed, this workup is made simpler since DCE imaging enables early detection of cancer foci that are hard to see on T2W or DWI or foci of enhanced vascularization that are often associated with cancer in the peripheral zone. Each visible lesion must obtain a score 1, 2, 3, 4 or 5 of suspicion for PCa due to the significant overlap between PCa and benign findings within mpMRI.(148) Initial guidelines advised a wholy subjective assessment that was only dependent on the radiologist's expertise (so-called Likert score).(149) The score of 5 represents a typical PCa lesion, i.e. a PZ nodule with low-signal intensity on T2 images, restriction of diffusion, and early contrast enhancement. In most cases scores of 4 for csPCa are due to inconclusive results on several pulse sequences, aberrant DW or DCE imaging findings or non-nodular appearance. Score 3 targets are interpreted as equivocal and exhibit mild signal alterations and/or unusual morphology. They may be either benign or malignant. In real life, the majority of scores of 2 are caused by benign tissue that has certain anomalies (scars and aberrant enhancement). The score of 1 depicts completely normal peripheral (bright and homogeneous on T2W images, without restriction or enhancement) or transition zone tissue and has a high likelihood of being benign.(150)

In an effort to harmonize practices, the European Society of Urogenital Radiology (ESUR) drafted guidelines, including the PI-RADS scoring system version 1 for prostate mpMRI. These guidelines were based on current evidence, the consensus view of experts and the

influence of comparable initiatives regarding breast cancer and associated mammography evaluation (BI-RADS).(151)

The risk stratification for the presence of csPCa (Gleason score 7, including 3+4) was shown by the assessment categories for PI-RADS: PI-RADS 1 (csPCa highly unlikely to be present), PI-RADS 2 (csPCA is unlikely to be present), PI-RADS 3 (csPCa is equivocal), PI-RADS 4 (csPCa is likely to be present) PI-RADS 5 (csPCa is highly likely to be present).(146, 151)

PI-RADS version 1 (v1) did not explicitly state, though, whether the "final" PI-RADS score of a suspicious lesion had to be a sum of the three or four individual scores (ranging from 3 to 15 or 4 to 20), an average score (ranging from 1 to 5), or just a decision support to allow the radiologist to assign the final score subjectively while taking into account further clinical information, which was not integrated within the PI-RADS system.(150)

Since it was published in 2012, PI-RADS v1 has been validated in certain clinical and research scenarios.(148, 152)

After three years of clinical use of the PI-RADS v1 in various centers worldwide Hamoen et al. performed a diagnostic meta-analysis including fourteen studies (1785 patients). The combined data analysis of the diagnostic accuracy for PCa diagnosis revealed a sensitivity of 0.78 (95% CI:0.70-0.84) and specificity of 0.79 (95% CI:0.68-0.86), with NPV ranging from 0.58 to 0.95. Interestingly, those studies that reported a clear description in the methodology and no adjustment of PI-RADS criteria, showed a pooled sensitivity of 0.82 (95% CI:0.72-0.89) and the specificity was 0.82 (95% CI:0.67-0.92). Studies using less stringent or altered PI-RADS criteria, or unclear technique descriptions, obtained a pooled sensitivity of 0.73 (95% CI:0.62-0.82) and specificity of 0.75 (95% CI:0.61-0.84).(153)

However, after the introduction of PI-RADS v1, significant deficiencies in the system were identified due to advances in technology and changes in clinical practice.(151) Consecutively, an international collaboration of the American College of Radiology (ACR), the ESUR and the AdMetech Foundation built a Steering Committee to revise PI-RADS v1. The aim was to promote global standardization and diminish variation in the acquisition, interpretation, and reporting of mpMRI examination, based on the best available evidence and expert consensus opinion. In December 2014 these efforts resulted in the PI-RADS version 2 (v2).(146, 154)

The most relevant differences between PI-RADS v1 and 2 are found within the mpMRI acquisition (no MR spectroscopy imaging option anymore beside T2, DWI and DCE; no delay in MRI post-biopsy if csPCA is suspected, anti-peristaltic medications recommended but no longer considered; Single MRI protocol recommended).

In addition, MRI protocols were revised (just one protocol for MRI of the prostate, with no separate parameters offered for 1.5 T protocols).

Furthermore, anatomical imaging was adjusted (Multiplanar T2WI should incorporate not only the axial, sagittal but also coronal planes). The DWI was also revised (minimum of 2 b-values from 50-100 s/mm2 (not b=0) and the highest should be 800-1000 s/mm2 instead of 3 b-values from 0, 100 and 800-1000 s/mm2.

The apparent diffusion co- efficient (ADC) should not include any b=0 data to avoid pseudo-perfusion effects and should utilize. a high b-value of no greater than 1000 s/mm2 for calculation purposes.(155)

Notably, the, acquisition of additional "high b-value" images is recommended, utilizing a b-value of at least 1400 s/mm^2, up to 2000 s/mm^2 (instead of a maximum of ≥ 800 s/mm$^{2)}$.

For the DCE a fat-suppressed sequence should be performed to improve lesion conspicuity. The injection rate of 2-3 ml/s should be employed, with a temporal resolution of <10 seconds instead of 15 seconds temporal resolution to depict focal early enhancement. The minimum length of acquisition post-injection to detect washout should be ≥2 minutes instead of 5 minutes.

With respect to mpMRI interpretation, any findings should not be influenced by relevant clinical factors (PSA, clinical history, or previous biopsy results). Sophisticated changes have been made to the five-point scoring systems for T2 findings in the PZ, TZ or for DWI. DCE-MRI has changed from a five-point scale to simply being either "positive" or "negative". According to the mpMRI report lesions with a PI-RADS score of 3, 4, or 5 should be described, (maximum of four targets). The index (dominant) lesion should be identified. This is defined as the lesion with the highest PI-RADS score, if this is assigned to two or more lesions, the index lesion should be the largest lesion (maximum diameter or one with extraprostatic growth).

PZ lesions should be measured on ADC maps and TZ lesions measured on T2. Unless direct lesion volumetry is available, overall gland volume should be recorded using the ellipse formula (maximum anteroposterior diameter X maximum transverse diameter X maximum longitudinal diameter X 0.52).(151)

Additionally, at the end of the document, example images should be provided for all PI-RADS categories for each of the three sequences in both the PZ and TZ. In addition, PI-RADS v2 recommends to divide the prostate into 36 sectors (with additional division of the anterior stroma levels into left and right including a further splitting of the TZ into an anterior and a posterior, plus two sectors for the seminal vesicles and one for the external urethral sphincter.(151, 156)

In 2017 Woo et al. published a meta-analysis with 21 studies (3857 patients) to review the diagnostic performance of PI-RADS v2 for the detection of PCa. The pooled sensitivity and specificity for PCa detection was 0.89 (95% CI:0.86–0.92) and 0.73 (95% CI:0.60–0.83), respectively. Six studies performed direct comparison of PI-RADS v1 and PI-RADS v2. PI-

RADS v2 demonstrated a higher pooled sensitivity of 0.95 (95% CI:0.85–0.98) compared to 0.88 (95% CI:0.80–0.93) for PI-RADS v1 (p=0.04). Nevertheless, the pooled specificity was not significantly different (0.73 [95% CI:0.47–0.89] vs 0.75 [95% CI:0.36–0.94], respectively; p=0.90). The authors concluded that PI-RADS v2 has a higher pooled sensitivity than PI-RADSv1 without significantly different specificity.(157)

As an effort to standardize prostate mpMRI evaluation, to enhance the detection of csPCa, to lower the prostate biopsy rate of indolent tumors, and to reduce the inter-reader variability, the PI-RADS v2.1 was attempted in March 2019 as an update to PI-RADS v2.0.(158) This new recommendation did not affect the established function of the DWI in the PZ or T2 relevance for the TZ analysis. However, the indication for DCE was restricted but should still be applied to find PI-RADS 3 lesions comprising csPCa and improve the interpretation of MRIs with poor diagnostic quality regarding the DWI or T2 sequence. Hence, DCE could support radiologists who have minimal expertise evaluating prostate MRIs.(159) Nevertheless, studies supporting the exclusion of DCE from MRI examinations have grown in number due to the risk of probable adverse effects of the contrast agent gadolinium, as well as the increased expense and time. Therefore, the DCE omitting biparametric (bp) MRI of the prostate has been investigated intensively. The most recent meta-analysis included 45 studies and 5217 patients regarding the diagnostic accuracy of bpMRI compared to mpMRI for overall PCa detection. The authors demonstrated a comparable pooled specificity for the bpMRI (0.81 [95% CI:0.76-0.85]) and mpMRI strategy (0.82 [95% CI:0.72-0.88]; p=0.169). In contrast sensitivity was significantly higher after performing mpMRI (0.84 [95% CI:0.78-0.89]) in relation to the bpMRI (0.77 [95% CI:0.73-0.81], p=0.001) approach.(160) Anyhow, due to study heterogeneity, PI-RADS evolution over time and the still underreported varying image quality represented by the Prostate Imaging Quality (PI-QUAL) system no definitive assumptions with respect to the superiority of one method over the other were possible.(159, 160)

1.5.7 Fusion prostate biopsy

Since the beginning of the last decade the utility of mpMRI of the prostate has been evaluated especially in men after previous prostate biopsies to indicate and perform rebiopsy. In 2013, the European Association of Urology (EAU) recommendations advised to perform a mpMRI first to rule out the potential of an anteriorly positioned PCa if clinical suspicion for PCa remained despite a prior negative prostate biopsy. Consecutively, a TRUS- or MRI-guided biopsy of the suspicious region should be performed.(161) This was based on two studies showing that mpMRI imaging had a high NPV to rule out csPCa and

LDB provided improved detection of PCa and csPCa in men with former negative prostate biopsy (FNB) and elevated PSA values.(162, 163)

At the time, in men with FNB results, Vourganti et al. reported a cancer detection rate of 37% utilizing the LDB approach.(164) Interestingly, Abd-Alazeez et al. observed an increased PCa rate of 63% when mpMRI was utilized to indicate prostate biopsy in individuals, with one FNB but transperineal template prostate biopsy was used additionally as CTB.(165)

Finally, one larger study using the mpMRI pathway combined LDB and CTB in FNB patients demonstrating a PCa detection rate of 65.0% (91/140) and observed that a higher level of suspicion on mpMRI was significantly associated with PCa detection ($p<0.001$) with an AUC of 0.74. The LDB and 12-core CTB equally found PC in 52.1% (73/140) and 48.6% (68/140), respectively ($p=0.435$). Nevertheless, LDB was more likely to detect csPCa when compared with the 12-core CTB (47.9% vs 30.7%; $p<0.001$).(166)

Since the invention of TRUS biopsy, the PCa diagnostic pathway was associated with 10 to 12 CTB cores in biopsy-naïve men presenting an elevated serum PSA and/or suspect DRE.(167) As a result, many men without cancer underwent unnecessary biopsies, clinically isPCa was often detected and csPCa was sometimes missed.(167, 168) Furthermore TRUS prostate biopsy was associated with a significant risk of sepsis.(169)

The mpMRI provides information not only on anatomy but also on tissue characteristics such as prostate volume, cellularity, and vascularity. Recent data demonstrated that mpMRI tends to detect higher risk disease and overlooks low-risk disease, systematically.(170) Therefore, Ahmed et al. assessed the diagnostic accuracy of mpMRI and TRUS biopsy in PCa in a paired validating confirmatory study. They found that regarding csPCa diagnosis mpMRI was more sensitive (93%; 95% CI:88–96%) than TRUS-biopsy (48%; 95% CI:42–55%; $p<0{\cdot}0001$) but less specific (41%; 95% CI:36–46% for mpMRI vs 96%; 95% CI:94–98% for TRUS biopsy; $p<0{\cdot}0001$). In addition, mpMRI, used as a triage test before first prostate biopsy, could decrease unnecessary biopsies in 25% and reduce the diagnosis of isPCa.(171)

The mpMRI pathway guideline update of the EAU in March 2019 recommends mpMRI first and advises performing LDB and CTB consecutively in biopsy naïve patients who are clinically suspected of having PCa.(172)

This recommendation mainly based on the PRECISION-, the MRI-FIRST- and the 4M-trials.(59, 61, 66)

In 2018 Kasivivanathan et al. (PRECISION trial) reported a multicenter, randomized, noninferiority trial including 500 men with elevated PSA or positive DRE who were unbiopsied (UB) and underwent mpMRI, with or without ‘fusion-guided mpMRI lesion directed prostate-biopsy’ (LDB) or CTB. Men in the mpMRI group underwent a LDB (without

CTB) if the MRI was suggestive of PCa. When the mpMRI results were not suspicious (PI-RADS <3) prostate biopsy was not offered. CTB was a 10-to-12–core, TRUS–guided biopsy. In total 72% showed a target lesion and in 38% of this patient group csPCa was found. In contrast, 26% of the CTB group received a csPCa diagnosis (adjusted difference 12%; 95% CI:4 to 20; p=0.005). In addition, less men showed isPCa in the MRI-LDB-group than in the CTB-group (adjusted difference -13%; 95% CI:−19 to−7%; p<0.001). The authors concluded that mpMRI, with or without LDB, was noninferior to CTB, and the 95%CI indicated the superiority of this strategy over CTB.(59)

Rouviere et al. performed a prospective paired diagnostic multicenter study (MRI-First study), including 251 eligible biopsy naïve patients with PSA of ≤20 ng/mL, PCa tumor stage ≤T2c and mpMRI ≤3 months before biopsy. An operator, masked to mpMRI results, did a CTB obtaining 12 cores and ≤2 cores targeting hypoechoic lesions. In the same patient, another operator targeted up to two lesions seen on MRI with a Likert score of 3 or higher (three cores per lesion) using LDB. Patients with negative mpMRI (Likert score ≤2) had CTB only. The primary outcome was the detection of csPCa (≥ISUP-2). In total, 37% of patients received a positive csPCa diagnosis, whereas 14%, and 20% of these were diagnosed by CTB or LDB solely and 66% using both techniques. The detection rate of csPCa by CTB (29.9%, 95% CI: 24.3–36.0) and LDB (32.3%, CI:26.5–38.4) was not different (p=0·38). csPCa was missed in 5.2% (95% CI: 2.8–8.7) when CTB was omitted and in 7.6% (4.6–11.6) if the LDB had not been performed. The authors stated that the detection rate of CTB and LDB according to ≥ISUP grade group 2 PCa did not differ but improved by combining both techniques showing an additional added value. Hence, authors concluded that mpMRI before biopsy in UB patients could improve the detection of csPCa although CTB is still essential.(61)

Van der Leest et al. reported the results of the prospective, comparative, multicenter study (4M trial), includeding 626 UB patients, who underwent mpMRI followed by CTB. In case of a positive mpMRI lesion (PI-RADS 3–5) an in-bore MRI guided biopsy was performed prior to CTB. An inconspicuous mpMRI was found in 49% of all patients and an immediate CTB detected csPCa in only 3%. The mpMRI pathway detected csPCa (ISUP ≥2) and isPCa in 25% and 14% of patients, respectively. The CTB approach detected csPCa in 23% and isPCa in 25%.

At the same time, CTB would have overdetected isPCa in 20% (63/309). Anyhow, in-bore MRI guided biopsy found less csPCa (50%) than LDB&CTB (57%) in PI-RADS 3-5 reports. Interestingly, the combination of LDB&CTB resulted in a slight reduction of isPCa (26%) vs. LDB alone (28%). The authors summarized that in UB patients, the mpMRI pathway compared with the CTB pathway resulted in an equal PCa detection rate, with significantly less isPCa cases.(66)

With focus on the diagnostic precision of different fusion techniques, Wegelin and colleagues performed a multicenter randomized controlled trial comparing LDB techniques after mpMRI and associated PCa diagnosis in FNB patients. In total only 35% (234/665) of patients were associated with PIRADS ≥3 lesions causing underpowering. Nevertheless, overall PCa diagnosis was comparable between LDB 49%, cognitive fusion prostate biopsy 44% or mpMRI in bore prostate biopsy 55% (p=0.4). In addition, no significant differences in the detection of csPCa between the LDB 34%, cognitive fusion prostate biopsy 33% and mpMRI in bore prostate biopsy 33% (p > 0.9) was noted.(173) However, no direct associations with biopsy naïve cohorts are valid.

In addition, a recently published review reported on the effectiveness of different LDB techniques. First, the authors described similar detection rates for the cognitive fusion biopsy technique compared to software fusion biopsy approaches, despite the necessity of a higher operator expertise and probably lower accuracy for smaller mpMRI lesions. Second, the mpMRI in bore prostate biopsy might have the potential to be the most precise mpMRI based target strategy as it does not require image fusion and the PCa detection rate is similar to other fusion strategies. Nevertheless, mpMRI in bore prostate biopsy is expensive and time intensive and does not account for mpMRI invisible lesions. Third, regarding the transrectal and transperineal prostate biopsy approach the csPCa detection rates were comparable.(174)

1.6 Study perspectives

The Epstein criteria simplified the famous Gleason grading and demonstrated an excellent prognosis of ISUP 1, a worse prognosis of ISUP 3 versus ISUP 2, and a poor prognosis of ISUP 5 PCa. In addition, on the basis of the PSA, the DRE and the Gleason grading/ISUP score, the risk of PSA failure as a sign of recurrent or persistent disease within 2 years after decisive local therapy could be stratified in different risk groups.(34, 67)

Despite it was reported that untreated localized csPCa is associated with higher metastatic potential, the ProtectT trial demonstrated that men with mainly low (76%) and less intermediate or high risk (34%) PCa under AS instead of curative treatment (surgery vs. radiotherapy), showed a comparable risk to die of PCa after 15 years follow up. Nevertheless, radical treatments reduced the risk of metastases, local progression, and ADT by 50%.(175-177) In contrast, the SPCG-4 study demonstrated that patients with locally symptomatic PCa and a life expectancy of at least 10 years had a significant survival

benefit after RP compared to the watchful waiting strategy. In addition, high risk disease (high Gleason score or extracapsular extension) within the RPS was associated with PCa specific death.(178) Therefore, early detection and correct classification of PCa may offer a better chance to outweigh patient risks, improve decision making and the chance for a cancer free life.

The accuracy of PCa diagnosis was altered by advances in prostate mpMRI during the past ten years.(150) To standardize the acquisition, interpretation, and reporting of prostate mpMRI, the PI-RADS v2 consensus recommendations were created.(146) These efforts in prostate mpMRI should enable less experienced centers to achieve results of specialized academic groups.(150) Nevertheless, the extent of variability in the diagnostic performance of prostate mpMRI between multiple centers in routine clinical practice is incompletely investigated, especially when it comes to the direct comparison of cohorts with different biopsy history.(179)

Combining the LDB approach and the CTB method has been shown to increase the rate of csPCa detection over the past five years in UB men, UB and former negative prostate biopsy (FNB) cohorts, or miscellaneous groups that additionally included patients with earlier diagnosed PCa due to prior prostatic biopsy (EDP).(58, 61, 66, 166, 180-187) This might be due to the fact that, mpMRI detects less than half of all PCa and less than two-thirds of csPCa foci, even after adoption of the PI-RADS v2.(188)

Ever since a significant proportion of EDP patients had been included in larger trials, to evaluate the effectiveness of the biopsy test in populations who had already had a biopsy. Interestingly, the authors never highlighted the bias of artificially increasing the PCa prevalence.(189) Furthermore, it has been demonstrated that follow up biopsy results in EDP men correlated significantly with PCa in general and csPCa findings.(187, 190)

In the past, no direct diagnostic performance comparison of biopsy strategies (LDB, CTB, or LDB&CTB) between UB and FNB patients seemed relevant, even though urologists face different guideline recommendations for both subgroups. Probably, this is attributed to the past advances such as the adoption of mpMRI and LDB of questionable regions for patients who continued to be under suspicion for PCa after a prior negative CTB and subsequent progressive use in the UB scenarios.(59, 61, 66, 161, 187)

National and international guideline panels have recommended a combined biopsy strategy (LDB&CTB) for UB men who were found to have a suspect lesion on mpMRI (i.e. PI-RADS ≥3) since the MRI-First study was released in 2019.(34, 61, 187, 191-194). On the other hand, the EAU advises FNB patients to solely undergo LDB after a PI-RADS ≥3 target was detected. This recommendation was based on a comprehensive assessment and meta-analysis indicating that compared to a CTB approach not including mpMRI, LDB showed a

higher benefit for identifying Gleason grade > 3+4 PCa and a reduced verification of isPCa.(34, 187, 195)

The guidelines of the urological association of America also stated for the FNB setting that an initial mpMRI of the prostate and a consecutive LDB finds PCa at a higher rate than a solitary

CTB (191, 196). They summarized that mpMRI targets, which have a high chance to be associated with PCa but were PCa negative after the first LDB, may receive a further LDB timely.(154, 164, 187).

On the contrary, the urological society of Canada advises to pursue the LDB&CTB strategy in FNB patients, whilst the association of medical oncology in Europe advocates LDB including or excluding CTB, in case of mpMRI positivity (PI-RADS ≥3), although the authors do not refer to any specific literature.(187, 192, 197)

Only one study noticed the missing evidence regarding the biopsy performance of LDB, CTB, and LDB&CTB within UB patients in comparison to FNB patients after positive mpMRI of the prostate (PI-RADS ≥3). Applying the LDB&CTB approach increased the number of csPCa in UB men or cohorts in which <2 FNB could be obtained.(181, 187)

These results are at odds with some international guidelines for FNB patients but the study had limitations regarding the non-prospective design, a minor sample size, missing sampling failures of both biopsy methods or the lack of direct comparison of the biopsy approach with the radical prostatectomy specimen (RPS).(34, 187, 191)

Furthermore, the PSAD cutoff point of ≥ 0.15 ng/ml/cm^3 has been previously assessed in combination with the PI-RADS category to determine the need to perform a prostate biopsy procedure in heterogeneous groups.(105, 108, 198-200)

In addition, the greatest csPCa detection rates (76–97%) regarding UB men were related to PI-RADS v2 scores of 4 and PSAD 0.15 ng/ml/cm^3, or PI-RADS v2 scores of 3 and PSA density 0.30 ng/mL/m, as well.(109) Even in patients with unsuspicious mpMRI of the prostate the NPV of harboring csPCa increased (from 79% up to 89%), when PSAD was 0.15 ng/ml/cm^3 or less.(105)

Just recently some groups recommended to perform LDB only in PIRADS 5 lesions with or without using a PSAD level of >0.15 ng/ml/cm^3 as additional marker for csPCa detection.(201, 202)

Others contend that because LDB&CTB had a greater likelihood of csPCa detection, they were unable to identify individuals who would benefit safely from LDB alone and instead advised concomitant CTB.(183, 203)

Anyhow further validation of PSAD cutoff values and its influence on biopsy performances within UB versus FNB patients is needed to support definitive implementations.

Last, up to this point, no conclusive efforts have been made to distinguish amongst identifiable PI-RADS 2 mpMRI abnormalities reflecting lesions that have been related to csPCa in 7% of cases and PI-RADS 2 findings indicating target less prostate mpMRI revealing csPCa within UB, FNB or EDP study groups in 3-11%, 16-21% or 24%, respectively. (66, 105, 171, 179, 190, 204) Consequently, we evaluated the association of PCa with intramural PI-RADS 2 targets in UB versus FNB patients after radiologic reevaluation.(187)

The aim of this study was to compare the unblinded PI-RADS v2 interrater correlation between extramural (non-academic radiologic institutions) and intramural (department of radiology, Medical University of Graz) radiologists. In addition, the effectiveness of LDB, CTB, or LDB&CTB between UB- and FNB men harboring PI-RADS 2-5 targets, with and without a PSAD cut off level of >0.15ng/ml/cm^3 has also been investigated.

The ISUP-grade of the RPS of men who selected RP as their therapeutic procedure was regarded as reference in order to improve the data currently available for future guideline recommendations.(187)

2 Material and Methods

2.1 Patient Selection

The project was authorized by the ethics committee of the Medical University of Graz (MUG) (32-091Ex19/20). All participants were UB or had at least one FNB, had elevated PSA and/or abnormal DRE, reevaluated PI-RADS 2-5 targets on their prostate mpMRI and agreed to have a prostate biopsy.(187)

Exclusion criteria were the absence of mpMRI visible prostate lesions according to the intramural mpMRI report, EDP patients or previous treatment for PCa.

Previous biopsy history, PSA (leading to mpMRI) and mpMRI data were collected retrospectively. Data from the standardized LDB&CTB process (intramural mpMRI data, DRE, number and location of cores, histopathological report) and RP reports were assessed prospectively and reported as described by the START-Consortium with exception for PCa core length.(205)

2.2 Multiparametric Magentic Resonance Imaging Tomography

Each study participant underwent endorectal coil free 1.5 or 3 Tesla mpMRI of the prostate either in the Department of radiology, MUG, or eligible extramural radiologic facilities. All imaging protocols followed the recommendations of the multinational PI-RADS v2 collaboration unit, which included high resolution T2-weighted and T1 sequences in the sagittal, coronal and axial planes, dynamic contrast enhanced as well as diffusion-weighted sequences.(146, 187)

In order to identify and categorize the risk for PCa, individuals harboring at least one prostate mpMRI target received PI-RADS reports of 2-5. Nine radiologists instructed by two specialists (G.F., H.S.; both having a profound 7 years expertise regarding mpMRI of the prostate) reassessed all the original mpMRI sequences and target findings in concordance with the PI-RADS v2 (including updates from PI-RADS v2.0 to v2.1).(187) The same reviewing radiologist then used the DynaCAD™ software (Philips, Eindhoven, Netherlands) to mark the prostate and any suspect areas in every target- and prostate including axial T2-weighted pictures prior to prostate biopsy.(187) This intramural reevaluation report was defined as the ‘Target defining and PI-RADS v2 evaluating radiologist report’ (TPR).

The most conspicuous PI-RADS score observed was noted for data assessment in situations of numerous lesions.(187)

2.3 Prostate Biopsy Process

The biopsy of suspect prostate lesions was conducted with the UroNav® (2.0, Invivo Corporation-Philips, Gainsville, USA) and TRUS system (BK 3000® and E14C4T® side-fire probe, BK Medical, Herley, Denmark) using prebiopsy coverage with oral antibiotics and peri-prostatic anesthetics (15ml of 1%-Xylanest) applied through the rectal wall at the seminal-prostatic recess on both sides by four devoted urologic consultants with 2 - 5 years of insight and four proctored assistant doctors according to a predefined standardized setting.(187) The workflow for LDB is demonstrated in figure 1.

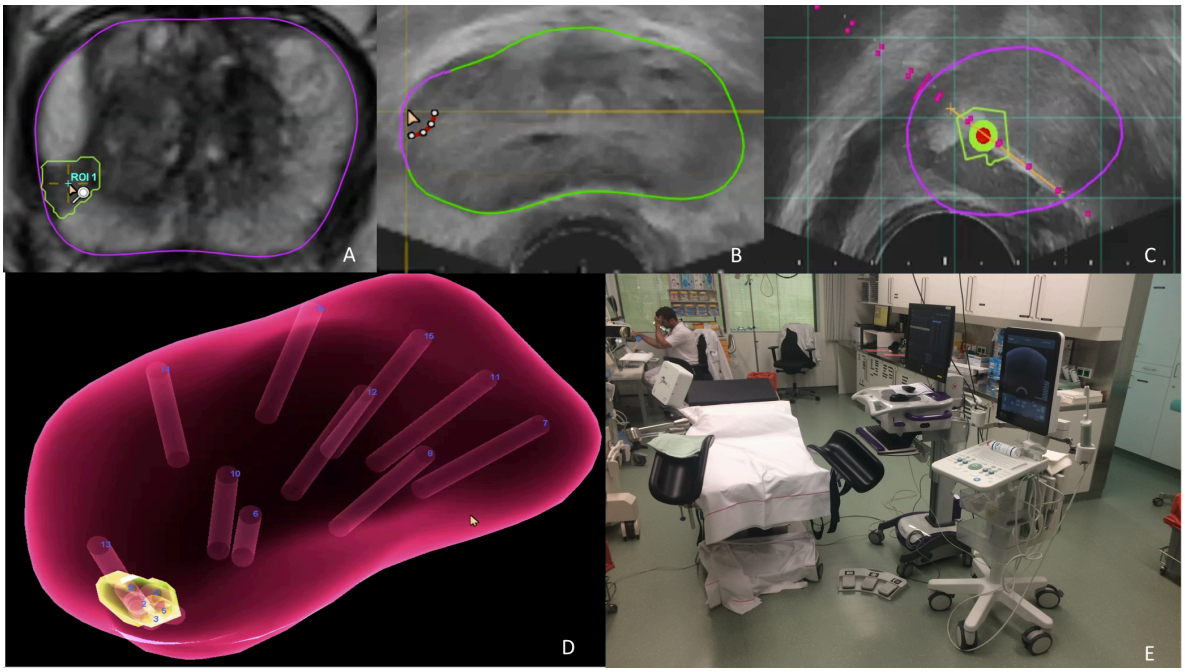

Figure 1: Workflow for mpMRI/TRUS-fusion lesion directed prostate biopsy:

A: Definition and localization of the suspicious lesion (outlined in green) according to PI-RADS Version 2 and the mpMRI prostate margin (outlined in purple) by the in-house radiologist.
B: Definition of the transrektal ultrasound prostate margin (green line) by the biopsy performing urologist.
C: mpMRI and TRUS elastic fusion with the Uronav® system and transrectal biopsy documentation of the biopsy core (i.e. yellow biopsy core line within the green target).
D: 3-dimensional post biopsy reconstruction of 4 'fusion-guided mpMRI lesion directed prostate-biopsies' and 12 conventional systematic prostate biopsies.
E: Uronav- and TRUS biopsy device at the Department of Urology, Medical University of Graz. The biopsy is performed in lithotomy position.

In case of a single target four biopsy cores were obtained. If more than two targets were identified, a dual biopsy core strategy from each target in the sagittal plane was pursued. To accurately depict the target region, we used a fan biopsy approach inside the maximum predicted size of the PI-RADS target.(187)

After changing the UroNav® configuration we deactivated the "target" biopsy session (visible target for the LDB procedure) and started the "other biopsies" mode. Consecutively, the target disappeared and a CTB could be obtained. LDB&CTB of one patient were performed by the same physician who was instructed to strictly perform CTB precluding the previously seen lesion or executed LDB cores.(187)

The German guidelines recommend a CTB standard procedure, which was constantly applied in every patient. This CTB approach was always initiated near the lateral boundary of the prostate and then more medial approaching the urethra at the bottom of the prostate in the peripheral sector on the right prostate hemisphere. Hereafter, the same process was carried out on the opposite lobe.(187) The prostate's peripheral, transitional, and/or central zones were often struck by CTB cores that were laterally and medially extracted from the middle prostate region. In order to clarify probable csPCa in the apical peripheral zone, fibromuscular parenchyma or anterior stroma, we lastly took very steep CTB cores at the medial and lateral apex on both sides.(187, 193) During this process the physician ascertained that the UroNav® MRI/TRUS fusion prostate outline was congruent with the TRUS visible prostate boundary in both planes. Subsequently, post each biopsy punch the TRUS-visible hyperechoic line was manually marked with the UroNav®-software and saved. Each core was recorded and gathered individually.

According to a real life setting the uro-pathologic working group composed of nine MUG experts examined biopsy cores and internal RP specimens including a comprehensive reevaluation of ambiguous histology results. The head of the study group (S.M.) has an uro-pathological expertise of 18 years. After diagnosing PCa, the greatest ISUP score for every biopsy technique as well as RPS in case of a RP was recorded.(187)

The D'Amico risk categories (adopted by the EAU) regarding the PSA relapse of non-metastatic PCa were evaluated in accordance with the prostate biopsy results. The intermediate-risk group (cT2b, PSA ≥10 but ≤20ng/ml or ISUP 2–3 score) and high-risk group (cT2c, PSA >20ng/ml or ISUP 4–5 score) were designated as csPCa.(34, 67, 187)

2.4 Treatment options and radical prostatectomy specimen workup

Besides the prospective assessment of RPS available from patients who opted for RP, other treatment options after PCa diagnosis including AS or systemic hormonal therapy with or without external-beam radiation were retrospectively collected. We evaluated agreement (no difference between the highest ISUP of the prostate biopsy and the RPS), upgrading (transition from a lower ISUP of the biopsy specimen to a higher ISUP of the RPS) or downgrading (transition from the highest ISUP grading of the biopsy specimen to a lower ISUP grading of the RPS).

2.5 Statistical Analysis

Chi-squared- and Fisher's exact test assessed the statistical significance of differences in proportions, and contingency analyses were used to confirm the dependency or independence of two or more nominally scaled variables. The Kappa-coefficient (κ) was calculated and defined as described by Landis et al. to assess the inter-rater agreement of extramural and intramural PI-RADS reports; excellent $\kappa>0.81$), substantial $\kappa=0.61–0.80$), moderate $\kappa=0.41–0.60$), fair $\kappa=0.21–0.40$) and poor $\kappa\leq0.20$).(187, 206)

McNemar's test was used on paired nominal data regarding correlations of the PI-RADS, the biopsy-technique (LDB vs. CTB vs. LDB&CTB) and the RPS with respect to the UB- or FNB-status. The threshold for a significant difference was set at a p value of <0.05.

The JMP® 15.0.0 software (SAS Institute Inc., Cary, NC, USA) was used to conduct all statistical analyses.(187)

3 Results

3.1 Study population

Overall, 874 individuals were assigned for LDB between January 2018 and August 2020. Due to a missing mpMRI lesion, an EDP history, an inconsistent LDB and CTB core number, or lack of documentation of the biopsy technique, 61 individuals were excluded from the final analysis. Finally, 813 participants were included into the study.(187) Of those 511 (63%) men were PCa positive and a RP was performed intramurally and extramurally in 131 and 20 patients, respectively (figure 2).

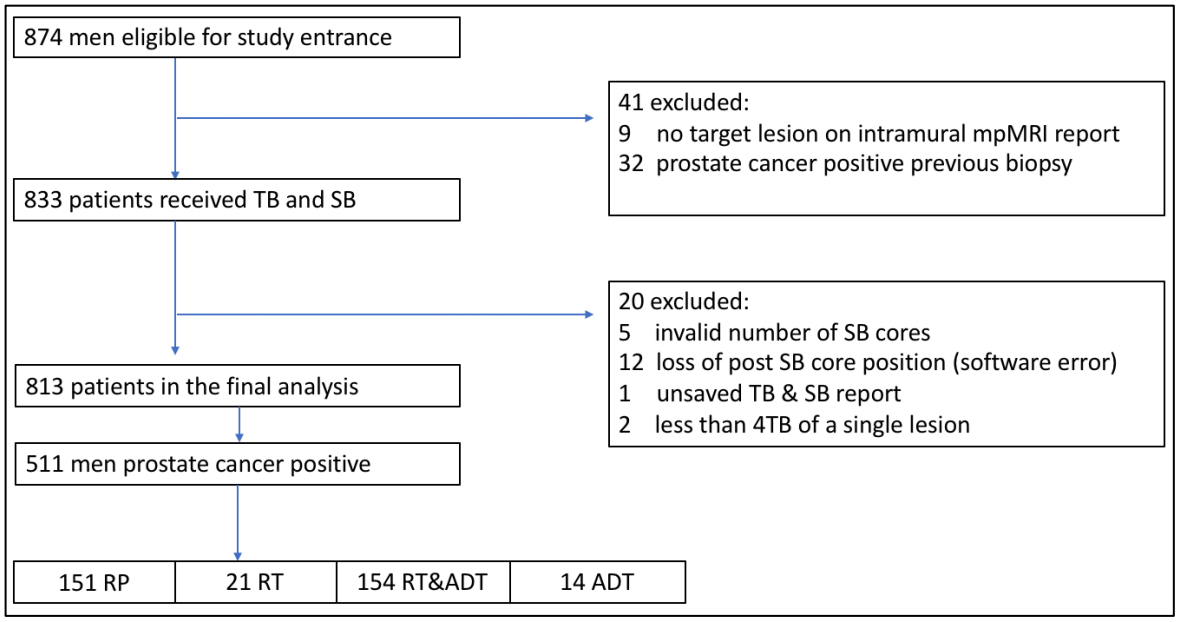

Figure 2: The flow diagram illustrates the research process. Males who had 'multiparametric magnetic resonance imaging' ((mpMRI) because of increased prostate specific antigen with or without abnormal results from a digital rectal evaluation. 'Fusion-guided mpMRI lesion directed prostate-biopsy' (LDB), Conventional systematic transrectal ultrasound guided prostate biopsy (CTB), Radical Prostatectomy (RP), Radiotherapy (RT), Androgen Deprivation Therapy (ADT). Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

Twenty-one patients (4%) received radiotherapy, 154 (30%) radiotherapy plus androgen deprivation therapy (ADT), and 14 patients (3%) ADT only.

Table 1 as well as table 2 demonstrate the research cohort's features in relation to the detection of csPCa and UB or FNB men, respectively.(187) We observed that 445 men

(55%) had csPCa. The diagnosis of csPCa was associated with a higher age (median 69a vs. 65a; p<0.0001) and shorter latency between mpMRI and fusion biopsy (median 77d vs 87d; p<0.0001). In addition, a FNB situation also showed a longer median "mpMRI to fusion biopsy" interval (UB 78d vs. FNB 90d; p<0.0001). Median PSA (7.2 vs. 6.3 ng/ml; p<0.0001) and PSA-density (0.16 vs. 0.11 ng/ml/cm^3; p<0.0001) were also significantly higher in csPCa patients but was not influenced by the biopsy history.(187) Inconspicuous DRE at the time of biopsy correlated significantly with csPCa negative patients and a FNB situation.

Characteristics	**Total**	**csPCa**	**Non-csPCa**	**p**
Age (median, IQR)	67, 61-73	69, 62-75	65, 58-71	**<0.0001**
Type of mpMRI (3 vs. 1.5 Tesla; %)	90 vs. 10	90 vs. 10	88 vs. 12	0.1
Time from mpMRI to LDB (d; median, IQR)	83, 58-111	77, 50-104	87, 65-125	**<0.0001**
Number of extramural/intramural mpMRIs (%)	97/3	98/2	97/3	0.3
Prostate specific antigen (ng/ml; median, IQR)	6.8, 4.9-9	7.2, 5-10.7	6.3, 4.6-8.5	**<0.0001**
Prostate specific antigen density (ng/ml/cm^3; median, IQR)	0.14, 0.09-0.22	0.16, 0.11-0.27	0.11, 0.08-0.17	**<0.0001**
Clinical Tumor (cT) DRE result (n, %)				
1c	572, 70	272, 61	300, 82	**<0.0001**
2a	86, 11	52, 12	34, 9	0.3
2b	97, 12	74, 17	23, 6	**<0.0001**
2c	53, 6	44, 10	9, 2	**<0.0001**
3	5, 1	3, 0.6	2, 0.5	0.8
UroNav® LDB Prostate volume (ml, median, IQR)	46, 34-64	42, 31-58	52, 38-74	**<0.0001**
mpMRI Dynacad Target volume (ml; median, IQR)	0.81, 0.45-1.45	0.87, 0.46-1.66	0.74, 0.44-1.3	**0.001**
Number of visible mpMRI lesions (median, IQR, min.-max.)	1, 1-1, 1-3	1, 1-1, 1-3	1, 1-1, 1-3	0.1
Number of visible mpMRI lesions: 1 vs. >1 (n, %)	739, 91 vs. 74, 9	400, 90 vs. 45, 10	339, 92 vs. 29, 8	0.3
Cores taken per target lesion (median, IQR, min.-max.)	4, 4-4, 4-8	4, 4-4, 4-8	4, 4-4, 4-6	0.06
Cores taken by conventional	12, 12-12, 12-12	12, 12-12, 12-12	12, 12-12, 12-12	1

systematic transrectal ultrasound guided prostate biopsy (median, IQR, min.-max.)				
Total No. of cores taken	16, 16-16, 16-20	16, 16-16, 16-20	16, 16-16, 16-18	0.4
Number of RPs (n, %)	151, 100	148, 98	3, 2	**<0.0001**
Time to RP (months, median, IQR)	4, 3-4	4, 3-4	5, 3-6	0.7

Table 1: The research cohort's features in relation to the detection of clinically significant prostate cancer (csPCa; defined by the 'European Association of Urologists risk stratification). 'fusion-guided mpMRI lesion directed prostate-biopsy' (LDB), multiparametric magnetic resonance imaging (mpMRI). Digital rectal examination (DRE), Interquartile range (IQR), Radical prostatectomy (RP). Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

In contrast, cT2b/c results were associated with csPCa diagnosis and cT2c results were reported more often in UB situations. Furthermore, the Uronav® post fusion MRI/TRUS prostate volume was significantly smaller when csPCa was detected (median; 42 vs. 52 ml) or in case of a UB status (both p<0.0001). On the other hand, the mpMRI 'Dynacad' target volume was significantly higher in csPCa positive patients (median 0.87 vs. 0.74 ml; p=0.001). We observed an equal time interval from LDB&CTB to RP between UB and FNB patients but the likelihood of FNB men having a RP was lower (p=0.002).(187)

Characteristics	**UB**	**FNB**	**p**
Age (median, IQR)	66, 60-73	67, 61-73	0.1
Type of mpMRI (3 vs. 1.5 Tesla; %)	90 vs. 10	90 vs. 10	0.5
Time from mpMRI to LDB (d; median, IQR)	78, 49-105	90, 69-128	**<0.0001**
Number of extramural/intramural mpMRIs (%)	483, 97/16, 3	309, 98/5, 2	0.2
Prostate specific antigen (ng/ml; median, IQR)	6, 4.4-9	7, 5.4-10.4	0.3
Prostate specific antigen density ($ng/ml/cm^3$; median, IQR)	0,14, 0.09-0.22	0,14, 0.09-0.24	0.9
Clinical Tumor (cT) DRE result (n, %)			
1c	333, 67	239, 76	**0.005**
2a	57, 11	29, 9.2	0.4
2b	64, 13	33, 10.5	0.3
2c	41, 8	12, 4	**0.01**
3	4, 1	1, 0.3	0.4

UroNav LDB prostate volume (ml; median, IQR)	43, 32-60	51, 37-71	**<0.0001**
mpMRI Dynacad target volume (ml; median, IQR)	0.78, 0.45-1.43	0.82, 0.5-1.48	0.2
Number of visible mpMRI lesions (median, IQR, min.-max.)	1, 1-1, 1-3	1, 1-1, 1-3	0.3
Number of visible mpMRI lesions: 1 vs. >1 (n, %)	449, 90 vs. 50, 10	290, 92 vs. 24, 8	0.3
Number of cores taken per target lesion (median, IQR, min.-max.)	4, 4-4, 4-6	4, 4-4, 4-8	0.5
Number of cores taken by conventional systematic transrectal ultrasound guided prostate biopsy (median, IQR, min.-max.)	12, 12-12, 12-12	12, 12-12, 12-12	1
Total Number of cores taken	16, 16-16, 16-18	16, 16-16, 16-20	0.1
Number of RPs (n, %)	110, 22	41, 13	**0.002**
Number of RPs with prostate specific antigen density >0.15 ng/ml/cm^3 (n, %)	47, 9	15, 5	0.1
RP performed intramural / extramural (n, %)	97,88 / 13,12	34, 83 / 7,17	0.4
Time to RP (months; median, IQR)	4, 3-4.5	4, 3-4	0.5

Table 2: Comparison of biopsy naïve (UB=green box) and former negative prostate biopsy (FNB=grey box) patient characteristics. 'Fusion-guided mpMRI lesion directed prostate biopsy' (LDB), multiparametric magnetic resonance imaging (mpMRI). Digital rectal examination (DRE), Interquartile range (IQR), Radical prostatectomy (RP). Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

The LDB&CTB strategy detected within the TPR 2, 3, 4, 5 all PCa and csPCa or isPCa in 11%, 40%, 71%, 79% (p<0.0001) and 8%, 30%, 61%, 75% (p<0.0001) or 3%, 10%, 10% and 4% (p=0.02), respectively (table 3). No difference of TPR 2, 3, 4, 5 distributions regarding 151 RP patients was found, even after stratification for a PSAD>0.15 ng/ml/cm^3. Most patients, who received RP were diagnosed with csPCa and were operated intramurally. In total 62 patients with a PSAD >0.15 ng/ml/cm^3 cut-off opted for a RP as curative treatment.(187)

Characteristics	**Total**	**TPR 2**	**TPR 3**	**TPR 4**	**TPR 5**	**p**
Total (n, %)	813, 100	36, 4	201, 25	364, 45	212, 26	
Prostate specific antigen density >0.15 ng/ml/cm^3 (n, %)	359, 44	13, 36	68, 34	148, 41	130, 61	

overall PCa LDB&CTB (n,%)	511, 63	4, 11	82, 40	258, 71	167, 79	**<0.0001**
csPCa LDB&CTB (n,%)	445, 55	3, 8	61, 30	222, 61	159, 75	**<0.0001**
csPCa LDB (n,%)	375, 46	2, 6	37, 18	185, 49	151, 71	**<0.0001**
csPCa CTB (n,%)	391, 48	1, 3	51, 25	191, 52	148, 70	**<0.0001**
csPCa solely by LDB (n,%)	43, 10	2, 67	8, 13	25, 11	8, 5	**0.001**
csPCa solely by CTB (n,%)	60, 13	1, 33	21, 34	32, 14	6, 4	**<0.0001**
csPCa detection simultaneously by LDB&CTB (n,%)	342, 77	0, 0	32, 52	165, 74	145, 91	**<0.0001**
IsPCa LDB (n,%)	47, 9	1, 3	11, 5	29, 8	6, 3	0.06
IsPCa CTB (n,%)	68, 13	1, 3	20, 10	37, 10	10, 5	0.06
IsPCa LDB&CTB) n, %)	66, 13	1, 3	21, 10	36, 10	8, 4	**0.02**
Radical prostatectomy (n, %)	151, 100	1, 0.7	29, 19	86, 57	35, 23	0.9
Prostate specific antigen density >0.15 ng/ml/cm^3 of pts. undergone RP (n, %)	62, 41	0	16, 26	30, 48	16, 26	1

Table 3: Biopsy performance according to the 'Target defining and Prostate Imaging–Reporting and Data System version 2' evaluating intramural radiologist report' (TPR) 2, 3, 4, 5 with respect to biopsy technique. 'mpMRI/TRUS-fusion lesion directed prostate biopsy' (LDB) and conventional systematic transrectal ultrasound guided prostate biopsy (CTB), combined biopsy (LDB&CTB). Clinically significant prostate cancer (csPCa) or insignificant (is) PCa was defined according to the European Association of Urologists (EAU) risk groups.

3.2 mpMRI Interpretation

According to a real world setting the 'primary PI-RADS v2 radiologist report' (PMP) was conducted in 15 different qualified Austrian radiologic institutions and PMPs were assigned by overall 45 radiologists. The TPR was performed unblinded by 9 radiologists. In total, 97% of all mpMRI studies were done extramurally with no difference according to csPCa diagnosis or biopsy-history between extramural and intramural mpMRIs.

PMP was rather performed by two radiologists, whereas TPR was mainly done by one dedicated radiologic consultant. (187)

In total, PMP compared to TPR showed an agreement, upgrading and downgrading of 78%, 12% and 10%, respectively. UB patients demonstrated a significantly higher agreement (83% vs. 71%, p<0.0001) but less upgrading (9% vs. 16%, p=0.006) or downgrading (8% vs. 13%, p=0.01) compared to FNB patients (table 4, 5, 6).(187) UB and FNB patients both showed no difference according to low agreement and high downgrading rates for PI-RADS 2 or agreement, upgrading or downgrading in PI-RADS 3 reports. In contrast, UB patients were associated with significantly more agreement and less upgrading in PI-RADS 4 (p=0.02 and p=0.003) and PI-RADS 5 reports (both; p=0.0005).

PI-RADS	**Agreement**			**p**
	Total	UB	FNB	UB vs. FNB
Total (n,%)	637, 78	414, 83	223, 71	**<0.0001**
1 (n,%)	n.a.			
2 (n,%)	4, 11	0	4, 16	0.2
3 (n,%)	150, 75	82, 73	68, 76	0.6
4 (n,%)	328, 90	219, 93	109, 85	**0.02**
5 (n,%)	155, 73	113, 81	42, 58	**0.0005**

Table 4: The interobserver agreement of the 'primary Prostate Imaging–Reporting and Data System version-2 (PI-RADS) radiologist report' (PMP) versus the 'intramural Target-defining and PI-RADS-version 2 evaluating radiologist report' (TPR) was assessed. The total cohort was sub stratified into unbiopsied (UB=green box) and former negative prostate biopsy (FNB=grey box) patients. Not applicable (n.a.).

PI-RADS	**Upgrading**			**p**
	Total	UB	FNB	UB vs. FNB
Total (n,%)	95, 12	46, 9	49, 16	**0.006**
1 (n,%)	n.a.			
2 (n,%)	0	0	0	n.a.
3 (n,%)	8, 4	7, 6	1, 1	0.06
4 (n,%)	30, 8	12, 5	18, 14	**0.003**
5 (n,%)	57, 27	27, 19	30, 42	**0.0005**

Table 5: The interobserver upgrading of the 'primary Prostate Imaging–Reporting and Data System version-2 (PI-RADS) radiologist report' (PMP) versus the 'intramural Target-defining and PI-RADS-version 2 evaluating radiologist report' (TPR) was assessed. The total cohort was sub stratified into unbiopsied (UB=green box) and former negative prostate biopsy (FNB=grey box) patients. Not applicable (n.a.).

PI-RADS	Downgrading			p
	Total	UB	FNB	UB vs FNB
Total (n,%)	81, 10	39, 8	42, 13	**0.01**
1 (n,%)	n.a.			
2 (n,%)	32, 89	11, 100	21, 84	0.2
3 (n,%)	43, 21	23, 21	20, 22	0.7
4 (n,%)	6, 2	5, 2	1, 1	0.3
5 (n,%)	0	0	0	n.a.

Table 6: The interobserver downgrading of the 'primary Prostate Imaging–Reporting and Data System version-2 (PI-RADS) radiologist report' (PMP) versus the 'intramural Target-defining and PI-RADS-version 2 evaluating radiologist report' (TPR) was assessed. The total cohort was sub stratified into unbiopsied (UB=green box) and former negative prostate biopsy (FNB=grey box) patients. Not applicable (n.a.).

The TPR was significantly associated with more PI-RADS-2 and -5 results as well as less PI-RADS-4 but comparable PI-RADS 3 results. UB-TPR were associated with equal PI-RADS 2 and 3, less PI-RADS 4 and more PI-RADS 5 lesions compared to UB-PMP results. In contrast, FNB-TPR findings showed significantly more PI-RADS 2 and PI-RADS 5 reports but less PI-RADS 3 and 4 reports than FNB-PMP (table 7).

PI-RADS	PMP			TPR			p		
	Total	UB	FNB	Total	UB	FNB	Total	UB	FNB
1 (n,%)	2, 0.2	2, 0.4	0	0	0	0	n.a.		
2 (n,%)	15, 2	8, 2	7, 0.2	36, 4	11, 2	25, 8	**0.001**	0.5	**0.002**
3 (n,%)	210, 26	100, 20	110, 35	201, 25	112, 22	89, 28	0.4	0.08	**0.008**
4 (n,%)	422, 52	269, 54	153, 49	364, 45	236, 47	128, 41	**<0.0001**	**<0.0001**	**0.002**
5 (n,%)	164, 20	120, 24	44, 14	212, 26	140, 28	72, 23	**<0.0001**	**0.001**	**<0.0001**

Table 7: Assessment of the 'primary Prostate Imaging–Reporting and Data System version-2 (PI-RADS) radiologist report' (PMP) versus the 'intramural Target-defining and PI-RADS-version 2 evaluating radiologist report' (TPR) according to the total cohort, unbiopsied (UB=green box) and former negative prostate biopsy (FNB=grey box) patients. Not applicable (n.a.).

The kappa coefficient (κ) for the general interobserver PI-RADS ≥2 evaluation regarding the total, UB and FNB group was 0.67 (κ 95% CI; 0.62-0.71), 0.73 (κ 95% CI; 0.68-0.78) and 0.57 (κ 95% CI; 0.49-0.64), respectively.

The k for PI-RADS ≥3 reports related to the total, UB- and FNB-cohort was 0.72 (κ 95% CI; 0.68-0.77), 0.78 (κ 95% CI; 0.73-0.83) and 0.63 (κ 95% CI; 0.55-0.70), respectively.
Table 5 demonstrates the interobserver correlation for each PI-RADS score 2, 3, 4, 5 with respect to the biopsy history. The κ reflected a slight match for PI-RADS 2 lesions (κ=0.13) but good accordance for PI-RADS 3 (κ=0.64), 4 (κ=0.68) or 5 (κ=0.77) reports between PMP and TPR. This observation was even more obvious for UB patients with less agreement for PI-RADS 2 lesions (κ=-0.02) but good accordance for PI-RADS 3 (κ=0.71) or 4 (κ=0.73) and excellent agreement for PI-RADS 5 (κ=0.82) reports in comparison to patients with a FNB history (table 8).

PI-RADS	**κ**			**κ 95% CI**		
	Total	UB	FNB	Total	UB	FNB
1 (n,%)	n.a.			n.a.		
2 (n,%)	0.13	-0.02	0.22	-0.002-0.3	-0.03-0.01	0.03-0.41
3 (n,%)	0.64	0.71	0.54	0.58-0.7	0.64-0.79	0.44-0.66
4 (n,%)	0.68	0.73	0.6	0.63-0.73	0.67-0.79	0.51-0.68
5 (n,%)	0.77	0.82	0.67	0.72-0.82	0.77-0.88	0.56-0.77

Table 8: Assessment of the 'primary Prostate Imaging–Reporting and Data System version-2 (PI-RADS) radiologist report' (PMP) versus the 'intramural Target-defining and PI-RADS-version 2 evaluating radiologist report' (TPR) according to the total cohort, unbiopsied (UB=green box) and former negative prostate biopsy (FNB=grey box) patients. Cohens-kappa-coeffecient (κ), not applicable (n.a.).

3.3 Comparison between different biopsy strategies

According to the LDB&CTB, LDB and CTB method PCa was detected in 63% (LDB&CTB vs. LDB vs. CTB; both p<0.0001) 52% and 57% (LDB vs. CTB; p=0.001), respectively (table 9).
In addition, csPCa was found with the LDB&CTB, LDB and CTB strategy in 55% (LDB&CTB vs. LDB vs. CTB; both p<0.0001), 46% and 48% (LDB vs. CTB; p=0.2), respectively.
With exception of TPR-3, which showed a higher csPCa diagnosis with CTB (p=0.02), we observed no difference for the csPCa detection between LDB and CTB for TPR-2, 4 or 5. The PSAD>0.15 ng/ml/cm^3 cut-off emphasized the same value of the LDB and CTB approach for detecting all and csPCa.(187)

LDB&CTB discovered a considerably higher number of csPCa compared to the LDB or CTB approach alone in the UB or FNB cohort according to TPR 3-5 reports. In contrast, we found no variation in the identification of csPCa among TPR 2 lesions in UB or FNB men.(187)
In addition, regarding a PSAD>0.15 ng/ml/cm^3, no changes for the rate of csPCa found by LDB and LDB&CTB according to UB-TPR-5 patients (n=79 vs. n=81; p=0.2) or any TPR 2 report were noticed. For all other correlations in the total, UB or FNB cohort including the PSAD>0.15 ng/ml/cm^3 cut-off we found a significantly higher csPCa detection rate with the LDB&CTB approach.
Furthermore, CTB and LDB&CTB detected significantly more isPCa than the LDB approach (CTB 8% vs. LDB 6%; p=0.007 and LDB&CTB 8% vs. LDB 6%; p=0.003), but we observed no difference between LDB&CTB and CTB (p=0.7).(187) The exclusive diagnosis of csPCa by one biopsy method was not significantly different compared to the other (LDB 10% vs CTB 13%, p=0.09). In addition, regarding ISUP results no difference between LDB and CTB was found.
However, LDB&CTB detected significantly more ISUP 1 (94 vs. 78; p=0.046), 2 (136 vs. 114; p=0.01), 3 (121 vs. 103; p=0.02), 4 (88 vs. 69; p=0.001) and 5 (72 vs. 57; p=0.0001) PCa than LDB. In contrast, no difference according to the detection of ISUP 1-3 between LDB&CTB and CTB was seen but more ISUP 4 (88 vs. 73; p=0.004) and 5 (72 vs. 57; p=0.0001) results were diagnosed with LDB&CTB than with CTB.
Moreover, within FNB patients LDB (3% both) discovered a lower number of isPCa compared to CTB (7%; p=0.02) or LDB&CTB (6%, p=0.01).(187) This difference was not observed for UB patients. We also found neither a difference for the csPCa detection solely by the LDB nor CTB method or any LDB ISUP score.

Specimen	**LDB**	**CTB**	**p**	**LDB&CTB Biopsy**	**p (LDB&CTB vs.LDB)/p(LDB&CTB vs.CTB)**
Overall PCa (n,%)	421, 52	459, 57	**0.001**	511, 63	**<0.0001/<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	229, 28	240, 30	0.2	274, 34	**<0.0001/<0.0001**
csPCa (n,%)	375, 46	391, 48	0.2	445, 55	**<0.0001/<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	216, 27	219, 27	0.7	249, 31	**<0.0001/<0.0001**
UB csPCa (n,%)	268, 54	283, 57	0.1	310, 62	**<0.0001/<0.0001**
+PSAD>0.15 ng/ml/cm3 (n,%)	161, 32	161, 32	1	176, 35	**0.0001/0.0001**
UB csPCa TPR-2 (n,%)	1, 9	0	0	1, 9	1/0
+PSAD>0.15 ng/ml/cm^3 (n,%)	0	0	0	0	0
UB csPCa TPR-3 (n,%)	23, 21	32, 29	**0.049**	38, 34	**0.0001/0.01**

+PSAD>0.15 ng/ml/cm^3 (n,%)	16, 14	18, 16	0.6	23, 21	**0.01/0.025**
UB cPCa TPR-4 (n,%)	132, 56	141, 60	0.1	155, 66	**<0.0001/0.0002**
+PSAD>0.15 ng/ml/cm^3 (n,%)	66, 28	67, 28	0.8	72, 31	**0.01/0.025**
UB csPCa TPR-5 (n,%)	112, 80	110, 79	0.5	116, 83	**0.0455/0.01**
+PSAD>0.15 ng/ml/cm^3 (n,%)	79, 56	76, 54	0.3	81, 58	0.2/**0.025**
FNB csPCa (n,%)	107, 34	108, 34	0.9	135, 43	**<0.0001/<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	55, 17	58, 18	0.6	73, 23	**<0.0001/0.0001**
FNB csPCa TPR-2 (n,%)	1, 4	1, 4	1	2, 8	0.3/0.3
+PSAD>0.15 ng/ml/cm^3 (n,%)	1, 4	1, 4	1	2, 8	0.3/0.3
FNB csPCa TPR-3 (n,%)	14, 16	19, 21	0.2	23, 26	**0.003/0.0455**
+PSAD>0.15 ng/ml/cm^3 (n,%)	6, 7	7, 8	0.7	10, 11	**0.046**/0.08
FNB csPCa TPR-4 (n,%)	53, 41	50, 39	0.6	67, 52	**0.0002/<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	25, 19	26, 20	0.8	34, 27	**0.003/0.005**
FNB csPCa TPR-5 (n,%)	39, 54	38, 53	0.7	43, 60	**0.0455/0.03**
+PSAD>0.15 ng/ml/cm^3 (n,%)	23, 32	24, 33	0.1	27, 38	**0.0455**/0.08
IsPCa (n,%)	47, 6	68, 8	**0.007**	66, 8	**0.003**/0.67
UB IPCa (n,%)	37, 7	47, 9	0.1	46, 9	0.1/0.8
FNB Is PCa (n,%)	10, 3	21, 7	**0.02**	20, 6	**0.01**/0.7
csPCa found solely by one biopsy method (n,%)	43, 10	60, 13	0.09		
csPCa TPR-2 (n,%)	2, 5	1, 3	0.6	3, 8	0.3/0.2
+PSAD>0.15 ng/ml/cm^3 (n,%)	1, 3	1, 3	1	2, 5	0.3/0.3
csPCa TPR-3 (n,%)	37, 18	51, 25	**0.02**	61, 30	**<0.0001/0.002**
+PSAD>0.15 ng/ml/cm^3 (n,%)	22, 11	25, 12	0.5	33, 16	**0.001/0.005**
csPCa TPR-4 (n,%)	185, 51	191, 52	0.5	222, 61	**<0.0001/<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	91, 25	93, 26	0.7	106, 29	**0.0001/0.0003**
csPCa TPR-5 (n,%)	151, 71	148, 70	0.5	159, 75	**0.005/0.001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	102, 48	100, 47	0.6	108, 51	**0.01/0.005**
ISUP 1 (n,%)	78, 15	92, 18	0.2	94, 18	**0.046**/0.74
ISUP 2 (n,%)	114, 22	126, 25	0.3	136, 27	**0.01**/0.12

ISUP3 (n,%)	103, 20	111, 22	0.4	121, 24	**0.02**/0.13
ISUP 4 (n,%)	69, 14	73, 14	0.7	88, 17	**0.001/0.004**
ISUP 5 (n,%)	57, 11	57, 11	1	72, 14	**0.0001/0.0001**

Table 9: Prostate biopsy outcome of the 'mpMRI/TRUS-fusion lesion directed prostate biopsy' (LDB), conventional systematic transrectal ultrasound guided prostate biopsy (CTB) and the combined biopsy (LDB&CTB) approach, correlated with overall & clinically significant prostate cancer (csPCa) according to 'Target-defining and Prostate Imaging–Reporting and Data System version 2 (PI-RADS) evaluating radiologist report (TPR)'-2, 3, 4, 5 and unbiopsied (UB=green box)- and 'former negative transrectal ultrasound guided prostate biopsy' (FNB=grey box) patients. Insignificant (is) PCa was defined according to the D'Amico-European Association of urologists (EAU)' risk groups with respect to the International Society of Urological Pathology (ISUP) grading. Prostate specific antigen (PSA), PSA Density (PSAD) ng/ml/cm^3. Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

No difference according to upgrading a negative or isPCa biopsy, ISUP-1 to ≥ISUP-2, ISUP-2 to ≥ISUP-3 or ISUP-3 to ≥ISUP-4 by the other biopsy method was seen (Table 10). Anyhow, the CTB upgraded a negative or any ISUP ≥1 LDB significantly more often than vice-versa (LDB 169 vs. CTB 106; p=0.0001).(187)

Specimen	**LDB**	**CTB**	**p**
Upgrading negative- or isPCa-biopsy by other biopsy method to csPCA (n, %)	71, 9	54, 7	0.1
Upgrading isPCa biopsy by other biopsy method to csPCa	11, 1	12, 1	0.8
Upgrading neg. or any ISUP ≥1 (n, %) by other biopsy mode	169, 21	106, 13	**0.0001**
Upgrading ISUP 1 to ≥ISUP 2 by other biopsy mode (n, %)	24, 5	17, 2	0.3
Upgrading ISUP 2 to ≥ISUP 3 by other biopsy mode (n, %)	28, 3	16, 2	0.07
Upgrading ISUP 3 to ≥ISUP 4 by other biopsy mode (n, %)	20, 2	16, 2	0.5

Table 10: Upgrading rates of the 'fusion-guided mpMRI lesion directed prostate-biopsy' (LDB) or conventional systematic transrectal ultrasound guided prostate biopsy (CTB) by

the other biopsy approach. Insignificant (is), prostate cancer (PCa), International Society of Urological Pathology (ISUP) grading.

3.4 Comparison of the biopsy technique referred to the biopsy history

All or csPCa was diagnosed by LDB&CTB in 71% and 49% or 62% and 43% of UB and FNB patients (all p<0.0001), respectively (Table 11). In addition, UB-LDB (54%) or UB-CTB (57%) detected more csPCa compared to FNB-LDB (34%; p<0.0001) or FNB-CTB (34%; p<0.0001). We observed the same correlations between the UB and FNB group for csPCa patients with a PSAD cut-off >0.15 ng/ml/cm^3.

UB men demonstrated a higher rate of csPCa regarding TPR 4 and 5 targets after LDB (p=0.01 and <0.0001) or LDB&CTB (0.01 and 0.002) was undertaken in comparison with the FNB cohort but this difference could not be found for PI-RADS 2 and 3 reports.(187) The incorporation of PSAD>0.15 ng/ml/cm^3 as a cut-off marker for csPCa being present demonstrated a critical elevation of csPCa positive UB-TPR 3, 4 and 5 after performing the LDB&CTB or LDB only approach.

Interestingly, csPCa was exclusively diagnosed by LDB in 7% of UB and 16% of FNB patients (p=0.002). In addition, 11% of UB and 19% of FNB patients showed csPCa solely diagnosed by CTB (p=0.02). In contrast to the csPCa-cohort, within the total cohort we found no apparent variation for the exclusive csPCa verification with the LDB- or CTB-approach between UB- or FNB-men. Furthermore, csPCa was detected in 82% of UB and 64% of FNB patients simultaneously with LDB and CTB (p<0.0001). These, observations were not influenced by the incorporation of the PSAD >0.15ng/ml/cm^3 as a threshold.

The LDB method discovered isPCa considerably more frequently in UB- (7%) than in FNB- (3%) individuals (p=0.01). Additionally, LDB identified isPCa less frequently in the FNB-patient group than the CTB (3% vs. 7%, p=0.02) or LDB&CTB (3% vs. 6%, p=0.01) approach.(187) For the discovery of isPCa in UB patients, we observed no statistically significant difference between the biopsy strategies (LDB&CTB 9% vs. LDB 7%; p=0.1 or CTB 9%; p=0.8). Furthermore, ISUP scores of radical prostatectomy specimens were equally distributed between UB and FNB patients.(187)

Characteristics	**UB**	**FNB**	**p**
Total (n;%, median, IQR, min.-max.)	499, 61	314; 39, 1, 1-2, 1-6	
TPR-2 (n,%)	11, 2	25, 8	**0.0001**
TPR-3 (n,%)	112, 22	89, 28	0.06

TPR-4 (n,%)	236, 47	128, 42	0.07
TPR-5 (n,%)	140, 28	72, 23	0.1
overall PCa detection LDB&CTB (n,%)	356, 71	155, 49	**<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	189, 38	85, 27	**<0.0001**
csPCa detection LDB&CTB (n,%)	310, 62	135, 43	**<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	176, 35	73, 23	**<0.0001**
csPCa detection LDB (n,%)	268, 54	107, 34	**<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	161, 32	55, 17	**<0.0001**
csPCa detection CTB (n,%)	283, 57	108, 34	**<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	161, 32	58, 18	**<0.0001**
csPCa detection solely by LDB total cohort (n,%)	21, 4	22, 7	0.08
+PSAD>0.15 ng/ml/cm^3 (n,%)	13, 3	15, 5	0.1
csPCa detection solely by LDB csPCA-cohort (n,%)	21, 7	22, 16	**0.002**
+PSAD>0.15 ng/ml/cm^3 (n,%)	13, 7	15, 20	**0.003**
csPCa detection solely by CTB total cohort (n,%)	34, 7	26, 8	0.44
+PSAD>0.15 ng/ml/cm^3 (n,%)	15, 3	16, 5	0.1
csPCa detection solely by CTB csPCA-cohort (n,%)	34, 11	26, 19	**0.02**
+PSAD>0.15 ng/ml/cm^3 (n,%)	15, 5	16, 12	**0.004**
csPCa detection simultaneously by LDB and CTB (n,%)	255, 82	87, 64	**<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	148, 84	42, 58	**<0.0001**
IsPCa detection LDB&CTB (n,%)	46, 9	20, 6	0.1
IsPCa detection LDB (n,%)	37, 7	10, 3	**0.01**
IsPCa detection CTB (n,%)	47, 9	21, 7	0.2
csPCa detection (LDB&CTB) TPR-2 (n,%)	1, 9	2, 8	0.9
+PSAD>0.15 ng/ml/cm^3 (n,%)	n.a.	n.a.	
csPCa detection (LDB&CTB) TPR-3 (n,%)	38, 34	23, 26	0.2
+PSAD>0.15 ng/ml/cm^3 (n,%)	23, 20	10, 11	**0.02**
csPCa detection (LDB&CTB) TPR-4 (n,%)	155, 66	67, 52	**0.01**
+PSAD>0.15 ng/ml/cm^3 (n,%)	72, 30	34, 26	**0.0002**
csPCa detection (LDB&CTB) TPR-5 (n,%)	116, 83	43, 60	**0.0002**
+PSAD>0.15 ng/ml/cm^3 (n,%)	81, 58	27, 38	**<0.0001**
csPCa detection (LDB) TPR-2 (n,%)	1, 9	1, 4	1
+PSAD>0.15 ng/ml/cm^3 (n,%)	1, 9	1, 4	1
csPCa detection (LDB) TPR-3 (n,%)	23, 21	14, 16	0.1
+PSAD>0.15 ng/ml/cm^3 (n,%)	16, 14	6, 7	**0.03**
csPCa detection (LDB) TPR-4 (n,%)	132, 56	53, 41	**0.01**
+PSAD>0.15 ng/ml/cm^3 (n,%)	66, 28	25, 19	**<0.0001**
csPCa (LDB) detection TPR-5 (n,%)	112, 80	39, 54	**<0.0001**
+PSAD>0.15 ng/ml/cm^3 (n,%)	79, 56	23, 32	**<0.0001**
RPS ISUP score			
ISUP 1 (n,%)	6, 5	2, 5	0.8
ISUP 2 (n,%)	39, 36	11, 27	0.3
ISUP 3 (n,%)	42, 38	15, 36	0.9
ISUP 4 (n,%)	9, 8	7, 17	0.1
ISUP 5 (n,%)	14, 13	6, 15	0.8

Table 11: Unbiopsied (UB=green box) and former negative prostate biopsy (FNB=grey box) patients and relations to the biopsy technique (combined biopsy (LDB&CTB), 'fusion-guided mpMRI lesion directed prostate-biopsy' (LDB) and conventional systematic transrectal ultrasound guided prostate biopsy (CTB)) and 'Target-defining and Prostate Imaging–Reporting and Data System version 2 (PI-RADS) evaluating radiologist report (TPR)'-2, 3,

4, 5. Clinically significant prostate cancer (csPCa) or insignificant prostate cancer (isPCa) was defined according to 'D'Amico EAU' risk groups. Prostate Specific Antigen (PSA), PSA Density (PSAD) ng/ml/cm^3, digital rectal examination (DRE), not applicable (n.a.), Radical prostatectomy specimen (RP). Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

3.5 Post combined prostate biopsy complication rates

The majority of post-procedural issues were classified as Grade II (n=33) or IIIa (n=13) and were noted as a consequence of catheterization in case of an acute urinary retention or an antibiotic treatment due to infection.(187) Contrarily, Grade I (n = 5), IIIb (n = 1), or IVa (n = 1) problems had only been found rarely. These Grade IIIb and IVa complications were related to endoscopic clipping of a rectal hemorrhage and critical care observation following pulmonary embolism and deep vein thrombosis.(187)

Altogether we noticed gross hematuria (n = 7), acute ischuria (n = 8), urinary infection (n = 28), rectal bleeding (n = 2), fever or shivering with or without bacteremia (n = 8) and one fracture of the bridge of nose after idiopathic post-biopsy fall, which did not need any surgical intervention. However, the UB or FNB status had no influence on complications.(187)

3.6 Diagnostic accuracy of the prostate biopsy method (ISUP-grade) on the basis of the RPS and with respect to biopsy history

3.6.1 Total cohort

Within the total cohort the accordance of the ISUP score, upgrading or downgrading with the RPS regarding the LDB&CTB vs. LDB vs. CTB approach was 53%, 28% or 19% vs. 40%, 50% or 10% vs. 42%, 45% or 13%, respectively (table 12).

The LDB&CTB ISUP score demonstrated a critically increased accordance with the RPS ISUP score than LDB or CTB (LDB&CTB 53% vs LDB 40% vs. CTB 42%; both p=0.001).(187)

Furthermore, LDB&CTB was significantly less upgraded by the RPS than LDB or CTB (LDB&CTB 28% vs. LDB 50% and CTB 45%; both p<0.0001).(187) An upgrading from ISUP 1 to ISUP ≥2 by the RPS was less seen with LDB&CTB (9%) compared to CTB (13%, p=0.03) but not different when compared to the LDB method.

In contrast, the total LDB&CTB technique (13%) was less associated with upgrading from ISUP 2 to ISUP ≥3 by the RPS ISUP score when compared to the LDB (17%, p=0.03) but this discrepancy was not seen for the CTB method.(187)

Ultimately, ISUP downgrading by the RPS ISUP score was significantly more frequently observed with the LDB&CTB strategy (19%) than with the LDB (10%; p=0.003) or CTB (13%, p=0.005) approach.(187) Downgrading to ISUP 2 by RPS were only more frequently found by the LDB&CTB (9%) compared to the LDB (4%; p=0.005) strategy.(187) Downgrading to ISUP 1 by the RPS were only seen after CTB and the LDB&CTB approach, therefore precluding further analysis.(187)

With respect to a PSAD >0.15ng/ml/cm^3 cut-off we found no significant difference for agreement between any of the applied biopsy techniques with the RPS. In general we observed a significantly lower upgrading rate for the LDB&CTB (19%) method when compared to the LDB (34%; p=0.03) or CTB (40%; p=0.0003) strategy. Other substratified upgrading correlations regarding ISUP 1 to ISUP ≥2 or ISUP 2 to ISUP ≥3 showed no discrepancy. Still, in general downgrading rates were significantly increased for the LDB&CTB (29% vs. LDB 16%; p=0.005 vs. CTB 19%; p=0.01) pathway but with respect to downgrading to ISUP 2 LDB&CTB (14%) was only more often downgraded than LDB (6%; p=0.03). In this subgroup downgrading to ISUP 1 with the RPS was only seen after a CTB in one patient.(187)

	Total LDB&CTB	**Total LDB&CTB PSAD >0.15 ng/ml/cm^3**	**Total LDB**	**Total LDB PSAD >0.15 ng/ml/cm^3**	**TotalCTB**	**Total CTB PSAD >0.15 ng/ml/cm^3**	**p Total LDB&CTB vs. LDB/CTB & LDB vs.CTB**	**p Total LDB&CTB vs. LDB/CTB & LDB vs.CTB PSAD >0.15 ng/ml/cm^3**
ISUP Agreement (n, %)	80, 53	32, 52	61, 40	31, 50	63, 42	25, 40	**0.001/ 0.001** & 0.8	0.8/0.07 & 0.2
ISUP Upgrading (n, %)	43, 28	12, 19	75, 50	21, 34	68, 45	25, 40	**<0.0001/ <0.0001**& 0.4	**0.003/ 0.0003**& 0.4

Upgrading ISUP 1 to ISUP ≥2 (n, %)	14, 9	5, 8	19, 13	5, 8	20, 13	6, 10	0.09/**0.03** & 0.8	1/0.6 & 0.6
Upgrading ISUP 2 to ISUP ≥3 (n, %)	20, 13	5, 8	26, 17	8, 13	22, 15	9, 14	**0.03**/0.5 & 0.3	0.08/0.1 &0.7
ISUP Downgrading (n, %)	28, 19	18, 29	15, 10	10, 16	20, 13	12, 19	**0.003/ 0.005** & 0.3	**0.005/ 0.01** & 0.6
Downgrading to ISUP 2 (n, %)	14, 9	9, 14	6, 4	4, 6	11, 7	6, 10	**0.005**/0.08 & 0.1	**0.03**/0.08 & 0.5
Downgrading to ISUP 1 (n, %)	2, 1	1, 2	0	0	2, 1	1, 2	n.a./1 & n.a.	n.a/1&n.a.

Table 12: Correctness of the 'multiparametric magnetic resonance imaging/transrectal ultrasound-fusion lesion directed prostate-biopsy' (LDB) approach, conventional systematic transrectal ultrasound guided prostate biopsy (CTB) and combined biopsy (LDB&CTB) technique to predict the International Society of Urological Pathology (ISUP) score of the 'radical prostatectomy specimen' (RPS) of men of the total cohort (n=151) and a subgroup of patients with a PSAD >0.15 ng/ml/cm^3(n=62), who opted for radical prostatectomy. Agreement = dark green, upgrading = red, downgrading = yellow. Not applicable (n.a.), Prostate Specific Antigen Density (PSAD) ng/ml/cm^3. Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

3.6.2 Unbiopsied cohort

Again, we also observed a significantly higher agreement rate for the LDB&CTB pathway within UB patients (UB-LDB&CTB 55% vs. UB-LDB 41%; p=0.003 and UB-CTB 47%; p=0.01).(187)

In addition, UB-LDB&CTB ISUP score upgrading (25%) was less frequently observed compared to the UB-LDB (50%; p<0.0001) or UB-CTB technique (37%; p=0.0003) (table 13).

Interestingly, only UB-LDBs were significantly more often upgraded than UB-CTBs (p=0.02). An upgrading from ISUP 1 to ISUP ≥2 by the RPS ISUP score was less seen with the UB-LDB&CTB (9%) vs. UB-CTB (13%, p=0.03) technique but not different when the UB-LDB&CTB was compared to the UB-LDB method.(187) In contrast, significantly less upgrading was noted from ISUP 2 to ISUP 3 with the UB-LDB&CTB (12%) when matched

with the UB-LDB technique (16%; p=0.03) but not different concerning the UB-CTB method (p=0.7).

An ISUP downgrading was significantly more frequently observed with the LDB&CTB approach (19%) than with the LDB (9%; p=0.001) or CTB (15%, p=0.045) method.(187) Downgradings to ISUP 2 by the RPS ISUP score were only more often found using the UB-LDB&CTB (10%) strategy compared to the UB-LDB (4%; p=0.01) method. Due to the fact that a downgrading to ISUP 1 by the RPS ISUP score was only seen in the UB-LDB&CTB or UB-CTB approach, no difference could be detected according to the biopsy method.

No significant difference for agreement between any of the applied biopsy techniques with the RPS after including a PSAD >0.15ng/ml/cm^3 cut-off could be found. In comparison to the LDB (32%; p=0.005) and CTB (32%; p=0.005) strategy, we saw a much lower upgrading rate for the LDB&CTB (15%) technique. We observed no difference in the results of other substratified upgrading correlations. The downgrading rates were in general and with respect to downgrading to ISUP 2 only significantly increased for the LDB&CTB pathway when compared to the LDB strategy but not for the CTB approach. Again, downgrading to ISUP 1 with the RPS was only found with a CTB in a single patient.(187)

	UB LDB& CTB	**UB LDB& CTB PSAD >0.15 ng/ml/ cm^3**	**UB LDB**	**UB LDB PSAD >0.15 ng/ml /cm^3**	**UB CTB**	**UB CTB PSAD >0.15 ng/ml /cm^3**	**p UB LDB& CTB vs. LDB/CTB & LDB vs. CTB**	**p UB LDB& CTB vs. LDB/ CTB & LDB vs. CTB PSAD >0.15 ng/ml/cm^3**
ISUP Agreement (n,%)	61, 55	26, 55	45, 41	25, 53	52, 47	21, 45	**0.003/ 0.01** & 0.3	0.8/ 0.06 &0.3
ISUP Upgrading (n,%)	28, 25	7, 15	55, 50	15, 32	41, 37	15, 32	**<0.0001/ 0.0003**& **0.02**	**0.005/ 0.005**&1
Upgrading ISUP 1 to ISUP ≥2 (n,%)	10, 9	2, 4	15, 14	2, 4	14, 13	4, 9	0.1/**0.03** & 0.05	1/0.2& 0.3
Upgrading ISUP 2 to ISUP ≥3 (n,%)	13, 12	4, 9	18, 16	7, 15	14, 13	6, 13	**0.03**/0.7 & 0.2	0.08/ 0.3 &0.7
ISUP Downgrading with **RPS** (n,%)	21, 19	14, 30	10, 9	7, 15	17, 15	11, 23	**0.001/ 0.045** & 0.1	**0.008**/ 0.08& 0.2

Downgrading to ISUP 2 by **RPS** (n,%)	11, 10	7, 15	5, 4	3, 6	9, 8	5, 11	**0.01**/0.2 & 0.2	**0.0455**/0.2 &0.4
Downgrading to ISUP 1 by **RPS** (n,%)	2, 2	1, 2	0	0	2, 2	1, 2	n.a./1 & n.a.	n.a./1&n.a

Table 13: Correctness of the 'multiparametric magnetic resonance imaging/transrectal ultrasound-fusion lesion directed prostate-biopsy' (LDB) approach, conventional systematic transrectal ultrasound guided prostate biopsy (CTB) and combined biopsy (LDB&CTB) technique to predict the International Society of Urological Pathology (ISUP) score of the 'radical prostatectomy specimen' (RPS) of unbiopsied (UB) men (n=110) and a subgroup of patients with a PSAD >0.15 ng/ml/cm^3(n=47), who opted for radical prostatectomy. Agreement = dark green, upgrading = red, downgrading = yellow. Not applicable (n.a.), Prostate Specific Antigen Density (PSAD) ng/ml/cm^3. Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

3.6.3 Former negative prostate biopsy cohort

Focusing on the FNB setting, again the LDB&CTB method showed higher agreement rates (46%) compared to the CTB technique (27%, p=.0.03) but there was no difference between the FNB-LDB&CTB vs. the FNB-LDB approach (39%; p=0.2). Furthermore, the LDB&CTB strategy (37%) demonstrated significantly less ISUP score upgrading by the RPS than the LDB (49%; p=0.03) or CTB (66%; p=0.0005) pathway. Regarding the upgrading from ISUP 1 to ISUP ≥2 or ISUP 2 to ≥3 by the RPS ISUP score equal results between all biopsy methods were observed. In addition, ISUP downgrading with the RPS ISUP score was obviously more often observed with FNB-LDB&CTB (17%) vs. FNB-CTB (7%; p=0.045). Nevertheless, there is no change when compared to the FNB-LDB mode.(187)

The downgrading rate to ISUP 2 by the RPS ISUP score was comparable between all biopsy settings, whereas a downgrading to ISUP 1 was not seen at all (table 14).

Focusing on the additional PSAD >0.15ng/ml/cm^3 subgroup we only observed a lower upgrading rate for the LDB&CTB strategy (33%) compared to the CTB (67%, p=0.03) approach. For all other correlations no statistically significant difference could be noted.(187)

	FNB LDB& CTB	FNB LDB& CTB PSAD >0.15 ng/ml/ cm^3	FNB LDB	FNB LDB PSAD >0.15 ng/ml/ cm^3	FNB CTB	FNB CTB PSAD >0.15 ng/ml/ cm^3	p FNB LDB& CTB vs. LDB/ CTB & LDB vs. CTB	p FNB LDB& CTB vs.LDB/CTB & LDB vs. CTB PSAD >0.15 ng/ml/ cm^3
ISUP Agreement (n,%)	19, 46	6, 40	16, 39	6, 40	11, 27	4, 27	0.2/ **0.03 &** 0.3	1/0.5& 0.5
ISUP Upgrading (n,%)	15, 37	5, 33	20, 49	6, 40	27, 66	10, 67	**0.03/ 0.0005 &** 0.09	0.3/ **0.03**& 0.1
Upgrading ISUP 1 to ISUP ≥2 (n,%)	4, 10	3, 20	4, 10	3, 20	6, 15	2, 13	1/0.3 & 0.3	1/0.3& 0.3
Upgrading ISUP 2 to ISUP ≥3 (n,%)	7, 17	1, 7	8, 20	1, 7	8, 20	3, 20	0.6/0.7 & 1	1/0.2& 0.2
ISUP Downgrading (n,%)	7, 17	4, 27	5, 12	3, 20	3, 7	1, 7	0.2/ **0.045** & 0.4	0.3/ 0.08&0 .3
Downgrading to ISUP 2 (n,%)	3, 7	2, 13	1, 2	1, 7	2, 5	1, 7	0.2/0.3 & 0.6	0.3/0.3 &1
Downgrading to ISUP 1 (n,%)	0	0	0	0	0	0	n.a./n.a & n.a.	n.a.

Table 14: Correctness of the 'multiparametric magnetic resonance imaging/transrectal ultrasound-fusion lesion directed prostate-biopsy' (LDB) approach, conventional systematic transrectal ultrasound guided prostate biopsy (CTB) and combined biopsy (LDB&CTB) technique to predict the International Society of Urological Pathology (ISUP) score of the 'radical prostatectomy specimen' (RPS) of former negative prostate biopsy (FNB) men (n=41) and a subgroup of patients with a PSAD >0.15 ng/ml/cm^3(n=15), who opted for radical prostatectomy. Agreement = dark green, upgrading = red, downgrading = yellow. Not applicable (n.a.), Prostate Specific Antigen Density (PSAD) ng/ml/cm^3. Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

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3.6.4 Biopsy approach regarding unbiopsied versus former negative prostate biopsy status

The head to head comparison of each biopsy method on the basis of UB versus FNB patients only showed a significantly higher RPS agreement (UB-CTB=47% vs. FNB-CTB=27%; p=0.02) and less upgrading (UB-CTB=37% vs. FNB-CTB=66%; p=0.002) for the UB-CTB method.

We observed no further agreement, upgrading or downgrading difference for the LDB&CTB approach and LDB or CTB method according to the biopsy history (table 15).(187)

	UB LDB& CTB	**FNB LDB& CTB**	**p**	**UB LDB**	**FNB LDB**	**p**	**UB CTB**	**FNB CTB**	**p**
ISUP Agreement (n,%)	61, 55	19, 46	0.3	45, 41	16, 39	0.8	52, 47	11, 27	**0.02**
ISUP Upgrading (n,%)	28, 25	15, 37	0.2	55, 50	20, 49	0.9	41, 37	27, 66	**0.002**
Upgrading ISUP 1 to ISUP ≥2 (n,%)	10, 9	4, 10	0.9	15, 14	4, 10	0.5	14, 13	6, 15	0.8
Upgrading ISUP 2 to ISUP ≥3 (n,%)	13, 12	7, 17	0.4	18, 16	8, 20	0.6	14, 13	8, 20	0.3
ISUP Downgrading (n,%)	21, 19	7, 17	0.8	10, 9	5, 12	0.6	17, 15	3, 7	0.2
Downgrading to ISUP 2 (n,%)	11, 10	3, 7	0.6	5, 4	1, 2	0.6	9, 8	2, 5	0.5
Downgrading to ISUP 1 (n,%)	2, 2	0	0.4	0	0	n.a	2, 2	0	0.4

Table 15: Comparison of unbiopsied (UB) and former negative prostate biopsy (FNB) patients regarding 'multiparametric magnetic resonance imaging/transrectal ultrasound-fusion lesion directed prostate-biopsy' (LDB), Conventional systematic transrectal ultrasound guided prostate biopsy (CTB) and combined biopsy (LDB&CTB) to predict the International Society of Urological Pathology (ISUP) score of the 'radical prostatectomy specimen' (RPS), who opted for radical prostatectomy. Agreement = dark green, upgrading = red, downgrading = yellow. Not applicable (n.a.). Reproduced from "Frontiers in surgery".(187) Authors of articles published in Frontiers journals retain copyright on their publications and are therefore free to re-publish their work.

In the group of patients with a PSAD>0.15ng/ml/cm^3 and focus on the biopsy history only the direct comparison of the CTB technique showed a significantly higher upgrading rate for the FNB cohort (UB-CTB 32% vs. FNB-CTB 67%; p=0.02) (table 16).

	UB LDB& CTB PSAD >0.15 ng/ml/ cm^3	**FNB LDB& CTB PSAD >0.15 ng/ml/ cm^3**	**p**	**UB LDB PSAD >0.15 ng/ml /cm^3**	**FNB LDB PSAD >0.15 ng/ml /cm^3**	**p**	**UB CTB PSAD >0.15 ng/ml /cm^3**	**FNB CTB PSAD >0.15 ng/ml /cm^3**	**p**
ISUP Agreement (n,%)	26, 55	6, 40	0.3	25, 53	6, 40	0.4	21, 45	4, 27	0.2
ISUP Upgrading (n,%)	7, 15	5, 33	0.1	15, 32	6, 40	0.6	15, 32	10, 67	**0.02**
Upgrading ISUP 1 to ISUP ≥2 (n,%)	2, 4	3, 20	0.05	2, 4	3, 20	0.05	4, 9	2, 13	0.6
Upgrading ISUP 2 to ISUP ≥3 (n,%)	4, 9	1, 7	0.8	7, 15	1, 7	0.4	6, 13	3, 20	0.5
ISUP Downgrading (n,%)	14, 30	4, 27	0.8	7, 15	3, 20	0.6	11, 23	1, 7	0.1
Downgrading to ISUP 2 (n,%)	7, 15	2, 13	0.9	3, 6	1, 7	0.9	5, 11	1, 7	0.6
Downgrading to ISUP 1 (n,%)	1, 2	0	0.6	0	0	n.a.	1, 2	0	0.6

Table 16: Prostate Specific Antigen Density (PSAD) ng/ml/cm^3 >0.15 subgroup and comparison of unbiopsied (UB) and former negative prostate biopsy (FNB) patients regarding 'multiparametric magnetic resonance imaging/transrectal ultrasound-fusion lesion directed prostate-biopsy' (LDB), conventional systematic transrectal ultrasound guided prostate biopsy (CTB) and combined biopsy (LDB&CTB) to predict the International Society of Urological Pathology (ISUP) score of the 'radical prostatectomy specimen' (RPS), after radical prostatectomy. Agreement = dark green, upgrading = red, downgrading = yellow. Not applicable (n.a.).

4 Discussion

The mpMRI-triggered diagnostic approach has proven benefits over the conventional CTB assessment. Lately, the GÖTEBORG-2 trial investigated whether screening for elevated PSA levels and associated CTB (irrespective of the mpMRI outcome) would result in more overdiagnosis of isPCa than screening according to a strategy that included elevated PSA (≥3ng/ml) followed by LDB alone in patients with positive mpMRI results. In total, 0.6% of the 11,986 participants who underwent mpMRI LDB only (experimental arm) had isPCa. In contrast, 1.2% of 5994 participants receiving a CTB and in case of a suspicious mpMRI concomitant LDB (reference group), were found to have isPCa (relative risk, 0.46; 95% CI, 0.33 to 0.64; P<0.001). In the experimental group compared to the reference group, the relative risk of csPCa was 0.81 (95% CI, 0.60 to 1.1). In the reference group csPCa was only detected by the CTB approach in 10 participants. Therefore, the authors conclude that the risk of isPCa overdiagnosis was cut in half by avoiding the CTB strategy in favor of MRI-directed LDB at the cost of a tiny percentage of individuals who had their intermediate-risk tumors detected later.(207)

In this study, once again mpMRI has proven to be a sufficient additional tool for PCa screening due to its impaired capability to visualize isPCa.(171) Nevertheless, the combined performance of the LDB and CTB approach to detect csPCa within the experimental arm and the potential influence of the biopsy history was not within the focus of the GÖTEBORG-2 study.

Our collaboration group observed that isPCa was less common in LDB than CTB (3% vs. 7%, p=0.02) or LDB&CTB (3% vs. 6%, p=0.01) regarding our FNB-cohort.(187) This result agrees with larger cohorts, which mostly consisted of rebiopsy and EDP patients (58, 184, 185) but also with FNB groups who showed less isPCa (ISUP-1) with LDB (6%) than CTB (9%) or LDB&CTB (12%; no p-values).(181, 187)

We found it remarkable that there was no significant difference regarding the isPCa detection rates by biopsy technique in UB males (LDB 7% vs. CTB 9% vs. LDB&CTB 9%), which was likely caused by the greater isPCa detection performance following UB-LDB (7%) compared to FNB-LDB (3%; p=0.01). Therefore, it could be assumed that in UB patients the advantage of the LDB&CTB strategy towards csPCa detection is not offset by an increased isPCa detection rate due to the CTB method. Various other publications support our findings and reported uniform isPCa detection rates between LDB and CTB, or LDB&CTB in UB cohorts with PI-RADS 3, 4, or 5 lesions, respectively.(66, 180-182, 187, 208)

Interestingly, there is a relevant degree of interobserver variation among radiologists evaluating prostate mpMRI results, although it is the profound basis of LDB-quality. Despite

standardization, it was shown that PI-RADS only provided modestly repeatable mpMRI scores for the identification of csPCa, with median overall κ scores of 0.46 and 0.55 for suspected malignancy.(209) This is probably the main objection associated with this triage test.(154)

In 2020 a consensus paper on mpMRI for the detection of csPCa stated that PI-RADS should be used as assessment tool. Additionally, conventional radiologists, dealing with the suspicion of PCa should be able to assess PI-RADS 1 and 2 vs 3, 4 and 5 lesions with at least 80% agreement compared to expert prostate mpMRI reports (52%; 23 of 44 panelists). On the contrary, no consensus could be found about impelling double-reading.(210)

In this context, Luzzago et al. investigated the PI-RADS v2 interreader agreement of 266 patients between peripheral centers and unblinded reevaluating radiologists of academic centers to avoid prostate biopsies after mpMRI second opinion. Peripheral centers observed no lesions (PI-RADS < 2) in 17 cases (6.5%). Target lesions were reported according to PI-RADS 2, 3, 4, 5 within 2 of 23 (8.5%), 3 of 85 (32%), 4 of 98 (37%), and 5 of 13 (5%) men, respectively. Initial clinical strategy involved performing a LDB (226; 85%) or CTB (8; 3%) after first reading of mpMRI. In 91 (38.5%) of mpMRI rereads, the target PI-RADS category remained the same, whereas in 20 cases (8.5%) and 125 cases (53%) it was upgraded or downgraded (κ= 0.23), respectively. In 113 patients (48%) (κ= 0.2), the clinical care altered. After receiving an unblinded reread of mpMRI, 102 targeted biopsies (51%) within 72 men (34.5%) could be avoided. The authors concluded that mpMRI second opinion could reduce discordance between mpMRI reports and decrease invasive diagnostics and morbidity.(211)

Furthermore, biopsy history associated inter-observer variation has not yet been investigated, neither in larger cohorts nor daily clinical practice. Just recently the effects of “real life” prostate mpMRI inter-observer variability among 11 different centers demonstrated a slight agreement (κ= 0.17) representing a downgrading, upgrading and agreement in 52%, 12%, and 37%, respectively.(212)

Nevertheless, in line with a current meta-analysis concerning 30 PI-RADS v2 interobserver studies with 4095 mainly FNB (93%) patients (medium 136; min. 33 – max. 456 patients), we likewise found a moderate interobserver agreement for declaring a PI-RADS 2, 3, 4 and 5 lesion as suspicious in the FNB-cohort.(213) In addition, despite a low number, the low concordance of PI-RADS-2 reports in our study influences the general agreement represented by a substantial interobserver-conformity when it comes to PI-RADS 3, 4, 5 reports (even for FNB-patients).

In the meanwhile, a moderate inter-reader agreement or diagnostic performance of PI-RADS v2 has been reported (154, 213, 214). This circumstance probably relies on the

impact of the image quality since there is no universally agreed imaging procedure, including spatial resolution, signal-to-noise ratio, or diffusivity measurements.(215)
Furthermore, single center PI-RADS analysis have shown a moderate overall interobserver accordance in PI-RADS v2 among radiologists improving with increasing experience (216, 217) but can potentially be biased by the association of local site imaging protocol and histologic correlations influencing radiologic interpretations.(154)
Multi institutional studies demonstrated, that the assessment of the peripheral zone with DWI compared to evaluation of the transitional zone with T2 sequences tended to have poorer inter-reader agreement.(154, 213)
In addition, Smith et al. reported on 102 UB patients with previously detected and biopsied lesions scored by four readers from four different institutions in a single center study. They showed that PI-RADS v2 overall inter-reader reproducibility was poor to moderate (κ= 0.24). Readers with more experience showed greater inter-observer reproducibility than readers with intermediate prostate MRI knowledge. The authors pointed out that more comprehensive standardized reader training for prostate MRI would be necessary.(218)
Nevertheless, in our distinct larger study the highest and substantial agreement was observed for UB-patients. Comparable results in a UB only patient cohort had been implied by Niu et al. showing an inter-reader reliability ranging from moderate to good for PI-RADS v2 (Cohen κ= 0.525–0.616).
In contrast, Rosenkrantz et al. demonstrated a general PI-RADS v2 ≥ 3 agreement of 79.2% between radiologists of six different institutions. We found a comparable agreement between PMP- and TPR reports of 78%. Interestingly, another group also observed an upgrading rate of 12% after reevaluation of PI-RADS v2 reports from eleven institutions by one uroradiologist. However, our group counted any higher TPR level after comparison to the PMP as upgrade, whereas Rosenzweig et al. selected a change of the PI-RADS score from <3 to ≥3 as upgrade.(212) Due to this cut-off definition, minor patient number and markedly higher general downgrading rate of 52 % (versus 10% in our cohort) our results may therefore not be directly comparable.
Despite the influence of a high interrater variability for PI-RADS 2 reports in our cohort, the overall percentage-agreement rate and the general interobserver PI-RADS ≥2 evaluation regarding the total-, UB- and FNB-men supposes that the PI-RADS constitutes a structured management of prostate mpMRI assuring consistent imaging reports(219), even among different centers. (154)
Anyhow, TPR readings seem to be more precise for UB patients represented by higher agreement, less upgrading and downgrading. That is based mainly on a higher agreement and less upgrading for UB patients with PI-RADS 4 and 5 reports. Interestingly, TPR findings detected more PI-RADS 5 and less PI-RADS 4 scores than PMP reports

independent of the biopsy history. Hereby, the inter-observer reliability was moderate and substantial for PI-RADS 4 and 5, respectively. Although, PMP and TPR reported an equal amount of total and UB PI-RADS 3 scores and associated substantial k-accordance, FNB-TPR demonstrated less PI-RADS 3 scores and only moderate k-accordance. Probably therefore, TPR leading to downgrading was mainly found in PI-RADS 2 reports (89%) irrespective of the biopsy history, whereas TPR readings produced more PI-RADS 2 reports in FNB patients than PMP. This may also be a result of a learning curve but could be biased by the fact that each patient was scheduled for LDB anyway, producing a perceived sense of clarification security.

With the exception of UB-PI-RADS 3 lesions, interestingly, we were able to demonstrate that the LDB and CTB techniques appear to be similar when it comes to the identification of csPCa within the whole collective, UB and FNB patients. In this context there are different opinions to find in the literature. One meta-analysis found that UB men who received mpMRI triggered LDB with or without CTB were associated with a higher number of csPCa compared to those who underwent CTB alone.(187, 220) This conclusion may demonstrate that the mpMRI -informed pathway increases the csPCa detection rate compared to the classic CTB without mpMRI. Though, these data make it difficult to draw firm conclusions about the performance of a concomitant CTB during LDB because about 50% of the evaluated studies did not apply LDB and CTB within one patient.(187)

However, confirming our findings, a recent meta-analysis and a prospective paired diagnostic-multi institutional study failed to find a statistically significant difference in detecting csPCa applying the LDB or CTB method in a cohort of UB men. (61, 187, 208)

These findings may support the theory that, a CTB approach within the mpMRI pathway is influenced by needle tracks of the previous LDB, which is more likely to hit csPCa. Anyhow, even when the surgeons are blinded, mpMRI informed biopsy strategies depicting suspicious lesions lead to better concomitant CTB results than the traditional single CTB.(221, 222)

Johnson et al. described one potential reason for the improved CTB accuracy within the mpMRI pathway. They found that despite at least one PI-RADS ≥3 index lesion mpMRI missed in general one csPCa focus in 34% of patients and in 45% of men with multifocal lesions compared to the RPS as gold-standard for the aggressiveness and locations of PCa. Smaller, low-grade, multifocal, non-index tumors with lower PSAD were more likely to be overlooked on multivariate analysis. Nevertheless, the selection bias in a group of prostatectomy patients may limit these assumptions.(188)

In comparison to our study, Preisser and colleagues reported the same biopsy sequence and CTB methodology (also according to the German S-3 guideline recommendation).(193)

In accordance with our results, this study group discovered comparable LDB and CTB csPCa detection rates in the entire patient group (45% vs. 46%), UB (52% vs. 54%), and FNB (32% vs. 31%) patients, respectively.(181, 187)

In mixed cohorts of UB and FNB patients, a prospective investigation by Exterkate and colleagues and a systematic review by Drost et al. directly evaluated the mpMRI-pathway in comparison to the CTB. They preferred the LDB technique for the identification of csPCa, but there was no comparison with a LDB&CTB strategy or RPS as a point of reference to draw comprehensive conclusions. (85, 187, 195)

Anyhow, today the traditional CTB method without using the mpMRI strategy is no longer state of the art. Some authors argue that individuals with PI-RADS 5 lesions with or without a PSAD ≥0.15ng/ml/cm^3 or anterior lesions have a limited benefit from a CTB following LDB. Thus, the CTB approach may be abandoned in these situations.(187, 201, 202, 223)

With respect to our study, omitting a concomitant CTB without losing the diagnostic certainty of a LDB&CTB strategy could only be suggested for all TPR-2 subgroups with or without a PSAD >0.15 ng/ml/cm^3 and more importantly within UB-TPR 5 patients with a PSAD >0.15 ng/ml/cm^3. Therefore, we suppose that the final recommendation of Tafuri et al. to omit the CTB in patients with a PI-RADS 5 and a PSAD >0.15ng/ml/cm^3 is influenced by a mainly UB study cohort (56%) and may only be suitable for a recommendation in UB situations.(202) We did not asses the correlations of the biopsy method and the RPS of the UB-PI-RADS 5 plus PSAD >0.15 ng/ml/cm^3 subgroup due to the low associated number of RPs (n=14).

Many other investigations have shown that they were unsuccessful in identifying individuals who would benefit from the LDB alone strategy and advised an additional CTB since LDB&CTB had a greater csPCa detection rate and false negative LDB missed csPCa in 9-27% of heterogeneous cohorts.(182-185, 187, 203)

In comparison with these findings our results of UB-men showed that the LDB&CTB technique identified considerably more csPCa than LDB or CTB alone with respect to TPR 3, 4, or 5, matching prior studies, which examined UB patients with a suspected PI-RADS 3, 4, or 5 lesion.(66, 180-182)

We also showed a significantly higher PI-RADS 3, 4 or 5 csPCa detection rate for the LDB&CTB strategy in our FNB patient cohort.(187) These results were consistent with Preisser et al. and Hofbauer et al. who found the highest absolute numbers for csPCa diagnosis in UB and FNB patients for the LDB&CTB approach vs. LDB or CTB.(181, 182, 187)

Unrelated to the biopsy approach, the increased csPCa detection rate in UB patients appeared to be in general influenced exclusively by TPR 4 and 5 lesions following

LDB&CTB. In addition, including a PSAD >0.15 ng/ml/cm^3, the higher csPCa diagnosis was also observed for patients with a TPR 3 after LDB&CTB or LDB alone.

After performing a LDB&CTB, 8% of the patients with a TPR 2 in our entire cohort were found to have csPCa. Interestingly, a broad and multi-institutional PCa-focus panel identified 614 PI-RADS 2 lesions that mostly got LDB&CTB and also reported that 7% of these men had ISUP 2 PCa.(179, 187) The csPCa detection rate of PI-RADS 2 did not differ amongst LDB, CTB, and LDB&CTB with regard to the whole cohort, UB, or FNB patients even though PI-RADS 2 lesions mostly concerned FNB men. Notwithstanding, our results suggest that a LDB could be adequate for patients who seek to elucidate the low csPCa risk in reevaluated PI-RADS 2 lesions. This finding has to be judged with extreme caution since the sample size of this subgroup was very small.(187)

Interestingly, just recently only Patel et al. hypothesized that the PI-RADS v2 score risk-stratification could be impaired in a FNB setting compared to a UB subgroup and investigated any or csPCa detection rates on a per PI-RADS score basis among these 2 groups. This prospective cohort, included a slightly larger patient number in comparison to our own study. They also used the UroNav system, but only focused on the LDB&CTB approach as PCa reference.(187) In total, FNB patients (n=420) exhibited smaller PI-RADS score distributions than UB men (n=480). After PI-RADS score stratification, FNB patients showed lower rates of both any PCa (27.9% vs 54.4%) and csPCa (ISUP ≥2; 20.0% vs 38.3%) than could be seen in UB men. In contrast, similar rates of csPCa were observed for PI-RADS categories ≤2 (FNB:5.6% vs UB:7.5%; p=0.7). In addition, among FNB men with a PI-RADS ≤ 3, csPCa was noticed in 5.3%.(224)

In any case, we wish to draw attention to the noteworthy result that, among csPCa-positive patients, FNB-patients were considerably more likely to experience a false negative LDB approach than UB-patients (19% vs. 11%; p=0.02).(187) In addition, this correlation was unchanged and even more significant after the incorporation of PSAD >0.15 ng/ml/cm^3 despite this cut-off parameter indicates a higher chance of finding csPCa(105, 106). In contrast, only Ploussard and colleagues mentioned the biopsy history associated added value of a concomitant CTB within the MRI-pathway and found no significant difference (11.2% vs 12.7%).(225) Anyhow, just patients after RP were analyzed, may leading to a selection bias and only 8% of men had a FNB resulting in a non-valid statistical analyses to draw any firm conclusion.

In this setting, it must be underlined that the recommendation for a sole LDB after a FNB in patients with PI-RADS 3, 4, or 5 reports, csPCa would have been missed in only 4% (1/25) of FNB-patients with PI-RADS 2 lesions but in 19% (25/135) of csPCa-patients in the FNB-cohort.(187) No other study has directly assessed the false negative csPCa rate of UB and FNB yet. Given that in TPR 2 lesions the csPCa diagnosis is independent of the biopsy

strategy our result for a false negative LDB within the FNB cohort would be in line with the results of Patel et al. (PI-RADS≤2 and FNB cohort: 5.6%).(224)

Anyhow, the rates for false negative LDB approaches show a substantial variation depending on the biopsy history of a study cohort. Literature shows larger studies which investigated the csPCa detection within PI-RADS ≥3 mpMRI reports. They found false negative LDB procedures in 5-22% or 4-20% and 6-20% regarding UB or mixed cohorts (UB and FNB men) and studies also including EDP patients, respectively.(61, 66, 166, 180, 182-185, 195, 226-228)

Regarding post biopsy complications all patients were counseled about obvious risks in our perioperative prostate biopsy setting and instructed to come to our outpatient clinic in case of an emergency. The majority of prostate biopsy related problems correlated with Grade II (n=48; 6%) of the Clavien-Dindo classification.(46) In line with our findings, major adverse events of the CTB approach and the LDB strategy (2% vs. 1.6%) were reported to be particularly rare but the CTB technique has been proven to cause greater 30-day complications than LDB alone. (59, 229) Anyhow, our results fit within the range of 2-10% of TRUS biopsy studies reporting on Grade II complications.(187, 229-231)

Presuming that the LDB research group shows a higher number of participants, we discovered that 30% of PCa patients in our total patient cohort underwent a RP, which seems to reflect a reasonable benchmark for patients opting RP as invasive curative treatment option (31%–39%).(66, 184, 186, 187, 203)

Importantly, the LDB&CTB strategy significantly outperformed either the LDB or CTB alone in predicting RPS-ISUP grade in both our total and UB cohorts.

These correlations are consistent with findings from heterogeneous biopsy populations also investigating LDB&CTB-RPS agreement results. At this point, we found a UB patient cohort by Maxeiner et al. (LDB&CTB 33% vs. LDB 27% vs CTB 29%; no p-value available)(180), the mixed study group of Ploussard et al. not including EDP patients (LDB&CTB 52% vs. LDB 45% vs CTB 36%; $p<0.001$)(225) or Diamand et al. also focusing on a composite patient category including 6% EDP study participants (LDB&CTB 63% vs. LDB 51% vs CTB 49%; $p<0.001$).(187, 232)

Adding the PSAD >0.15ng/ml/cm^3 cut-off to the biopsy-RPS agreement correlations, our study demonstrated that excluding the CTB approach from the LDB&CTB strategy would have been sufficient to achieve comparable agreement with the RPS as with the LDB&CTB approach in the total, UB and FNB subgroup. Obviously, after adding PSAD >0.15ng/ml/cm^3 the higher agreement rate for UB-LDB&CTB, UB-LDB or UB-CTB patients compared to FNB situations did not influence this observation.

Including a higher PSAD cut-off, Ploussard et al. stated that patients with a PSAD less than 0.20ng/ml/cm^3, applying CTB after LDB had a considerably better risk reclassification and

improvements concerning the ISUP score concordance. Nevertheless, they concluded that maintaining CTB in patients with PSAD more than 0.20ng/ml/cm^3 still seemed essential due to its additional benefit. But it would be debatable in patients with a PSAD below this threshold since it increased the detection rate less than 10%.(225)

In our biopsy analysis only TPR 2 (plus/minus PSAD >0.15 ng/ml/cm^3) or UB-TPR 5 patients including a PSAD cut-off over ≥0.15 ng/ml/cm^3 were not associated with a diagnostic benefit for csPCa after applying a concomitant CTB to the LDB procedure. Therefore, the CTB strategy within the mpMRI pathway may be omitted for these subgroups without missing a significant amount of csPCa patients or loosing agreement accuracy regarding the biopsy-RPS correlation.

Interestingly, with respect to the total-, UB, and FNB-cohort we discovered that the RPS much less frequently upgraded LDB&CTB-ISUP outcomes than those of either biopsy method alone.

Irrespective of the total-, UB, and FNB-cohort we discovered that the RPS much less frequently upgraded LDB&CTB-ISUP outcomes than the LDB or CTB mode.

Our upgrading findings are verified by the outcomes of Ahdoot and colleagues, who included patients with a UB situation or after a prior biopsy (EDP percentage of 48%) (LDB&CTB 14% vs. LDB 31% vs. CTB 42%), Gandaglia and colleagues investigating a heterogeneous cohort with mainly UB patients (LDB&CTB 27% vs.LDB 32%), Diamand et al. (LDB&CTB 24% vs. LDB 39% vs. CTB 43%), Ploussard et al. (LDB&CTB 32% vs. LDB 41% vs CTB 57%) and Maxeiner et al. (LDB&CTB 16% vs. LDB 34% vs CTB 29%).(180, 184, 187, 225, 232, 233) The higher upgrading rate for the FNB-CTB approach in comparison to the UB-CTB setting seemed to have no influence on the generally lower upgrading performance of the LDB&CTB pathway. This significant advantage in terms of less upgrading was also observed for the PSAD >0.15 ng/ml/cm^3 subgroup after the LDB&CTB approach in the total, UB and FNB cohort. Again, the higher rate of upgraded FNB-LDB patients compared to the UB-LDB group with a PSAD >0.15 ng/ml/cm^3 had no effect on the lower upgrading risk after LDB&CTB. These data show the high relevance of the LDB&CTB strategy to ascertain a correct prediction of the PCa aggressiveness and diagnostic or treatment strategy.

However, increased downgrading rates for the LDB&CTB mode within the total- and the UB cohorts appear to be a condition that needs to be to achieve a better agreement and lower upgrading rates.(184, 225, 232) Interestingly, downgrading to ISUP-1 PCa was observed solely in the total and UB (1-2%) cohort and not noticed regarding FNB patients, even after incorporating the PSAD >0.15 ng/ml/cm^3 cut-off, This is most likely due to a low number of patients in these subgroups and the fact that PSAD >0.15 ng/ml/cm^3 mainly preselects higher risk PCa patients. Consistent with our findings Ahdoot et al. also described a

downgrading to ISUP 1 PCa on the RPS as uncommon (3.7%), but most frequently seen following the LDB&CTB approach.(184) Therefore, we advocate that the LDB&CTB strategy minimizes the diagnostic ambiguity in UB- and FNB-patients. This might limit over- and under-treatment after PCa diagnosis. Regarding the biopsy-RPS concordance we suppose that the solitary LDB strategy may have the same value as the LDB&CTB approach in a FNB cohort harboring a PSAD >0.15 ng/ml/cm^3.

As far as we know, this is the only study to examine the PCa-detection rate of EDP-free patients with a suspicious PI-RADS 2, 3, 4, or 5 lesion. At the same a direct comparison is made between the UB- and FNB-patients regarding the biopsy-modality outcomes. Additionally the RPS will be used as a reference test in patients who chose RP as their curative treatment, incorporating PSAD >0.15 ng/ml/cm^3 as an established csPCa marker in a large tertiary academic single center setting.(187)

In addition, we assume that the use of EAU risk groups to define the level for csPCa is preferable because they were developed based on D'Amico's classification system, which evaluates the risk of biochemical recurrence in patients who underwent curative therapy due to localized and locally progressed PCa.(67, 187)

4.1 Limitations:

Nevertheless, some study limitations have to be mentioned:

It is debatable that the in-house radiologists were not blinded from the primary extramural reports, leading to a PI-RADS selection bias.

Anyhow, we wanted to investigate the real-world conditions of a high-volume academic hospital to understand the impact of unblinded mpMRI reevaluation (second opinion) on PI-RADS outcomes and the biopsy performance in terms of biopsy history and RPS as an ideal reference standard to minimize biopsy sampling errors.(188)

We did not explicitly account for the stepwise implementation of PI-RADS v2.0 to PI-RADS v2.1 in 2019/2020.

The PI-RADS v2.1 makes several minor modifications without changing the overall framework for acquisition or interpretation using the principles of the dominant sequence paradigm.(234) A recent systematic review concluded that some authors suggest a substantial improvement between v2.1 and v2.0, while others report no statistically significant difference. The clinical impact of this progress may therefore be marginal and the most crucial element in the identification of PCa continues to be radiologist expertise in mpMRI interpretation.(235)

The practice of always performing LDB&CTB appears to be widespread in other analyses as well. However it may be questioned as it may introduce a biopsy performance bias due to the knowledge of the just in advance completed LDB.(180-182, 203) On the other hand,

conducting CTB initially could compromise the diagnostic accuracy of the LDB mode to diagnose csPCa associated with the suspicious mpMRI lesion.(61)

Regarding the prostate biopsy associated complications we were unable to account–for patients who were unconcerned by clinically modest or self-limiting symptoms such as hematospermia or hematuria.(187)

Additionally, after referral of a patient for LDB, prebiopsy clinical factors like biopsy history, PSA and PMP were collected retrospectively. However, the intramural PI-RADS reevaluation, biopsy outcomes, the intraoperative DRE and the RP outcome were all collected prospectively.(187)

Unfortunately, due to patients lost to follow-up, we were unable to examine every treatment decision made following PCa diagnosis. Although we mainly analyzed the characteristics of a single focal lesion, in situations of more than one target being present we only considered the highest PI-RADS score. Additionally, none of the in-house radiologists regularly reviewed the same mpMRI report or routinely rerated a patient's mpMRI data set of in-house colleagues.(187) Consecutively, we were unable to report the in-house PI-RADS intraclass and interclass correlation coefficients.(187)

Although, generally negative mpMRIs of the prostate account for 27 - 44% of all patients with mpMRI before a prostate biopsy we observed a small number of internal PI-RADS 2 lesions. (236-238) This may limit the validity of our findings but can be explained by the widespread consensus that PI-RADS 2 reports are very rarely associated with csPCa.

Therefore, invasive diagnostic steps are rarely recommended for these patients, although PI-RADS 2 reporting is approximately 18%.(204)

Conversely, 89% of TPR 2 findings were downgraded PMP ≥ 3 reports, likely depending on the moderate interobserver agreement for PI-RADS v2 and/or a clarification-bias in men who were planned for LDB anyway due to an extramurally attested suspicious lesion. (213)

The interpretation of the biopsy-RPS concordance may be restricted due to a low number of patients in certain subgroups.

Finally, the lack of a centralized, complementary assessment by one pathologist may also be considered a disadvantage.

Nevertheless, our uro-pathologic specialists analyzed all biopsy cores and internal prostatectomy specimens intramurally according to the most recent ISUP-scoring method.(239) This process is consistent, generates biopsy core findings that are extremely accurate and facilitates a greater concordance with the final pathology.(240)

4.2 ***Conclusions***

In conclusion, the PI-RADS interobserver agreement is substantial and more accurate in UB situations.

The LDB&CTB procedure appears to detect a significantly higher number of csPCa within PI-RADS 3, 4, or 5 reports in both UB and FNB men.(187)

Furthermore, csPCa within reassessed PI-RADS 2 lesions can be equally clarified by the LDB, CTB, or LDB&CTB- procedure, regardless of biopsy history or PSAD >0.15 ng/ml/cm^3.

Moreover, concurrent CTB could be omitted in reevaluated UB-PI-RADS 5 patients with a PSAD >0.15 ng/ml/cm3 without compromising the csPCa diagnostic accuracy of a LDB&CTB procedure.

The exclusion of a concomitant CTB in FNB-men would have generated significantly more false negative targets in the group of patients who were tested positive for csPCa.

In both the total - and UB patient cohorts, the LDB&CTB approach demonstrated the best ISUP-grade prediction and consistently had the lowest upgrading rates. Even after including a PSAD >0.15 ng/ml/cm^3 upgrading was significantly lower for the LDB&CTB strategy in the total and UB cohort. In terms of the biopsy-RPS concordance we hypothesize that the single LDB technique may be as valuable as the LDB&CTB approach only in FNB men harboring a PSAD >0.15 ng/ml/cm^3.

These findings highlight the importance of the LDB & CTB procedure even in FNB situations.(187)

5 Bibliography

1. Verze P, Cai T, Lorenzetti S. The role of the prostate in male fertility, health and disease. Nature reviews Urology. 2016;13(7):379-86.

2. Price DW-A, H. The accessory reproductive glands of mammals. Sex and internal secretions Williams and Wilkins; Baltimore: 1961.Vol. 1.(3.):p. 366-448.

3. Mitterberger M, Horninger W, Aigner F, Pinggera GM, Steppan I, Rehder P, et al. Ultrasound of the prostate. Cancer imaging : the official publication of the International Cancer Imaging Society. 2010;10(1):40-8.

4. Sugimura Y, Cunha GR, Donjacour AA, Bigsby RM, Brody JR. Whole-mount autoradiography study of DNA synthetic activity during postnatal development and androgen-induced regeneration in the mouse prostate. Biology of reproduction. 1986;34(5):985-95.

5. Hayward SW, Baskin LS, Haughney PC, Cunha AR, Foster BA, Dahiya R, et al. Epithelial development in the rat ventral prostate, anterior prostate and seminal vesicle. Acta anatomica. 1996;155(2):81-93.

6. Hayward SW, Brody JR, Cunha GR. An edgewise look at basal epithelial cells: three-dimensional views of the rat prostate, mammary gland and salivary gland. Differentiation; research in biological diversity. 1996;60(4):219-27.

7. Soeffing WJ, Timms BG. Localization of androgen receptor and cell-specific cytokeratins in basal cells of rat ventral prostate. Journal of andrology. 1995;16(3):197-208.

8. Hayward SW, Baskin LS, Haughney PC, Foster BA, Cunha AR, Dahiya R, et al. Stromal development in the ventral prostate, anterior prostate and seminal vesicle of the rat. Acta anatomica. 1996;155(2):94-103.

9. Timms BG. Prostate development: a historical perspective. Differentiation; research in biological diversity. 2008;76(6):565-77.

10. Aaron L, Franco OE, Hayward SW. Review of Prostate Anatomy and Embryology and the Etiology of Benign Prostatic Hyperplasia. The Urologic clinics of North America. 2016;43(3):279-88.

11. Bartsch G, Müller HR, Oberholzer M, Rohr HP. Light microscopic stereological analysis of the normal human prostate and of benign prostatic hyperplasia. The Journal of urology. 1979;122(4):487-91.

12. McNeal JE. Normal histology of the prostate. Am J Surg Pathol. 1988;12(8):619-33.

13. Gnanapragasam VJ, McCahy PJ, Neal DE, Robson CN. Insulin-like growth factor II and androgen receptor expression in the prostate. BJU international. 2000;86(6):731-5.

14. Marker PC, Donjacour AA, Dahiya R, Cunha GR. Hormonal, cellular, and molecular control of prostatic development. Developmental biology. 2003;253(2):165-74.

15. Fujikawa S, Matsuura H, Kanai M, Fumino M, Ishii K, Arima K, et al. Natural history of human prostate gland: Morphometric and histopathological analysis of Japanese men. The Prostate. 2005;65(4):355-64.

16. Lee CH, Akin-Olugbade O, Kirschenbaum A. Overview of prostate anatomy, histology, and pathology. Endocrinology and metabolism clinics of North America. 2011;40(3):565-75, viii-ix.

17. OS. L. The development of the human prostate gland with reference to the development of other structures at the neck of the urinary bladder. Am J Anat. 1912;13:299–349.

18. McNeal JE. Regional morphology and pathology of the prostate. American journal of clinical pathology. 1968;49(3):347-57.

19. McNeal JE. Normal and pathologic anatomy of prostate. Urology. 1981;17(Suppl 3):11-6.

20. Alves EF, de Freitas Ribeiro BLM, Costa WS, Gallo CBM, Sampaio FJB. Histological and quantitative analyzes of the stromal and acinar components of normal human prostate zones. The Prostate. 2018;78(4):289-93.

21. Laczkó I, Hudson DL, Freeman A, Feneley MR, Masters JR. Comparison of the zones of the human prostate with the seminal vesicle: morphology, immunohistochemistry, and cell kinetics. The Prostate. 2005;62(3):260-6.

22. Srodon M, Epstein JI. Central zone histology of the prostate: a mimicker of high-grade prostatic intraepithelial neoplasia. Human pathology. 2002;33(5):518-23.

23. Cohen RJ, Shannon BA, Phillips M, Moorin RE, Wheeler TM, Garrett KL. Central zone carcinoma of the prostate gland: a distinct tumor type with poor prognostic features. The Journal of urology. 2008;179(5):1762-7; discussion 7.

24. Leimgruber C, Quintar AA, Sosa LD, García LN, Figueredo M, Maldonado CA. Dedifferentiation of prostate smooth muscle cells in response to bacterial LPS. The Prostate. 2011;71(10):1097-107.

25. Zhang Y, Nojima S, Nakayama H, Jin Y, Enza H. Characteristics of normal stromal components and their correlation with cancer occurrence in human prostate. Oncology reports. 2003;10(1):207-11.

26. Costa WS, de Carvalho AM, Babinski MA, Chagas MA, Sampaio FJ. Volumetric density of elastic and reticular fibers in transition zone of controls and patients with benign prostatic hyperplasia. Urology. 2004;64(4):693-7.

27. Krušlin B, Ulamec M, Tomas D. Prostate cancer stroma: an important factor in cancer growth and progression. Bosnian journal of basic medical sciences. 2015;15(2):1-8.

28. Powell MS, Li R, Dai H, Sayeeduddin M, Wheeler TM, Ayala GE. Neuroanatomy of the normal prostate. The Prostate. 2005;65(1):52-7.

29. Costello LC, Franklin RB. A comprehensive review of the role of zinc in normal prostate function and metabolism; and its implications in prostate cancer. Archives of biochemistry and biophysics. 2016;611:100-12.

30. Gilany K, Minai-Tehrani A, Savadi-Shiraz E, Rezadoost H, Lakpour N. Exploring the human seminal plasma proteome: an unexplored gold mine of biomarker for male infertility and male reproduction disorder. Journal of reproduction & infertility. 2015;16(2):61-71.

31. de Lamirande E, Lamothe G. Levels of semenogelin in human spermatozoa decrease during capacitation: involvement of reactive oxygen species and zinc. Human reproduction (Oxford, England). 2010;25(7):1619-30.

32. Chughtai B, Sawas A, O'Malley RL, Naik RR, Ali Khan S, Pentyala S. A neglected gland: a review of Cowper's gland. International journal of andrology. 2005;28(2):74-7.

33. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. International journal of cancer. 2021.

34. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European urology. 2021;79(2):243-62.

35. Kimura T, Sato S, Takahashi H, Egawa S. Global Trends of Latent Prostate Cancer in Autopsy Studies. Cancers. 2021;13(2).

36. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015;136(5):E359-86.

37. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. International journal of cancer. 2015;137(7):1749-57.

38. Chornokur G, Dalton K, Borysova ME, Kumar NB. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. The Prostate. 2011;71(9):985-97.

39. Breslow N, Chan CW, Dhom G, Drury RA, Franks LM, Gellei B, et al. Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. International journal of cancer. 1977;20(5):680-8.

40. Barber L, Gerke T, Markt SC, Peisch SF, Wilson KM, Ahearn T, et al. Family History of Breast or Prostate Cancer and Prostate Cancer Risk. Clinical cancer research : an official journal of the American Association for Cancer Research. 2018;24(23):5910-7.

41. Bratt O, Drevin L, Akre O, Garmo H, Stattin P. Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study. Journal of the National Cancer Institute. 2016;108(10).

42. Madersbacher S, Alcaraz A, Emberton M, Hammerer P, Ponholzer A, Schröder FH, et al. The influence of family history on prostate cancer risk: implications for clinical management. BJU international. 2011;107(5):716-21.

43. Chen YC, Page JH, Chen R, Giovannucci E. Family history of prostate and breast cancer and the risk of prostate cancer in the PSA era. The Prostate. 2008;68(14):1582-91.

44. Beebe-Dimmer JL, Kapron AL, Fraser AM, Smith KR, Cooney KA. Risk of Prostate Cancer Associated With Familial and Hereditary Cancer Syndromes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(16):1807-13.

45. Aschelter AM, Giacinti S, Caporello P, Marchetti P. Genomic and epigenomic alterations in prostate cancer. Front Endocrinol (Lausanne). 2012;3:128-.

46. Rubin MA, Demichelis F. The Genomics of Prostate Cancer: emerging understanding with technologic advances. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2018;31(S1):S1-11.

47. Das S, Salami SS, Spratt DE, Kaffenberger SD, Jacobs MF, Morgan TM. Bringing prostate cancer germline genetics into clinical practice. The Journal of urology. 2019;202(2):223-30.

48. Giri VN, Hegarty SE, Hyatt C, O'Leary E, Garcia J, Knudsen KE, et al. Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. The Prostate. 2019;79(4):333-9.

49. Page EC, Bancroft EK, Brook MN, Assel M, Al Battat MH, Thomas S, et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. European urology. 2019;76(6):831-42.

50. James D. Brierley (Editor) MKGE, Christian Wittekind (Editor). TNM classification of malignant tumors. UICC International Union Against Cancer. 2017;8th edn. .

51. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. The Journal of urology. 1974;111(1):58-64.

52. Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. The American journal of surgical pathology. 2005;29(9):1228-42.

53. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. The American journal of surgical pathology. 2016;40(2):244-52.

54. Danneman D, Drevin L, Robinson D, Stattin P, Egevad L. Gleason inflation 1998-2011: a registry study of 97,168 men. BJU international. 2015;115(2):248-55.

55. Esserman LJ, Thompson IM, Reid B, Nelson P, Ransohoff DF, Welch HG, et al. Addressing overdiagnosis and overtreatment in cancer: a prescription for change. The Lancet Oncology. 2014;15(6):e234-42.

56. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. European urology. 2015;68(6):1045-53.

57. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. Jama. 1994;271(5):368-74.

58. Filson CP, Natarajan S, Margolis DJ, Huang J, Lieu P, Dorey FJ, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: The role of systematic and targeted biopsies. Cancer. 2016;122(6):884-92.

59. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. The New England journal of medicine. 2018;378(19):1767-77.

60. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. European urology. 2011;59(1):61-71.

61. Rouviere O, Puech P, Renard-Penna R, Claudon M, Roy C, Mege-Lechevallier F, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. The Lancet Oncology. 2019;20(1):100-9.

62. Kepner GR, Kepner JV. Transperineal prostate biopsy: analysis of a uniform core sampling pattern that yields data on tumor volume limits in negative biopsies. Theoretical biology & medical modelling. 2010;7:23.

63. Wolters T, Roobol MJ, van Leeuwen PJ, van den Bergh RC, Hoedemaeker RF, van Leenders GJ, et al. A critical analysis of the tumor volume threshold for clinically insignificant prostate cancer using a data set of a randomized screening trial. The Journal of urology. 2011;185(1):121-5.

64. Stamey TA, Freiha FS, McNeal JE, Redwine EA, Whittemore AS, Schmid HP. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. Cancer. 1993;71(3 Suppl):933-8.

65. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecornet E, Freeman A, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. The Journal of urology. 2011;186(2):458-64.

66. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. European urology. 2019;75(4):570-8.

67. D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, Kaplan I, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(1):168-72.

68. Chaloupka M, Apfelbeck M, Pfitzinger P, Bischoff R, Lellig E, Rath L, et al. Multiparametric magnetic resonance imaging and multiparametric magnetic resonance imaging-guided biopsy in the diagnostic pathway of prostate cancer. Der Radiologe. 2020;60(Suppl 1):63-9.

69. Flocks RH, Urich VC, Patel CA, Opitz JM. Studies on the antigenic properties of prostatic tissue. I. The Journal of urology. 1960;84:134-43.

70. Ablin RJ, Soanes WA, Bronson P, Witebsky E. Precipitating antigens of the normal human prostate. Journal of reproduction and fertility. 1970;22(3):573-4.

71. Hara M, Inoue T, Koyanagi Y, Goto J, Yamazaki H, Fukuyama T. Preparation and immunoelectrophoretic assessment of antisera to human seminal plasma. Nippon Hoigaku Zasshi. 1966;20:356.

72. Li TS, Beling CG. Isolation and characterization of two specific antigens of human seminal plasma. Fertility and sterility. 1973;24(2):134-44.

73. Sensabaugh GF. Isolation and characterization of a semen-specific protein from human seminal plasma: a potential new marker for semen identification. Journal of forensic sciences. 1978;23(1):106-15.

74. Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. Investigative urology. 1979;17(2):159-63.

75. Papsidero LD, Wang MC, Valenzuela LA, Murphy GP, Chu TM. A prostate antigen in sera of prostatic cancer patients. Cancer research. 1980;40(7):2428-32.

76. Kuriyama M, Wang MC, Papsidero LD, Killian CS, Shimano T, Valenzuela L, et al. Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay. Cancer research. 1980;40(12):4658-62.

77. Barry MJ. Clinical practice. Prostate-specific-antigen testing for early diagnosis of prostate cancer. The New England journal of medicine. 2001;344(18):1373-7.

78. Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. The Journal of the American Board of Family Practice. 2003;16(2):95-101.

79. Higashihara E, Nutahara K, Kojima M, Okegawa T, Miura I, Miyata A, et al. Significance of free prostate-specific antigen and gamma-seminoprotein in the screening of prostate cancer. The Prostate Supplement. 1996;7:40-7.

80. Nadler RB, Humphrey PA, Smith DS, Catalona WJ, Ratliff TL. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. The Journal of urology. 1995;154(2 Pt 1):407-13.

81. Tchetgen MB, Song JT, Strawderman M, Jacobsen SJ, Oesterling JE. Ejaculation increases the serum prostate-specific antigen concentration. Urology. 1996;47(4):511-6.

82. Herschman JD, Smith DS, Catalona WJ. Effect of ejaculation on serum total and free prostate-specific antigen concentrations. Urology. 1997;50(2):239-43.

83. Zhou CK, Check DP, Lortet-Tieulent J, Laversanne M, Jemal A, Ferlay J, et al. Prostate cancer incidence in 43 populations worldwide: An analysis of time trends overall and by age group. International journal of cancer. 2016;138(6):1388-400.

84. Harvey P, Basuita A, Endersby D, Curtis B, Iacovidou A, Walker M. A systematic review of the diagnostic accuracy of prostate specific antigen. BMC urology. 2009;9:14.

85. Exterkate L, Wegelin O, Barentsz JO, van der Leest MG, Kummer JA, Vreuls W, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate? European urology oncology. 2020;3(2):216-23.

86. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. Jama. 1995;273(4):289-94.

87. Sershon PD, Barry MJ, Oesterling JE. Serum prostate-specific antigen discriminates weakly between men with benign prostatic hyperplasia and patients with organ-confined prostate cancer. European urology. 1994;25(4):281-7.

88. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. Jama. 1997;277(18):1452-5.

89. Babaian RJ, Johnston DA, Naccarato W, Ayala A, Bhadkamkar VA, Fritsche HH, Jr. The incidence of prostate cancer in a screening population with a serum prostate specific antigen between 2.5 and 4.0 ng/ml: relation to biopsy strategy. The Journal of urology. 2001;165(3):757-60.

90. Catalona WJ, Ramos CG, Carvalhal GF, Yan Y. Lowering PSA cutoffs to enhance detection of curable prostate cancer. Urology. 2000;55(6):791-5.

91. Carter HB. A PSA threshold of 4.0 ng/mL for early detection of prostate cancer: the only rational approach for men 50 years old and older. Urology. 2000;55(6):796-9.

92. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery--what we have learned and where we are going. The Journal of urology. 1999;162(2):293-306.

93. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. Jama. 1998;279(19):1542-7.

94. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. The New England journal of medicine. 2009;360(13):1310-9.

95. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. The New England journal of medicine. 2012;366(11):981-90.

96. Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. Jama. 2018;319(9):883-95.

97. Halpern JA, Shoag JE, Artis AS, Ballman KV, Sedrakyan A, Hershman DL, et al. National trends in prostate biopsy and radical prostatectomy volumes following the US Preventive Services Task Force guidelines against prostate-specific antigen screening. JAMA surgery. 2017;152(2):192-8.

98. Bibbins-Domingo K, Grossman DC, Curry SJ. The US Preventive Services Task Force 2017 Draft Recommendation Statement on Screening for Prostate Cancer: An Invitation to Review and Comment. Jama. 2017;317(19):1949-50.

99. Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. Jama. 2014;311(11):1143-9.

100. Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ (Clinical research ed). 2018;362:k3519.

101. Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. The Journal of urology. 1992;147(3 Pt 2):815-6.

102. Benson MC, Whang IS, Olsson CA, McMahon DJ, Cooner WH. The use of prostate specific antigen density to enhance the predictive value of intermediate levels of serum prostate specific antigen. The Journal of urology. 1992;147(3 Pt 2):817-21.

103. Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. European urology. 2013;63(4):597-603.

104. Chung DY, Goh HJ, Koh DH, Kim MS, Lee JS, Jang WS, et al. Clinical significance of multiparametric MRI and PSA density as predictors of residual tumor (pT0) following radical prostatectomy for T1a-T1b (incidental) prostate cancer. PloS one. 2018;13(12):e0210037.

105. Distler FA, Radtke JP, Bonekamp D, Kesch C, Schlemmer HP, Wieczorek K, et al. The Value of PSA Density in Combination with PI-RADS™ for the Accuracy of Prostate Cancer Prediction. The Journal of urology. 2017;198(3):575-82.

106. Stevens E, Truong M, Bullen JA, Ward RD, Purysko AS, Klein EA. Clinical utility of PSAD combined with PI-RADS category for the detection of clinically significant prostate cancer. Urologic oncology. 2020;38(11):846.e9-.e16.

107. Bhat NR, Vetter JM, Andriole GL, Shetty AS, Ippolito JE, Kim EH. Magnetic Resonance Imaging-Defined Prostate-Specific Antigen Density Significantly Improves the

Risk Prediction for Clinically Significant Prostate Cancer on Biopsy. Urology. 2019;126:152-7.

108. Hansen NL, Kesch C, Barrett T, Koo B, Radtke JP, Bonekamp D, et al. Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy. BJU international. 2017;120(5):631-8.

109. Washino S, Okochi T, Saito K, Konishi T, Hirai M, Kobayashi Y, et al. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naïve patients. BJU international. 2017;119(2):225-33.

110. Venderink W, van Luijtelaar A, Bomers JGR, van der Leest M, Hulsbergen-van de Kaa C, Barentsz JO, et al. Results of Targeted Biopsy in Men with Magnetic Resonance Imaging Lesions Classified Equivocal, Likely or Highly Likely to Be Clinically Significant Prostate Cancer. European urology. 2018;73(3):353-60.

111. Rais-Bahrami S, Siddiqui MM, Vourganti S, Turkbey B, Rastinehad AR, Stamatakis L, et al. Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. BJU international. 2015;115(3):381-8.

112. Boesen L, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thestrup KC, et al. Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7-10 Prostate Cancer in Biopsy-naïve Men. European urology oncology. 2019;2(3):311-9.

113. Joseph A. Smith J, MD, Stuart S. Howards, MD, Glenn M. Preminger, MD, Roger R. Dmochowski, MD, FACS. Hinman's atlas of urologic surgery. 4th edition, Philadelphia, PA : Elsevier, [2017]. 2017; 4th EDITION, Philadelphia, PA : Elsevier:83.

114. Smith DS, Catalona WJ. Interexaminer variability of digital rectal examination in detecting prostate cancer. Urology. 1995;45(1):70-4.

115. Naji L, Randhawa H, Sohani Z, Dennis B, Lautenbach D, Kavanagh O, et al. Digital Rectal Examination for Prostate Cancer Screening in Primary Care: A Systematic Review and Meta-Analysis. Annals of family medicine. 2018;16(2):149-54.

116. Cupp MR, Oesterling JE. Prostate-specific antigen, digital rectal examination, and transrectal ultrasonography: their roles in diagnosing early prostate cancer. Mayo Clinic proceedings. 1993;68(3):297-306.

117. Wysock JS, Xu A, Orczyk C, Taneja SS. HistoScanning(TM) to Detect and Characterize Prostate Cancer-a Review of Existing Literature. Current urology reports. 2017;18(12):97.

118. Oesterling JE. Prostate specific antigen. Its role in the diagnosis and staging of prostate cancer. Cancer. 1995;75(S7):1795-804.

119. Smeenge M, Barentsz J, Cosgrove D, de la Rosette J, de Reijke T, Eggener S, et al. Role of transrectal ultrasonography (TRUS) in focal therapy of prostate cancer: report from a Consensus Panel. BJU international. 2012;110(7):942-8.

120. Onur R, Littrup PJ, Pontes JE, Bianco FJ, Jr. Contemporary impact of transrectal ultrasound lesions for prostate cancer detection. The Journal of urology. 2004;172(2):512-4.

121. Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. European urology. 2013;63(2):214-30.

122. Scattoni V, Zlotta A, Montironi R, Schulman C, Rigatti P, Montorsi F. Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: a critical analysis of the literature. European urology. 2007;52(5):1309-22.

123. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet (London, England). 2014;384(9959):2027-35.

124. Pummer K, Rieken M, Augustin H, Gutschi T, Shariat SF. Innovations in diagnostic imaging of localized prostate cancer. World journal of urology. 2014;32(4):881-90.

125. Shigeno K, Igawa M, Shiina H, Wada H, Yoneda T. The role of colour Doppler ultrasonography in detecting prostate cancer. BJU international. 2000;86(3):229-33.

126. Burns PN, Wilson SR. Microbubble contrast for radiological imaging: 1. Principles. Ultrasound quarterly. 2006;22(1):5-13.

127. Halpern EJ, Verkh L, Forsberg F, Gomella LG, Mattrey RF, Goldberg BB. Initial experience with contrast-enhanced sonography of the prostate. AJR American journal of roentgenology. 2000;174(6):1575-80.

128. Wink M, Frauscher F, Cosgrove D, Chapelon JY, Palwein L, Mitterberger M, et al. Contrast-enhanced ultrasound and prostate cancer; a multicentre European research coordination project. European urology. 2008;54(5):982-92.

129. Li Y, Tang J, Fei X, Gao Y. Diagnostic performance of contrast enhanced ultrasound in patients with prostate cancer: a meta-analysis. Academic radiology. 2013;20(2):156-64.

130. Phipps S, Yang TH, Habib FK, Reuben RL, McNeill SA. Measurement of tissue mechanical characteristics to distinguish between benign and malignant prostatic disease. Urology. 2005;66(2):447-50.

131. Teng J, Chen M, Gao Y, Yao Y, Chen L, Xu D. Transrectal sonoelastography in the detection of prostate cancers: a meta-analysis. BJU international. 2012;110(11 Pt B):E614-20.

132. Palmeri ML, Miller ZA, Glass TJ, Garcia-Reyes K, Gupta RT, Rosenzweig SJ, et al. B-mode and acoustic radiation force impulse (ARFI) imaging of prostate zonal anatomy: comparison with 3T T2-weighted MR imaging. Ultrasonic imaging. 2015;37(1):22-41.

133. Zhai L, Madden J, Foo WC, Palmeri ML, Mouraviev V, Polascik TJ, et al. Acoustic radiation force impulse imaging of human prostates ex vivo. Ultrasound in medicine & biology. 2010;36(4):576-88.

134. Zhai L, Polascik TJ, Foo WC, Rosenzweig S, Palmeri ML, Madden J, et al. Acoustic radiation force impulse imaging of human prostates: initial in vivo demonstration. Ultrasound in medicine & biology. 2012;38(1):50-61.

135. Palmeri ML, Glass TJ, Miller ZA, Rosenzweig SJ, Buck A, Polascik TJ, et al. Identifying Clinically Significant Prostate Cancers using 3-D In Vivo Acoustic Radiation

Force Impulse Imaging with Whole-Mount Histology Validation. Ultrasound in medicine & biology. 2016;42(6):1251-62.

136. Yang Y, Zhao X, Zhao X, Shi J, Huang Y. Value of shear wave elastography for diagnosis of primary prostate cancer: a systematic review and meta-analysis. Medical ultrasonography. 2019;21(4):382-8.

137. Braeckman J, Autier P, Garbar C, Marichal MP, Soviany C, Nir R, et al. Computer-aided ultrasonography (HistoScanning): a novel technology for locating and characterizing prostate cancer. BJU international. 2008;101(3):293-8.

138. Scheipers U, König K, Sommerfeld HJ, Garcia-Schürmann M, Senge T, Ermert H. Sonohistology - ultrasonic tissue characterization for prostate cancer diagnostics. Cancer biomarkers : section A of Disease markers. 2008;4(4-5):227-50.

139. Schiffmann J, Fischer J, Tennstedt P, Beyer B, Böhm K, Michl U, et al. Comparison of prostate cancer volume measured by HistoScanning™ and final histopathological results. World journal of urology. 2014;32(4):939-44.

140. Porres D, Kuru TH, Epplen R, Eck A, Zugor V, Kennes LN, et al. Sextant-Specific Analysis of Detection and Tumor Volume by HistoScanning™. Urologia internationalis. 2016;96(2):194-201.

141. Simmons LAM, Kanthabalan A, Arya M, Briggs T, Charman SC, Freeman A, et al. Prostate Imaging Compared to Transperineal Ultrasound-guided biopsy for significant prostate cancer Risk Evaluation (PICTURE): a prospective cohort validating study assessing Prostate HistoScanning. Prostate cancer and prostatic diseases. 2019;22(2):261-7.

142. Orczyk C, Rosenkrantz AB, Deng FM, Melamed J, Babb J, Wysock J, et al. A prospective comparative analysis of the accuracy of HistoScanning and multiparametric magnetic resonance imaging in the localization of prostate cancer among men undergoing radical prostatectomy. Urologic oncology. 2016;34(1):3.e1-8.

143. Simmons LA, Ahmed HU, Moore CM, Punwani S, Freeman A, Hu Y, et al. The PICTURE study -- prostate imaging (multi-parametric MRI and Prostate HistoScanning™) compared to transperineal ultrasound guided biopsy for significant prostate cancer risk evaluation. Contemporary clinical trials. 2014;37(1):69-83.

144. Rohrbach D, Wodlinger B, Wen J, Mamou J, Feleppa E. High-Frequency Quantitative Ultrasound for Imaging Prostate Cancer Using a Novel Micro-Ultrasound Scanner. Ultrasound in medicine & biology. 2018;44(7):1341-54.

145. Klotz L, Lughezzani G, Maffei D, Sánchez A, Pereira JG, Staerman F, et al. Comparison of micro-ultrasound and multiparametric magnetic resonance imaging for prostate cancer: A multicenter, prospective analysis. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2021;15(1):E11-e6.

146. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. European urology. 2016;69(1):16-40.

147. Puech P, Villers A, Ouzzane A, Lemaitre L. Prostate cancer: diagnosis, parametric imaging and standardized report. Diagnostic and interventional imaging. 2014;95(7-8):743-52.

148. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. European radiology. 2012;22(4):746-57.

149. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. European urology. 2011;59(4):477-94.

150. Barret E, Turkbey B, Puech P, Durand M, Panebianco V, Fütterer JJ, et al. Update on the ICUD-SIU consultation on multi-parametric magnetic resonance imaging in localised prostate cancer. World journal of urology. 2019;37(3):429-36.

151. Barrett T, Turkbey B, Choyke PL. PI-RADS version 2: what you need to know. Clinical radiology. 2015;70(11):1165-76.

152. Rosenkrantz AB, Kim S, Lim RP, Hindman N, Deng FM, Babb JS, et al. Prostate cancer localization using multiparametric MR imaging: comparison of Prostate Imaging Reporting and Data System (PI-RADS) and Likert scales. Radiology. 2013;269(2):482-92.

153. Hamoen EH, de Rooij M, Witjes JA, Barentsz JO, Rovers MM. Use of the Prostate Imaging Reporting and Data System (PI-RADS) for prostate cancer detection with

multiparametric magnetic resonance imaging: a diagnostic meta-analysis. European urology. 2015;67(6):1112-21.

154. Rosenkrantz AB, Ginocchio LA, Cornfeld D, Froemming AT, Gupta RT, Turkbey B, et al. Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists. Radiology. 2016;280(3):793-804.

155. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology. 1988;168(2):497-505.

156. Barentsz J, Villers A, Schouten M. Reply to Letter to the Editor re: ESUR prostate MR guidelines. European radiology. 2013;23(8):2322.

157. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic Performance of Prostate Imaging Reporting and Data System Version 2 for Detection of Prostate Cancer: A Systematic Review and Diagnostic Meta-analysis. European urology. 2017;72(2):177-88.

158. Walker SM, Türkbey B. PI-RADSv2.1: Current status. Turkish journal of urology. 2021;47(Supp. 1):S45-s8.

159. Belue MJ, Yilmaz EC, Daryanani A, Turkbey B. Current Status of Biparametric MRI in Prostate Cancer Diagnosis: Literature Analysis. Life (Basel, Switzerland). 2022;12(6).

160. Liang Z, Hu R, Yang Y, An N, Duo X, Liu Z, et al. Is dynamic contrast enhancement still necessary in multiparametric magnetic resonance for diagnosis of prostate cancer: a systematic review and meta-analysis. Translational andrology and urology. 2020;9(2):553-73.

161. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. European urology. 2014;65(1):124-37.

162. Arumainayagam N, Ahmed HU, Moore CM, Freeman A, Allen C, Sohaib SA, et al. Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. Radiology. 2013;268(3):761-9.

163. Sonn GA, Chang E, Natarajan S, Margolis DJ, Macairan M, Lieu P, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. European urology. 2014;65(4):809-15.

164. Vourganti S, Rastinehad A, Yerram N, Nix J, Volkin D, Hoang A, et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. The Journal of urology. 2012;188(6):2152-7.

165. Abd-Alazeez M, Ahmed HU, Arya M, Charman SC, Anastasiadis E, Freeman A, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level--can it rule out clinically significant prostate cancer? Urologic oncology. 2014;32(1):45.e17-22.

166. Salami SS, Ben-Levi E, Yaskiv O, Ryniker L, Turkbey B, Kavoussi LR, et al. In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy? BJU international. 2015;115(4):562-70.

167. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European urology. 2017;71(4):618-29.

168. Abraham NE, Mendhiratta N, Taneja SS. Patterns of repeat prostate biopsy in contemporary clinical practice. The Journal of urology. 2015;193(4):1178-84.

169. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. European urology. 2013;64(6):876-92.

170. Turkbey B, Brown AM, Sankineni S, Wood BJ, Pinto PA, Choyke PL. Multiparametric prostate magnetic resonance imaging in the evaluation of prostate cancer. CA: a cancer journal for clinicians. 2016;66(4):326-36.

171. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet (London, England). 2017.

172. N. Mottet (Chair) RCNvdB, E. Briers (Patient Representative), P. Cornford (Vice-chair), M. De Santis, S. Fanti, S. Gillessen, J. Grummet, A.M. Henry,, T.B. Lam MDM, T.H. van der Kwast, H.G. van der Poel, O. Rouvière, D. Tilki, T. Wiegel, Guidelines Associates: T. Van den Broeck MC, N. Fossati, T. Gross, M. Lardas, M. Liew, L. Moris, I.G. Schoots, P-P.M. Willemse. EAU - EANM - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer [PDF Guidline on Prostate Cancer]. 2019 [updated PROSTATE CANCER - UPDATE MARCH 2019. Available from: https://uroweb.org/wp-content/uploads/EAU-EANM-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Cancer-2019.pdf.

173. Wegelin O, Exterkate L, van der Leest M, Kummer JA, Vreuls W, de Bruin PC, et al. The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies. European urology. 2019;75(4):582-90.

174. Sugano D, Kaneko M, Yip W, Lebastchi AH, Cacciamani GE, Abreu AL. Comparative Effectiveness of Techniques in Targeted Prostate Biopsy. Cancers. 2021;13(6).

175. Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. The New England journal of medicine. 2017;377(2):132-42.

176. Neal DE, Metcalfe C, Donovan JL, Lane JA, Davis M, Young GJ, et al. Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received. European urology. 2020;77(3):320-30.

177. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. New England Journal of Medicine. 2023.

178. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. The New England journal of medicine. 2018;379(24):2319-29.

179. Westphalen AC, McCulloch CE, Anaokar JM, Arora S, Barashi NS, Barentsz JO, et al. Variability of the Positive Predictive Value of PI-RADS for Prostate MRI across 26

Centers: Experience of the Society of Abdominal Radiology Prostate Cancer Disease-focused Panel. Radiology. 2020;296(1):76-84.

180. Maxeiner A, Kittner B, Blobel C, Wiemer L, Hofbauer SL, Fischer T, et al. Primary magnetic resonance imaging/ultrasonography fusion-guided biopsy of the prostate. BJU international. 2018;122(2):211-8.

181. Preisser F, Theissen L, Wenzel M, Humke C, Bodelle B, Köllermann J, et al. Performance of Combined Magnetic Resonance Imaging/Ultrasound Fusion-guided and Systematic Biopsy of the Prostate in Biopsy-naïve Patients and Patients with Prior Biopsies. European urology focus. 2019.

182. Hofbauer SL, Maxeiner A, Kittner B, Heckmann R, Reimann M, Wiemer L, et al. Validation of Prostate Imaging Reporting and Data System Version 2 for the Detection of Prostate Cancer. The Journal of urology. 2018;200(4):767-73.

183. Dell'Oglio P, Stabile A, Soligo M, Brembilla G, Esposito A, Gandaglia G, et al. There Is No Way to Avoid Systematic Prostate Biopsies in Addition to Multiparametric Magnetic Resonance Imaging Targeted Biopsies. European urology oncology. 2020;3(1):112-8.

184. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. The New England journal of medicine. 2020;382(10):917-28.

185. Sathianathen NJ, Warlick CA, Weight CJ, Ordonez MA, Spilseth B, Metzger GJ, et al. A clinical prediction tool to determine the need for concurrent systematic sampling at the time of magnetic resonance imaging-guided biopsy. BJU international. 2019;123(4):612-7.

186. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. Jama. 2015;313(4):390-7.

187. Mischinger J, Schöllnast H, Zurl H, Geyer M, Fischereder K, Adelsmayr G, et al. Combining targeted and systematic prostate biopsy improves prostate cancer detection and correlation with the whole mount histopathology in biopsy naïve and previous negative biopsy patients. Frontiers in surgery. 2022;9:1013389.

188. Johnson DC, Raman SS, Mirak SA, Kwan L, Bajgiran AM, Hsu W, et al. Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging. European urology. 2019;75(5):712-20.

189. Duncan RC CR, and Miller MC III. Introductory Biostatistics for the Health Sciences. John Wiley and Sons, New York. 1983;2nd ed.

190. Sonn GA, Fan RE, Ghanouni P, Wang NN, Brooks JD, Loening AM, et al. Prostate Magnetic Resonance Imaging Interpretation Varies Substantially Across Radiologists. European urology focus. 2019;5(4):592-9.

191. Bjurlin MA, Carroll PR, Eggener S, Fulgham PF, Margolis DJ, Pinto PA, et al. Update of the Standard Operating Procedure on the Use of Multiparametric Magnetic Resonance Imaging for the Diagnosis, Staging and Management of Prostate Cancer. The Journal of urology. 2020;203(4):706-12.

192. Mason RJ, Marzouk K, Finelli A, Saad F, So AI, Violette PD, et al. UPDATE - 2022 Canadian Urological Association recommendations on prostate cancer screening and early diagnosis Endorsement of the 2021 Cancer Care Ontario guidelines on prostate multiparametric magnetic resonance imaging. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2022;16(4):E184-e96.

193. S3-Leitlinie LO. Prostatakarzinom: Version 6.2 – Oktober 2021 AWMF-Registernummer: 043/022OL; 2021 [updated Octobre 2021. page 75]. Available from: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Prostatatkarzinom/Version_6/LL_Prostatakarzinom_Langversion_6.2.pdf.

194. UK NGUT. Prostate cancer: diagnosis and management. 2019.

195. Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. The Cochrane database of systematic reviews. 2019;4(4):Cd012663.

196. Mendhiratta N, Meng X, Rosenkrantz AB, Wysock JS, Fenstermaker M, Huang R, et al. Prebiopsy MRI and MRI-ultrasound Fusion-targeted Prostate Biopsy in Men With Previous Negative Biopsies: Impact on Repeat Biopsy Strategies. Urology. 2015;86(6):1192-8.

197. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2020;31(9):1119-34.

198. Oishi M, Shin T, Ohe C, Nassiri N, Palmer SL, Aron M, et al. Which Patients with Negative Magnetic Resonance Imaging Can Safely Avoid Biopsy for Prostate Cancer? The Journal of urology. 2019;201(2):268-76.

199. Aminsharifi A, Howard L, Wu Y, De Hoedt A, Bailey C, Freedland SJ, et al. Prostate Specific Antigen Density as a Predictor of Clinically Significant Prostate Cancer When the Prostate Specific Antigen is in the Diagnostic Gray Zone: Defining the Optimum Cutoff Point Stratified by Race and Body Mass Index. The Journal of urology. 2018;200(4):758-66.

200. Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate cancer and prostatic diseases. 2018;21(1):57-63.

201. Drobish JN, Bevill MD, Tracy CR, Sexton SM, Rajput M, Metz CM, et al. Do patients with a PI-RADS 5 lesion identified on magnetic resonance imaging require systematic biopsy in addition to targeted biopsy? Urologic oncology. 2021;39(4):235.e1-.e4.

202. Tafuri A, Iwata A, Shakir A, Iwata T, Gupta C, Sali A, et al. Systematic Biopsy of the Prostate can Be Omitted in Men with PI-RADS™ 5 and Prostate Specific Antigen Density Greater than 15. The Journal of urology. 2021:101097ju0000000000001766.

203. Lodeta B, Trkulja V, Kolroser-Sarmiento G, Jozipovic D, Salmhofer A, Augustin H. Systematic biopsy should not be omitted in the era of combined magnetic resonance imaging/ultrasound fusion-guided biopsies of the prostate. International urology and nephrology. 2021;53(11):2251-9.

204. Liang L, Qi F, Cheng Y, Zhang L, Cao D, Cheng G, et al. Analysis of risk factors for determining the need for prostate biopsy in patients with negative MRI. Scientific reports. 2021;11(1):6048.

205. Moore CM, Kasivisvanathan V, Eggener S, Emberton M, Futterer JJ, Gill IS, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. European urology. 2013;64(4):544-52.

206. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

207. Hugosson J, Månsson M, Wallström J, Axcrona U, Carlsson SV, Egevad L, et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. New England Journal of Medicine. 2022;387(23):2126-37.

208. Zhu K, Qin Z, Xue J, Miao C, Tian Y, Liu S, et al. Comparison of prostate cancer detection rates between magnetic resonance imaging-targeted biopsy and transrectal ultrasound-guided biopsy according to Prostate Imaging Reporting and Data System in patients with PSA ≥4 ng/mL: a systematic review and meta-analysis. Translational andrology and urology. 2019;8(6):741-53.

209. Muller BG, Shih JH, Sankineni S, Marko J, Rais-Bahrami S, George AK, et al. Prostate cancer: interobserver agreement and accuracy with the revised prostate imaging reporting and data system at multiparametric MR imaging. Radiology. 2015;277(3):741.

210. de Rooij M, Israël B, Tummers M, Ahmed HU, Barrett T, Giganti F, et al. ESUR/ESUI consensus statements on multi-parametric MRI for the detection of clinically significant prostate cancer: quality requirements for image acquisition, interpretation and radiologists' training. European radiology. 2020;30(10):5404-16.

211. Luzzago S, Petralia G, Musi G, Catellani M, Alessi S, Di Trapani E, et al. Multiparametric Magnetic Resonance Imaging Second Opinion May Reduce the Number of Unnecessary Prostate Biopsies: Time to Improve Radiologists' Training Program? Clinical genitourinary cancer. 2019;17(2):88-96.

212. Rosenzweig B, Laitman Y, Zilberman DE, Raz O, Ramon J, Dotan ZA, et al., editors. Effects of "real life" prostate MRI inter-observer variability on total needle samples and indication for biopsy. Urologic Oncology: Seminars and Original Investigations; 2020: Elsevier.

213. Park KJ, Choi SH, Lee JS, Kim JK, Kim M-h. Interreader Agreement with Prostate Imaging Reporting and Data System Version 2 for Prostate Cancer Detection: A Systematic Review and Meta-Analysis. Journal of Urology. 2020;204(4):661-70.

214. Brembilla G, Dell'Oglio P, Stabile A, Damascelli A, Brunetti L, Ravelli S, et al. Interreader variability in prostate MRI reporting using Prostate Imaging Reporting and Data System version 2.1. European radiology. 2020;30(6):3383-92.

215. Padhani AR, Barentsz J, Villeirs G, Rosenkrantz AB, Margolis DJ, Turkbey B, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. Radiology. 2019;292(2):464-74.

216. Mussi TC, Yamauchi FI, Tridente CF, Tachibana A, Tonso VM, Recchimuzzi DZ, et al. Interobserver agreement of PI-RADS v. 2 lexicon among radiologists with different levels of experience. Journal of magnetic resonance imaging : JMRI. 2020;51(2):593-602.

217. Ke Z, Wang L, Min XD, Feng ZY, Kang Z, Zhang PP, et al. Diagnostic Performance and Interobserver Consistency of the Prostate Imaging Reporting and Data System Version 2: A Study on Six Prostate Radiologists with Different Experiences from Half a Year to 17 Years. Chinese medical journal. 2018;131(14):1666-73.

218. Smith CP, Harmon SA, Barrett T, Bittencourt LK, Law YM, Shebel H, et al. Intra- and interreader reproducibility of PI-RADSv2: A multireader study. Journal of magnetic resonance imaging : JMRI. 2019;49(6):1694-703.

219. Ahmed HM, Ebeed AE, Hamdy A, El-Ghar MA, Razek AAKA. Interobserver agreement of Prostate Imaging–Reporting and Data System (PI-RADS–v2). Egyptian Journal of Radiology and Nuclear Medicine. 2021;52(1):5.

220. Goldberg H, Ahmad AE, Chandrasekar T, Klotz L, Emberton M, Haider MA, et al. Comparison of Magnetic Resonance Imaging and Transrectal Ultrasound Informed Prostate Biopsy for Prostate Cancer Diagnosis in Biopsy Naïve Men: A Systematic Review and Meta-Analysis. The Journal of urology. 2020;203(6):1085-93.

221. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. European urology. 2015;68(3):438-50.

222. Fourcade A, Payrard C, Tissot V, Perrouin-Verbe MA, Demany N, Serey-Effeil S, et al. The combination of targeted and systematic prostate biopsies is the best protocol for the detection of clinically significant prostate cancer. Scandinavian journal of urology. 2018;52(3):174-9.

223. Gomez-Gomez E, Moreno Sorribas S, Valero-Rosa J, Blanca A, Mesa J, Salguero J, et al. Does Adding Standard Systematic Biopsy to Targeted Prostate Biopsy in PI-RADS 3 to 5 Lesions Enhance the Detection of Clinically Significant Prostate Cancer? Should All Patients with PI-RADS 3 Undergo Targeted Biopsy? Diagnostics (Basel, Switzerland). 2021;11(8).

224. Patel HD, Koehne EL, Shea SM, Bhanji Y, Gerena M, Gorbonos A, et al. Risk of prostate cancer for men with prior negative biopsies undergoing magnetic resonance imaging compared with biopsy-naive men: A prospective evaluation of the PLUM cohort. Cancer. 2022;128(1):75-84.

225. Ploussard G, Beauval JB, Lesourd M, Almeras C, Assoun J, Aziza R, et al. Added Value of Concomitant Systematic and Fusion Targeted Biopsies for Grade Group Prediction Based on Radical Prostatectomy Final Pathology on Positive Magnetic Resonance Imaging. The Journal of urology. 2019;202(6):1182-7.

226. Schouten MG, van der Leest M, Pokorny M, Hoogenboom M, Barentsz JO, Thompson LC, et al. Why and Where do We Miss Significant Prostate Cancer with Multi-parametric Magnetic Resonance Imaging followed by Magnetic Resonance-guided and Transrectal Ultrasound-guided Biopsy in Biopsy-naïve Men? European urology. 2017;71(6):896-903.

227. Rastinehad AR, Turkbey B, Salami SS, Yaskiv O, George AK, Fakhoury M, et al. Improving detection of clinically significant prostate cancer: magnetic resonance imaging/transrectal ultrasound fusion guided prostate biopsy. The Journal of urology. 2014;191(6):1749-54.

228. Radtke JP, Kuru TH, Boxler S, Alt CD, Popeneciu IV, Huettenbrink C, et al. Comparative analysis of transperineal template saturation prostate biopsy versus magnetic resonance imaging targeted biopsy with magnetic resonance imaging-ultrasound fusion guidance. The Journal of urology. 2015;193(1):87-94.

229. Wenzel M, Theissen L, Preisser F, Lauer B, Wittler C, Humke C, et al. Complication Rates After TRUS Guided Transrectal Systematic and MRI-Targeted Prostate Biopsies in a High-Risk Region for Antibiotic Resistances. Frontiers in surgery. 2020;7:7.

230. Herrera-Caceres J, Villeda-Sandoval C, Ruiz-Quinones J, De-La-Rosa-Leiva P, Castillejos-Molina R, Feria-Bernal G, et al. Single-dose piperacillin/tazobactam as prophylaxis in transrectal prostate biopsy. Revista Mexicana de Urología. 2015;75(5):272-7.

231. Wegelin O, Exterkate L, van der Leest M, Kelder JC, Bosch J, Barentsz JO, et al. Complications and Adverse Events of Three Magnetic Resonance Imaging-based Target Biopsy Techniques in the Diagnosis of Prostate Cancer Among Men with Prior Negative Biopsies: Results from the FUTURE Trial, a Multicentre Randomised Controlled Trial. European urology oncology. 2019;2(6):617-24.

232. Diamand R, Oderda M, Al Hajj Obeid W, Albisinni S, Van Velthoven R, Fasolis G, et al. A multicentric study on accurate grading of prostate cancer with systematic and MRI/US fusion targeted biopsies: comparison with final histopathology after radical prostatectomy. World journal of urology. 2019;37(10):2109-17.

233. Gandaglia G, Ploussard G, Valerio M, Mattei A, Fiori C, Roumiguié M, et al. The Key Combined Value of Multiparametric Magnetic Resonance Imaging, and Magnetic Resonance Imaging-targeted and Concomitant Systematic Biopsies for the Prediction of Adverse Pathological Features in Prostate Cancer Patients Undergoing Radical Prostatectomy. European urology. 2020;77(6):733-41.

234. Barrett T, Rajesh A, Rosenkrantz AB, Choyke PL, Turkbey B. PI-RADS version 2.1: one small step for prostate MRI. Clinical radiology. 2019;74(11):841-52.

235. Annamalai A, Fustok JN, Beltran-Perez J, Rashad AT, Krane LS, Triche BL. Interobserver Agreement and Accuracy in Interpreting mpMRI of the Prostate: a Systematic Review. Current urology reports. 2022;23(1):1-10.

236. Wang RS, Kim EH, Vetter JM, Fowler KJ, Shetty AS, Mintz AJ, et al. Determination of the Role of Negative Magnetic Resonance Imaging of the Prostate in Clinical Practice: Is Biopsy Still Necessary? Urology. 2017;102:190-7.

237. Lu AJ, Syed JS, Nguyen KA, Nawaf CB, Rosoff J, Spektor M, et al. Negative Multiparametric Magnetic Resonance Imaging of the Prostate Predicts Absence of Clinically Significant Prostate Cancer on 12-Core Template Prostate Biopsy. Urology. 2017;105:118-22.

238. Ploussard G, Nicolaiew N, Marchand C, Terry S, Allory Y, Vacherot F, et al. Risk of repeat biopsy and prostate cancer detection after an initial extended negative biopsy: longitudinal follow-up from a prospective trial. BJU international. 2013;111(6):988-96.

239. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. European urology. 2016;69(3):428-35.

240. Bravi CA, Vertosick E, Tin A, Scuderi S, Fallara G, Rosiello G, et al. Relative Contribution of Sampling and Grading to the Quality of Prostate Biopsy: Results from a Single High-volume Institution. European urology oncology. 2020;3(4):474-80.

Appendix

Publication that is based on the thesis:

Mischinger J, Schöllnast H, Zurl H, Geyer M, Fischereder K, Adelsmayr G et al. Combining targeted and systematic prostate biopsy improves prostate cancer detection and correlation with the whole mount histopathology in biopsy naïve and previous negative biopsy patients. Frontiers in Surgery. 2022 Oct 6;9:1013389. doi: 10.3389/fsurg.2022.1013389. eCollection 2022.