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Ist eine präoperative MRT-Untersuchung beim lokal begrenzten Prostatakarzinom sinnvoll?

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1. Abkürzungsverzeichnis

1.1. Abkürzungen in der Einleitung

CT	Computertomographie
DRU	Digitale rektale Untersuchung
mp-MRT	Multiparametrische Magnetresonanztomographie
MRT	Magnetresonanztomographie
PET	Positronen-Emissions-Tomographie
PI-RADS	Prostate Imaging Reporting and Data System
PSA	Prostataspezifisches Antigen
PSMA	Prostataspezifisches Membranantigen
TNM-Stadien	Malignomstadieneinteilung nach Tumorausdehnung, regionären Lymphknotenmetastasen und Fernmetastasen
TRUS	Transrektaler Ultraschall

1.2. Abkürzungen inden Veröffentlichungen

3-D TPM	3-D transperineal template mapping
DCE-MRI	dynamic contrast-enhanced MRI
DWI	diffusion-weighted imaging
ECE	extracapsular extension
ESUR	European Society of Urogenital Radiology
IRB	Institutional Review Board
LAD	lymphadenectomy
LND	lymph node dissection
LNI	lymph node involvement
mp-MRI	multiparametric magnetic resonance tomography
MRI	magnetic resonance tomography
NS	nerve sparing
NVB	neurovascular bundles
PI-RADS	Prostate Imaging Reporting und Data System
PSA	prostate-specific antigen
RRP	radical retropubic prostatectomy
SVI	seminal vesicle invasion
TRUS	transrectal ultrasound

2. Publikationsliste

Billing A., Buchner A., Stief C., Roosen A. Preoperative mp-MRI of the prostate provides little information about staging of prostate carcinoma in daily clinical practice. World Journal of Urology, 2015 Jul; 33(7):923-8.

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3. Einleitung

3.1. Epidemiologie des Prostatakarzinoms

In Deutschland ist das Prostatakarzinom die häufigste Krebserkrankung des Mannes. Das Lebenszeitrisiko zu erkranken beträgt 13%, das heißt einer von acht Männern wird im Laufe seines Lebens ein Karzinom der Prostata entwickeln [1]. Obwohl die Sterberate der Betroffenen im Vergleich zu anderen Malignomen relativ gering ist, steht das Prostatakarzinom wegen seines häufigen Auftretens nach Lungen- und Darmkrebs an dritter Stelle der Krebstodesursachen bei Männern in Deutschland [2, 3].Wichtig für die Prognose der Patienten ist neben der Aggressivität des Tumors dessen Stadium bei Diagnosestellung. Nicht metastasierte und auf die Prostata begrenzte Karzinome (TNM-Stadien T1 und T2) weisen eine deutlich niedrigere Mortalität auf als Malignome, die die Prostatakapsel bereits überschritten (TNM-Stadien T3 und T4) oder lymphogene oder hämatogene Metastasen (TNM-Stadien N1 bzw. M1) gebildet haben [4].Um den Erkrankten ein möglichst langes Überleben zu gewährleisten, sind deshalb ein frühes Erkennen des Karzinoms und eine frühzeitig eingeleitete, adäquate Therapie von großer Bedeutung.

3.2. Diagnostik des Prostatakarzinoms

Seit 1974 wird wegen der fehlenden Frühsymptome und der hohen Erkrankungshäufigkeit im Rahmen der gesetzlichen Krebsvorsorge eine jährliche Früherkennungsuntersuchung für Männer ab dem 45. Lebensjahr angeboten. Dabei wird das äußere Genitale untersucht und die Prostata getastet [5]. Allerdings lassen nach Sieverding et al. [6] weniger als die Hälfte aller Männer zwischen 45 und 70 Jahren eine regelmäßige Vorsorgeuntersuchung der Prostata (digital rektale Untersuchung und / oder PSA-Wert-Bestimmung) vornehmen.

Besteht ein Verdacht auf das Vorliegen eines Prostatakarzinoms, sind die Hauptpfeiler der Diagnostik die PSA-Wert-Bestimmung und die transrektale, ultraschallgesteuerte Stanzbiopsie. Durch diese Diagnosemethoden kann allenfalls abgeschätzt werden, wie weit das Karzinom innerhalb der Drüse fortgeschritten ist und ob es bereits die Prostatakapsel überschritten oder Metastasen gebildet hat. Deshalb ist der Einsatz von bildgebenden Verfahren nötig, um das Tumorstadium vor Einleitung der Therapie beurteilen zu können.

Im Folgenden sollen die angesprochenen diagnostischen Möglichkeiten näher dargestellt werden.

3.2.1. Digital rektale Untersuchung

Bei der digital rektalen Untersuchung (DRU) werden die Größe der Prostata, die Abgrenzbarkeit, Konsistenz, Lage, Größe und Form einer möglichen Veränderung und die Verschieblichkeit der Rektumschleimhaut beurteilt. Da das Prostatakarzinom meist in der zum Mastdarm gelegenen peripheren Zone der Prostata wächst [7], ist das Erkennen eines Malginoms durch die digital rektale Untersuchung möglich. Allerdings ist die DRU eine eher

ungenaue Diagnosemethode, da nur Karzinome ab einem Durchmesser von etwa 7mm erkannt werden können [8] und das Untersuchungsergebnis stark von der Erfahrung des Arztes abhängig ist [9]. Desweiteren können die verschiedenen Tumorstadien durch Tasten nicht verlässlich unterschieden [10, 11] und nur Karzinome, die sich in der posterior gelegenen Prostataregion befinden, entdeckt werden.

3.2.2. Prostataspezifisches Antigen

Das prostataspezifische Antigen (PSA), das 1979 zum ersten Mal isoliert werden konnte [9], ist eine spezifische Protease, die fast nur von Epithelzellen der Prostata gebildet wird. Deshalb korreliert eine Änderung des PSA-Spiegels eng mit pathologischen Veränderungen der Prostata. Ursache eines PSA-Anstiegs können aber nicht nur ein Prostatakarzinom, sondern auch benigne Prostataerkrankungen wie die Prostatitis oder die benigne Prostatahyperplasie sein.

Obwohl der PSA-Spiegel nicht zwischen gut- und bösartigen Erkrankungen unterscheiden kann und ein PSA-Anstieg unspezifisch für ein Karzinom ist, wird die Untersuchung seit den 1990er Jahren sehr häufig durchgeführt und ist, obwohl sie von den gesetzlichen Krankenkassen nicht vergütet wird, Teil der Standarddiagnostik beim Prostatakarzinom [12]. Eine großangelegte, prospektiv-randomisierte europäische Studie konnte eine Senkung der Mortalität des Prostatakarzinoms durch ein PSA-Screening belegen [13]. Eine ähnliche amerikanische Studie [14], aus der eine gegenteilige Aussage abgeleitet wurde, weist erhebliche Qualitätsmängel auf, wie jüngst dargelegt werden konnte [15].

3.2.3. Prostatastanzbiopsie

Ergibt sich aus der DRU und der Bestimmung des PSA-Wertes der Verdacht auf ein Prostatakarzinom, wird heute am häufigsten eine transrektale, ultraschallgesteuerte Stanzbiopsieuntersuchung der Prostata durchgeführt [16]. Dabei werden in der Regel Proben aus mindestens sechs Regionen der Prostata entnommen (apikale, zentrale und basale Zone jeweils für den rechten und linken Prostatalappen) [17].

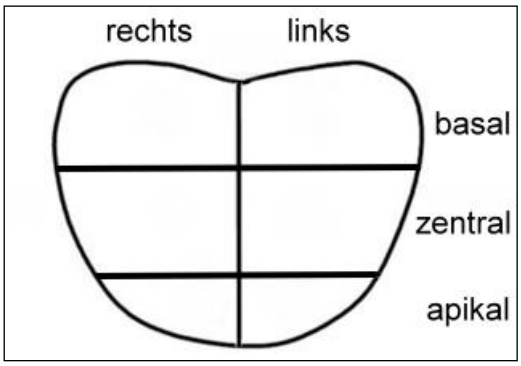

Abb. 1: Nach dem Sextantenschema eingeteilte Prostata

Gemäß den letzten S3-Leitlinien der Deutschen Gesellschaft für Urologie [18] sollten diese Regionen noch einmal jeweils in lateral und medial aufgeteilt werden, sodass sich hieraus ein Zwölferschema –Dodekantenbiopsie– ergibt. Die Stanzzylinder werden histologisch auf ein Karzinom untersucht. Dadurch kann beurteilt werden, ob überhaupt ein Malignom in der Prostata vorhanden ist und wie aggressiv es sich entsprechend des Gleason-Schemas verhält. Zur Einteilung in das Gleason-Schema werden die in der Biopsie vorhandenen Gewebsformationen entsprechend ihrer Differenzierung einem Grad zwischen eins und fünf zugeordnet. Die Muster eins und zwei sind in Stanzbiopsien, die aus der peripheren Zone der Prostata entnommen werden, normalerweise nicht nachweisbar, da Tumore dieser Differenzierungsgrade nahezu ausschließlich in der Transitionalzone zu finden sind. Die Werte der häufigsten und der am schlechtesten differenzierten Gewebsmuster werden addiert. Somit wird bei den Stanzbiopsien ein Gleason-Score zwischen sechs (3+3) und zehn (5+5) erreicht. Je höher dieser ist, desto höher ist auch der Grad der Entdifferenzierung und damit die Aggressivität des Tumors [19]. Anhand des Gleason-Scores wird das Prostatakarzinom in Graduierungsstufen eingeteilt, die mit dem Grading anderer Tumore vergleichbar sind.
Da etwa 30% der Tumore durch die Stanzbiopsie nicht entdeckt werden [20-22], kann zwar eine Verdachtsdiagnose bestätigt, aber die Existenz eines Karzinoms durch negative Proben nicht ausgeschlossen werden. Wird die Anzahl der Biopsien erhöht, kann die Identifikationswahrscheinlichkeit eines Tumors deutlich verbessert werden [17, 22-24]. In den letzten Jahren wurden immer häufiger MRT-gesteuerte Stanzbiopsieuntersuchungen durchgeführt. Es wird zwischen einer kognitiven und einer digitalen MRT-TRUS-Fusion unterschieden. Bei der kognitiven Variante werden die in den MRT-Bildern oder -Befunden als suspekt erkannten Areale der Prostata vom Untersucher gedanklich auf das Ultraschallbild übertragen und dann mittels Stanznadel anvisiert und biopsiert. Dagegen werden bei der digitalen MRT-TRUS-Fusion die MRT-Datensätze mit den aktuellen Ultraschallbildern durch eine spezielle Software verbunden und bewegen sich bei der Biopsieentnahme parallel zu den Ultraschallbildern mit [25]. Durch diese Techniken konnte häufiger und vor allem bei Patienten mit vorher negativen ultraschallgesteuerten Biopsien ein Karzinom identifiziert werden [26-29].

3.2.4. Bildgebende Verfahren

Bildgebende Verfahren hatten wegen der inhomogenen Parenchymtextur der Prostata und der völlig uneinheitlichen bildmorphologischen Charakteristika des Prostatakarzinoms bis vor kurzem einen untergeordneten Stellenwert bei der Diagnostik des Prostatakarzinoms. Die technische Fortentwicklung der Sonographie, vor allem aber der Kernspintomographie, hat diese Modalitäten in den letzten Jahren aber wieder in den Vordergrund treten lassen. Momentan vollzieht sich geradezu ein Paradigmenwechsel, an dessen Ende die MRT als das entscheidende Diagnostikum beim Prostatakarzinom steht und so die Biopsie in den Hintergrund drängen könnte.

Außerdem ist die Ausbreitungsdiagnostik die Domäne der Bildgebung. Zum Einsatz kommen unter anderem der transrektale Ultraschall, die Computertomographie, ggf. mit Positronen-Emissions-Tomographie, die Knochenszintigraphie und die Magnetresonanztomographie.

3.2.4.1. Transrektaler Ultraschall

Bei der Durchführung der randomisierten Stanzbiopsieentnahme ist der Einsatz des transrektalen Ultraschalls (TRUS) seit Jahren nicht mehr wegzudenken. So können die einzelnen Areale der Prostata unter Sicht punktiert werden [30]. Desweiteren werden die Form, Anatomie und das Volumen der Prostata mit dem TRUS adäquat beurteilt.
Die Detektions-, Lokalisations- [31-33] und Staginggenauigkeit [9, 11, 32-35] selbst ist jedoch eher gering einzuschätzen, da sich die Malignome teilweise echogleich zum normalen Prostatagewebe darstellen und deshalb kaum erkannt werden können [36]. Aufgrund der bei einem Prostatakarzinom vorliegenden veränderten Elastizität und Durchblutungseigenschaften können durch neuere Techniken, wie dem Kontrastmittelultraschall oder der Elastographie, bessere Ergebnisse bei der Detektion des Karzinoms erzielt werden. So stieg bei Wijkstra et al. die Wahrscheinlichkeit ein Malignom mit Kontrastmittelultraschall zu entdecken von 60 auf 78% an [37-39].

3.2.4.2. Computertomographie und Positronen-Emissions-Tomographie

Das Gewebe der gesunden Prostata unterscheidet sich bezüglich der Dichte kaum von der eines Karzinoms. Deshalb und wegen des geringen Weichteilkontrasts der Computertomographie (CT) spielt dieses bildgebende Verfahren kaum eine Rolle bei der Detektion und dem lokalen Staging von Prostatakarzinomen [35, 40, 41].
Zur Ausbreitungsdiagnostik wird häufig eine Kombination aus der CT und der Positronen-Emissions-Tomographie (PET) eingesetzt. Bei der PET wird die Verteilung radioaktiv markierter Substanzen im Organismus dargestellt. Zusätzlich zur morphologischen Darstellung können so pathologische Stoffwechselvorgänge im Körper lokalisiert werden. Zum Beispiel stellt das in Prostatakarzinomgewebe nahezu exklusiv exprimierte prostataspezifische Membranantigen (PSMA) eine Zielstruktur für mit radioaktiv markierte Gallium oder Technetium gekoppelte PSM-Antikörper dar. Dies wird sich bei der PSMA-PET zunutze gemacht. Dadurch wird die Genauigkeit bezüglich der Suche nach suspekten Lymphknoten- oder Fernmetastasen deutlich verbessert [42-45].

3.2.4.3. Szintigraphie

Bei der Szintigraphie werden ebenfalls Radiopharmaka eingesetzt, die sich in bestimmten Geweben besonders anreichern. Sie wird aber nicht zur Detektion oder zum lokalen Staging des Prostatakarzinoms genutzt, sondern ist momentan noch der Goldstandard beim Erkennen von Knochenmetastasen. Diese so genannte Knochenszintigraphie, bei der radioaktiv

markierte Bisphosphonate verwendet werden, übertrifft dabei sowohl die Computer- als auch die Magnetresonanztomographie in der Genauigkeit und Detektionswahrscheinlichkeit [46, 47]. Sie könnte in Zukunft durch das PSMA-PET (s.o.) abgelöst werden.

3.2.4.4. Magnetresonanztomographie

Die Magnetresonanztomographie (MRT) wird gemeinhin als das beste bildgebende Verfahren für das Auffinden und Lokalisieren von Karzinomen der Prostata bezeichnet [48]. In den 1980er Jahren wurde sie erstmals bei der Diagnostik des Prostatakarzinoms beschrieben [49, 50]. Inzwischen wurde die Gerätetechnik weiterentwickelt. Zum einen wurde die Feldstärke der Magnetresonanztomographen erhöht, was die Untersuchungsdauer verkürzt und bessere räumliche Auflösung und Signal-Rausch-Verhältnisse liefert. Zum anderen kann seit Ende der 80er Jahre statt einer Beckenoberflächenspule eine endorektale Spule eingesetzt werden, deren Verwendung für die Patienten bei der Durchführung der Kernspinuntersuchung zwar unangenehmer ist, aber die Darstellbarkeit der Prostata [51] und die Genauigkeit der Lokalisations- [52] und Stagingdiagnostik [53] verbessert. In einigen Studien wurde allerdings keine Erhöhung der Staginggenauigkeit durch den Einsatz einer Endorektalspule [54] bzw. durch größere Feldstärken [55, 56] erzielt.

Seit etwa zehn Jahren werden die T1- und T2-Wichtungen durch verschiedene Zusatzuntersuchungen unterstützt, welche unter dem Begriff „multiparametrisches MRT – mp-MRT“ zusammengefasst werden. So erhält man neben der anatomischen auch funktionelle Darstellungen der Prostata [57]. Die angewendeten Zusatzuntersuchungen sind die Spektroskopie, bei der die Konzentrationen verschiedener Moleküle (Kreatin, Cholin, Zitrat) im Gewebe gemessen werden [40], die Diffusionsrestriktionswichtung, die auf der Diffusion von Wassermolekülen im Gewebe beruht [58], und die Perfusionsbildgebung, bei der Kontrastmittel (Gadolinium) eingesetzt wird. Das Prostatakarzinom zeigt aufgrund der höheren Zelldichte eine vermehrte Diffusionsrestriktion [59] und bei der Kontrastmittelgabe einen früheren Beginn der Signalsteigerung und ein höheres Singalintensitätsniveau [60]. Bei der Spektroskopie steigt die Konzentration von Cholin im Vergleich zu Citrat an [61]. Durch die Anwendung dieser zusätzlichen Untersuchungen konnte die genaue Wiedergabe der Lokalisation und Ausdehnung des Karzinoms verbessert werden [62-72]. Insgesamt liefern zahlreiche bisher durchgeführte Studien aber sehr unterschiedliche Ergebnisse bezüglich der Genauigkeit. Die Werte für die Sensitivität und Spezifität bei der Lokalisation der Malignome reichten dabei von 21 bis 96% bzw. von 41 bis 100% [52, 66, 68, 72-79]. Auch die Ergebnisse des Stagings wiesen eine große Spannweite für die Sensitivität und Spezifität auf. Diese reichten bei dem Auffinden von extrakapsulären Tumorwachstum von 17 bis 92% bzw. von 67 bis 100% und bei der Diagnose von befallenen Samenblasen von 27 bis 100% bzw. von 66 bis 100% [54, 56, 62, 63, 69, 71, 76, 80-98]. Auch bei den Untersuchungen zur Genauigkeit des Erkennens von

Lymphknotenmetastasen, auf die in den bisher durchgeführten Studien nur selten eingegangen wurde, wurden uneinheitliche Resultate erzielt [76, 86, 96, 99, 100].

Die 2012 von der ESUR eingeführte PI-RADS-Klassifikation hat jedoch zu einer Standardisierung der Beurteilung der multiparametrischen Prostata-MRT durch den Radiologen und damit zu einer erheblichen Verbesserung der Genauigkeit geführt. Bei der PI-RADS-Klassifikation handelt es sich um eine Leitlinie zur Befunderhebung der multiparametrischen MRTs. Die Prostata wird in mindestens 16 Areale unterteilt und für jedes Gebiet und jede Untersuchungsmethode (T2-Wichtung und mindestens zwei Zusatzuntersuchungen: Diffusionsrestriktionswichtung, Kontrastmitteluntersuchung, Spektroskopie) ein Wert zwischen eins und fünf vergeben. Je höher der Wert für ein Areal ist, desto höher ist der Verdacht auf das Vorliegen eines Karzinoms. Zuletzt wird ein Gesamtwert berechnet und dieser in den PI-RADS-Score konvertiert [61]. Bei einem PI-RADS-Score von eins ist das Vorkommen eines klinisch relevanten Karzinoms sehr unwahrscheinlich, bei dem Höchstwert von fünf dagegen sehr wahrscheinlich. Im Jahr 2014 wurde die PI-RADS-Klassifikation überarbeitet und eine zweite Version entwickelt. Bei dieser ist für die Beurteilung der zentralen Drüsenareale in erster Linie die T2-Wichtung und für die periphere Zone die Diffusionsrestriktionswichtung bedeutend. Desweiteren werden nun insgesamt 39 verschiedene Areale bewertet [101, 102]. Neuere Studien, in denen die MRT-Untersuchungen nach dem PI-RADS-Schema ausgewertet wurden, zeigten eine relevante Steigerung in der Genauigkeit sowohl der Lokalisation der Karzinome als auch des Stagings. Dabei wurden mit Hilfe der zweiten Version der PI-RADS-Klassifikation eine Sensitivität von 85 bis 88%, eine Spezifität von 55 bis 71% für die Lokalisation der Karzinome [103, 104] und eine Detektionsgenauigkeit von 94% in der peripheren und von 95% in der Transitionszone [105] erreicht. Die Sensitivität und Spezifität extrakapsuläres Tumorwachstum zu erkennen, lagen durch die Verwendung der PI-RADS-Klassifikation bei 60% bzw. 68% [106].

Die MRTs wurden bei den meisten Studien jedoch bei ausgewählten Patienten angefertigt und größtenteils von sehr erfahrenen Radiologen ausgewertet, was in der Regel nicht dem klinischen Alltag entspricht. Vielmehr stellen sich die Patienten mit multiparametrischen Bildern und Befunden zur weiteren Therapie vor, die in nicht-akademischen radiologischen Einheiten ohne speziellen uroradiologischen Schwerpunkt und häufig ohne Berücksichtigung der PI-RADS-Klassifikation angefertigt werden. Diese sind wegen ihrer unterschiedlichen Erstellungs- und Auswertungsmethoden durch die zitierten Studien nicht reell abgebildet. Unter realen Bedingungen wurde die multiparametrische Kernspindiagnostik bezüglich ihrer Staginggenauigkeit nur von Brajtbord et al. untersucht. Die Sensitivitäten für das Erkennen von extrakapsulärem Tumorwachstum bzw. eines Samenblasenbefalls lagen bei 43% und 33%, die Spezifitäten bei 73% und 89% [87]. Somit konnte der MRT im klinischen Alltag nur ein begrenzter Wert in der Prostatakarzinomdiagnostik eingeräumt werden.

In mehreren Studien wurde demonstriert, inwieweit die Erfahrungen des befundenden Radiologen Einfluss auf die korrekte Wiedergabe der Lokalisation und Ausdehnung des Prostatakarzinoms hatten. Dabei wurde erwartungsgemäß festgestellt, dass Radiologen mit mehr Erfahrung deutlich bessere Ergebnisse ablieferten als weniger erfahrene Ärzte [62, 81, 82, 107, 108]. Die Genauigkeit konnte allerdings durch gezieltes Training der Radiologen, die zusätzliche Durchführung einer Diffusionsrestriktionswichtung und den Einsatz von Kontrastmittel gesteigert werden [62, 81, 107]. Dies zeigt wiederum, dass die aktuellen Studien eher die maximalen diagnostischen Möglichkeiten der leistungsstärksten MRTs in spezialisierten Einrichtungen widerspiegeln als die Versorgungsrealität.

3.3. Therapie des lokal begrenzten Prostatakarzinoms

Die Therapiemöglichkeiten des lokal begrenzten Prostatakarzinoms sind vielfältig. So wird bei der „active surveillance“ die Karzinomtherapie unter engmaschiger Überwachung aufgeschoben, bis der Patient eine Therapie wünscht oder der Tumor fortschreitet. Daneben kommen Bestrahlung, Brachytherapie, Kryotherapie, neue fokale Therapieformen und die antiandrogene Hormonentzugstherapie zum Einsatz. Der Goldstandard der kurativen Therapie eines stanzbioptisch gesicherten, lokalisierten Prostatakarzinoms ist aber die radikale Prostatovesikulektomie. Sie wird im Laufe der Behandlung bei 90% der Patienten mit einem nicht organüberschreitend wachsenden Karzinom durchgeführt [91]. Dabei wird soweit möglich versucht, die neurovaskulären Bündel, die seitlich außerhalb der Prostatakapsel verlaufen und Verbände von Blut-, Lymphgefäßen und Nervenbahnen enthalten, zu schonen. Damit ist die Wahrscheinlichkeit einer postoperativ erhaltenen Erektionsfähigkeit und Kontinenz der Patienten wesentlich erhöht, was eine deutliche Steigerung der Lebensqualität nach der Operation mit sich bringt [83, 91]. Wird trotz eines vorhandenen organüberschreitenden Wachstums des Karzinoms, das bevorzugt in der Nähe der neurovaskulären Bündel auftritt [109], nervenschonend operiert, bleiben mit hoher Wahrscheinlichkeit positive Resektionsränder zurück, die zu Rezidiven führen können [110]. Aus diesem Grund ist eine präoperative Kenntnis der Lokalisation des Karzinoms innerhalb der Drüse und eines möglichen kapselüberschreitenden Wachstums von entscheidender Bedeutung für den Operateur.

Oberstes Ziel der radikalen Prostatovesikulektomie ist es, das Karzinom vollständig zu entfernen und tumorfreie Resektionsränder zu hinterlassen. Im Wesentlichen kommen dabei drei verschiedene Operationsmethoden in Frage. Welche davon angewendet wird, hängt vor allem von der Ausdehnung des Karzinoms ab. Das nervenschonendste Operationsverfahren ist das intrafasziale Vorgehen. Dabei wird das Gewebe der Prostata, die von zwei Faszien umgeben ist, von der inneren Faszie abgeschält und entfernt. Es bleiben also beide Faszien und die neurovaskulären Bündel erhalten. Dagegen bleibt bei der interfaszialen Prostatovesikulektomie die innere Faszie nicht zurück. Die Gefäß-Nerven-Bündel, die beiderseits der äußeren Faszie verlaufen, bleiben aber zu einem Großteil erhalten. Das aggres-

sivste Vorgehen ist die erweiterte Operationsmethode („wide excision“). Hierbei wird die Prostata samt ihrer beiden Faszien und den neurovaskulären Bündeln entnommen.
In bisherigen Studien konnte gezeigt werden, dass das präoperative MRT-Ergebnis Einfluss darauf hat, ob nervenschonend operiert wird oder nicht [83, 85, 109]. So wurden die Gefäß-Nerven-Bündel häufiger bei Tumoren, die im MRT präoperativ als organüberschreitend eingeschätzt wurden (T3), reseziert als bei den Karzinomen, die im MRT als ein T2-Tumor, also ein noch auf die Prostata begrenztes Malignom, eingeschätzt wurden [98, 111]. Allerdings wurde bislang nicht geklärt, ob sich diese Tendenz auch in den abschließenden histopathologischen Resultaten niederschlägt. Ob die präoperativen Kernspinergebnisse die Entscheidung zur Resektion der lokoregionären Lymphknoten (Fossa obturatoria) beeinflussen, wurde bisher ebenfalls nicht untersucht.

3.4. Vorstellung der durchgeführten Studie

Trotz des unklaren Wertes der Kernspintomographie in der realen klinischen Situation bringen immer mehr Patienten ihre auswärtig angefertigten MRT-Befunde zur Operation mit. Das Ziel unserer Arbeit war es herauszufinden, inwieweit diese MRT-Befunde das Vorliegen, die Lokalisation und die Ausdehnung der Prostatakarzinome im Vergleich zu den pathologischen Ergebnissen korrekt beschreiben und ob sie einen Einfluss auf die Wahl der Operationsmethode haben.
Hierzu führten wir eine Studie an insgesamt 94 in der Urologischen Klinik des Universitätsklinikums Großhadern der Ludwig-Maximilians-Universität München radikal prostatektomierten Patienten durch. Es wurden retrospektiv der präoperative PSA-Wert, die Ergebnisse der transrektalen Ultraschall-, der digital-rektalen, der Stanzbiopsie- und der auswärts durchgeführten, multiparametrischen MRT-Untersuchung mit dem histopathologischen Befundbericht nach der radikalen Prostatektomie verglichen. Zusätzlich wurden die Operationsberichte ausgewertet.
Um die MRT-Befunde bezüglich der Lokalisation des Karzinoms innerhalb der Prostata mit den Ergebnissen der histopathologischen Aufarbeitung der Biopsate und des endgültigen Prostatektomiepräparates vergleichbar zu machen, wurden sechs Regionen in der Prostata definiert. Dabei wurden jeweils der rechte und linke Prostataseitenlappen in kraniokaudaler Richtung in drei Areale unterteilt und so folgende Regionen unterschieden: Rechts basal, rechts zentral, rechts apikal, links basal, links zentral und links apikal. Für jeden der Sextanten wurde dokumentiert, ob karzinomatöses Gewebe in den unterschiedlichen Untersuchungsmethoden gefunden worden ist. Zusätzlich wurden die Größe der Prostata und des Tumors, extrakapsuläres Tumorwachstum, Samenblasen- und Lymphknotenbefall vermerkt und die Ergebnisse der verschiedenen Untersuchungen miteinander verglichen.
Aus den Operationsberichten wurde die jeweils angewandte Operationstechnik, also intra-, interfaszial oder erweitert, vermerkt und dokumentiert, ob eine Lymphadenektomie erfolgt ist.

Zusätzlich konnte festgestellt werden, inwieweit der Operateur über die Ergebnisse präoperativer Untersuchungen, wie Stanzbiopsie-, Kernspin-, TRUS-, Labor- und der digital-rektalen Untersuchung, informiert war.

Die gewonnen Daten wurden mit SPSS-Software (Version IBM SPSS Statistics 21) statistisch analysiert und mit der bisher veröffentlichten Literatur verglichen. Die Ergebnisse konnten in zwei Artikeln im World Journal of Urology– jeweils mit der Doktorandin als Erstautor - veröffentlicht werden. In beiden Veröffentlichungen wird die Relevanz der präoperativ vom niedergelassenen Radiologen durchgeführten MRT-Untersuchungen diskutiert. Der erste Artikel beschreibt die Staginggenauigkeit der MRT-Untersuchungen und den Einfluss der MRT-Befunde auf die Wahl der Operationsmethode der Prostatektomie. Die zweite Studie untersucht die Genauigkeit eines routinemäßig in der präoperativen Umfelddiagnostik durchgeführten multiparametrischen MRTs, ein Karzinom innerhalb der Prostata zu lokalisieren.

4. Zusammenfassung

4.1. Zusammenfassung in deutscher Sprache

Die Standardisierung der Befunderhebung von MRTs der Prostata durch die PI-RADS Klassifikation führte zu einer Verbesserung der Qualität der MRT-Berichte. In diesbezüglichen Studien wurden jedoch meist Ärzte eingebunden, die in der Anwendung des PI-RADS System geschult und speziell im Bereich der Uroradiologie ausgebildet sind. Diese Spezialisten arbeiten selten in den radiologischen Praxen, in denen die Mehrzahl der MRTs vor der radikalen Prostatektomie durchgeführt wird. Um die Genauigkeit dieser multiparametrischen MRTs bei der Lokalisierung der Karzinome innerhalb der Prostata und des Stagings zu analysieren, führten wir eine Studie durch, in der die Befunde der MRT-Untersuchung der niedergelassenen Radiologen mit den Ergebnissen einer pathologischen Untersuchung nach Prostatektomie und der Stanzbiopsien verglichen wurden. So wurden anhand der Daten von 94 Patienten, die zwischen Januar 2011 bis Juni 2012 im Klinikum Großhadern prostatektomiert wurden, die Genauigkeit des Stagings sowie der Tumorlokalisation innerhalb der Prostata ermittelt. Außerdem wurde der Einfluss der MRT-Befunde auf die durchgeführte Operationsmethode untersucht.

Die Sensitivität und Spezifität der Tumorlokalisation betrugen für die in sechs Regionen unterteilte Prostata 25 bis 62% bzw. 60 bis 94%. Der Durchschnittswert einen Sextanten korrekt als karzinombefallen oder gesund zu identifizieren (3,1 bis 4,0), war nicht signifikant höher als der erratene Wert (3,0). Die Sensitivität und Spezifität extrakapsuläres Tumorwachstum zu diagnostizieren, lagen bei 30% und 93%, das Erkennen des Befalls der Samenblasen bei 64% und 93%. Demnach konnten mit den durchgeführten MRT-Untersuchungen die Karzinome nicht genau innerhalb der Prostata lokalisiert werden. Auch ein bestehender Samenblasenbefall und das Tumorwachstum außerhalb der Prostatakapsel konnten nicht sicher ausgeschlossen werden. Weder der Gebrauch einer endorektalen Spule noch der Einsatz höherer Feldstärken der MRT-Geräte konnten die Genauigkeiten verbessern. Auffällig war, dass die Patienten, bei denen der Operateur die MRT-Befunde kannte, signifikant häufiger nervenschonend operiert wurden (links: 93 %; rechts: 89 % vs. links: 75 %; rechts: 75 %). Dabei stieg der Anteil der positiven Resektionsränder trotz der weniger invasiven Operationsmethode nicht an.

Wir kamen zu dem Ergebnis, dass die häufig im niedergelassenen Setting ohne PI-RADS-Bewertungsschema und ohne spezielle uroradiologische Kenntnisse durchgeführten MRT-Untersuchungen zur Feststellung der präzisen Tumorlokalisation innerhalb der Prostata und zum Staging der Prostatkarzinome nur unzureichend geeignet sind. In Anbetracht der zusätzlichen Kosten für das Gesundheitssystem und der Unannehmlichkeiten für die Patienten ist die Durchführung einer solchen Untersuchung nicht gerechtfertigt.

4.2. Zusammenfassung in englischer Sprache

Standardization with PI-RADS resulted in both increased reporting quality and reduced interobserver variability. However such trials were performed by academic radiologists specialized in genitourinary MRI as well as trained in the PI-RADS classification and reflect the best diagnostic performance of mp-MRI. Those specialists are rare in non-academic institutions where still the majority of MRIs of the prostate are being conducted. Nevertheless, an increasing number of patients routinely undergo MRI in these “non PI-RADS institutions” prior to radical prostatectomy - independent of their clinical stage or biopsy Gleason sum. For these patients, we evaluated the accuracy of mp-MRI in localizing intraprostatic cancer lesions by correlation with preoperative biopsies and histopathologic findings on prostatectomy specimen. The aim of our study was to evaluate the practical value of routinely performed, “non-PIRADS” mp-MRI for cancer localization.

Data from 94 patients who underwent a retropubic prostatectomy between January 2011 and June 2012 were used to determine the accuracy of staging as well as localizing the tumour within the gland. Additionally the influence of the MRI results on the individual surgical approach was investigated. To compare the histopathological with MRI results the prostate was divided into six sections. For each single sextant, sensitivity and specificity of correct cancer detection amounted to 25-62 % and 60-94 %, respectively. The mean number of correctly identified sextants per patient was between 3.11 and 4.00 and, thus, insignificantly above the value of 3 that one would obtain by tossing the coin.

The sensitivity and specificity of diagnosing extracapsular extension were 30.0 % and 93.3 %, of discovering positive seminal vesical invasion 63.6 % and 92.9 %, respectively. Therefore we concluded that routinely performed MRI examinations cannot localize cancer within the prostate accurately. Neither existing seminal vesicle invasion nor extracapsular tumour extension can be safely excluded. Moreover, neither higher field force nor the use of an end rectal coil could enhance the accuracy of mp-MRI. Of note, in case the surgeon was aware of an existing MRI, there was a significantly higher percentage of nerve protection (left: 93 %; right: 89 % vs. left: 75 %; right: 75 %). This did not result in a higher level of positive resection margins although the performed technique of surgery was less invasive.

We conclude that in routine clinical practice, mp-MRI at non-academic centres without the use of PI-RADS classification and without uroradiologic experience has very limited clinical value in predicting extracapsular extension and seminal vesical invasion. Given the costs for the health care system, patients‘ discomfort and the low reliability of the investigation, performing a “poor standard” MRI prior to radical prostatectomy on a routine basis is not justified.

5. Erste Veröffentlichung:

Preoperative mp-MRI of the prostate provides little information about staging of prostate carcinoma in daily clinical practice

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TOPIC PAPER

Preoperative mp-MRI of the prostate provides little information about staging of prostate carcinoma in daily clinical practice

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Abstract
Purpose To evaluate the staging accuracy of preoperative multiparametric MRI (mp-MRI), its influence on the technique of radical retropubic prostatectomy (RRP), and its value for daily clinical practice.
Methods A total of 106 patients underwent RRP (January 2011–June 2012) and had preoperative MRI staging data available for review. Staging results acquired by mp-MRI were correlated to both biopsy and histopathology results. Surgical reports were reviewed for intraoperative aspect of tumor extension, technique of RRP (nerve sparing or extended), and extent of lymphadenectomy.
Results The accuracy of diagnosing extracapsular extension (ECE) was 72.2 %, with an overall sensitivity and specificity of 30.0 and 93.3 %, respectively. The negative predictive value was 72.7 %. The sensitivity and specificity to diagnose positive seminal vesical invasion (SVI) were 63.6 and 92.9 %, respectively. Neither higher field force nor the use of an endorectal coil could enhance the accuracy of mp-MRI. In case of awareness of an existing MRI, there was a significantly higher percentage of nerve protection (left: 93 %; right: 89 % vs. left 75 %; right: 75 %). The higher percentage of nerve sparing surgery did not result in a higher level of positive resection margins.
Conclusions In routine clinical practice, mp-MRI at non-academic centers has very limited clinical value in predicting ECE and SVI. Our data support the current recommendations against the widespread preoperative use of mp-MRI because it is not adding reliable predictive information on the extent of prostate cancer.

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Keywords Prostate cancer · Multiparametric MRI · Staging accuracy · Radical retropubic prostatectomy

Introduction

Prostate cancer is the most common cancer and second most common cause of cancer death in men. Both PSA screening and increasing life expectancy result in a rising incidence [1]. In 80 % of the cases, prostate cancer is diagnosed at an organ-confined stage, and many patients undergo radical retropubic prostatectomy (RRP). The surgical challenge lies with the balance between total cancer removal and minimal postoperative morbidity. The neurovascular bundles (NVB), which mediate erectile function and continence [2], run posterolaterally to the prostatic capsule—the majority of prostate cancers are located in the peripheral zone. Preoperative knowledge of extracapsular growth is likely to have an impact on the surgeon's attempt to preserve the NVB: Imaging suggesting locally advanced disease might lead the surgeon to resect the bundle on the affected side. However, the role of MR imaging is still under scrutiny because it is expensive, not everywhere available, and imposes significant discomfort on the patient [3, 4]. Thus, many urologists consider MRI still not suitable for preoperative assessment [5]. The latest diagnostic consensus meeting of the European Society of Urogenital Radiology (ESUR) recommended anatomic T2-weighted imaging combined with at least two functional techniques: diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), and optionally MR spectroscopy [6].

Reports about the accuracy of multiparametric MRI (mp-MRI) in staging prostate cancer are at variance, some suggesting a sensitivity and specificity as well as a negative

predictive value for detecting T3 disease of >90 % [7, 8]. These results insinuate that MRI might play an important role for the preoperative detection of extracapsular growth [9]. However, such trials were performed by academic radiologists specialized in MRI as well as in the genitourinary system and reflect the best diagnostic performance of mp-MRI. Those specialists are rare in non-academic institutions where the vast majority of MRIs of the prostate are conducted.

Prosperity of the metropolitan area of Munich as well as the affluence of German private health insurance companies is the reason why many patients from this region undergo preoperative MRI independent of their preoperative PSA level, clinical stage, biopsy core involvement, or biopsy Gleason sum. For these patients, we evaluated the accuracy of mp-MRI in predicting the presence of extracapsular extension (ECE) and seminal vesicle invasion (SVI) by correlation with preoperative biopsies and histopathologic findings on prostatectomy specimens. Further, we assessed whether or not this preoperative information had an influence on the RRP technique. The aim of our study was to evaluate the practical value of mp-MRI prostate cancer staging for daily clinical practice.

Materials and methods

An institutional database of 455 RRP performed by a single surgeon (C.S.) was queried for those who underwent mp-MRI. MRI was always initiated by the referring local office urologist and performed at various regional non-academic radiology institutions. We retrospectively identified 106 patients who underwent open RRP (January 2011–June 2012) and had preoperative MRI staging data available for review. Formal approval by our Institutional Review Board (IRB) was not required for this observational study.

In all patients, prostate cancer was detected by TRUS guided sextant biopsy performed by an experienced urologist. Biopsies were taken from the base, the middle, and the apex of the right and left side of prostate.

The original radiology reports were reviewed for visibility, localization and extension of the carcinoma within the gland, ECE, SVI, lymph node involvement (LNI), field force (1.5 or 3 Tesla), placement of an endorectal coil, and sequences performed in multiparametric imaging. All MRIs were interpreted by board certified radiologists.

Surgical reports were reviewed for the intraoperative aspect of tumor extension as judged by the surgeon, the technique of RRP (nerve sparing or extended), performance and extent of lymphadenectomy (LAD), and whether or not the surgeon had knowledge of the MRI report (as was always commented on in the surgical report). The surgeon was unaware of preoperative MRI results when neither radiology report nor original images could be retrieved at the day of admission. However, the surgeon was always informed about the biopsy (Gleason sum, number, and distribution of positive cores) and PSA value. In all RRP, preparation of the NVB was carried out independently for both sides. Criteria for nerve sparing were PSA level $\leq$15 ng/ml, number of positive cores not more than 50 % on the side of nerve sparing, Gleason sum of the biopsy $\leq$7, and the intraoperative aspect suggesting an organ-confined tumor.

Pathological reports were reviewed for Gleason score and sum, extension and localization of tumor within the gland, ECE, SVI, surgical margin, and LNI. Positive surgical margins were defined as any evidence for cancer extending to the inked margin of the prostatectomy specimen. Pathological examination was performed by experienced genitourinary pathologists.

For comparison between biopsy, MRI, and histopathology, tumor localization was always allocated to the six sextants: basal, midgland, and apical—left and right.

Data were analyzed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to compare categorical variables as SVI, ECE, and LNI and to determine the statistical coherence between MRI stage and technique of RRP. Sensitivity, specificity, and likelihood ratios (positive and negative) were calculated. Quantitative variables were described as mean ($\pm$standard deviation). $p < 0.05$ was considered statistically significant for all statistical analyses two-tailed tests.

Results

Preoperative and postoperative histopathological characteristics

Twelve patients had to be excluded from the study because of previous radiation, transurethral resection therapy, missing consent, or insufficient MRI data. A total of 94 patients remained in the study.

The patients had a mean age of 65.5 years (range 43–80 years) and a mean preoperative PSA value of 11.7 ng/ml (range 1.1–87.9 ng/ml). The mean number of performed biopsies per patient was 13.0 (2–26). The number of positive biopsies averaged 5.0 (0–22). The Gleason sum were four, five, six, seven, eight, nine, and ten in one, one, 30, 48, three, ten, and one patients, respectively. The mean number of prostate regions with cancer detected was 3.3 (0–6).

The pathological stage of the RRP specimen were T1a, T2a, T2b, T2c, T3a, T3b, and T4 in one, three, two, 55, 16, 15, and two patients, respectively. The Gleason sum averaged 7.2 (6–10).

Table 1 Accuracy of preoperative MRI regarding ECE, SVI, and LNI

	ECE (%)	SVI (%)	LNI (%)
Sensitivity	30.0	63.6	66.7
Specificity	93.3	92.9	92.1
PPV	69.2	63.6	66.7
NPV	72.7	94.6	92.1
Accuracy	72.2	88.1	87.2

ECE was detected in 32 patients (34.0 %), while 62 carcinomas (66.0 %) did not penetrate the prostatic capsule. 17 patients (18.9 %) had SVI. While 40 of 94 patients (42.6 %) were operated without LAD, in 54 patients (57.4 %), LAD was performed. Eleven of them had positive lymph nodes (20.4 %).

A total of 70 patients (74.5 %) had negative surgical margins (R0), while 24 (25.5 %) showed positive margins (R1).

Surgical procedure

In all RRP, preparation of the NVB was carried out independently for both sides: On the right side, RRP was performed in a nerve sparing technique in 44 (57.9 %) and extended in 32 cases (42.1 %). On the left side, RRP was carried out in a nerve sparing technique in 42 (53.9 %) and extended in 36 cases (46.2 %). No data were available for 18 patients for the right side and 16 patients for the left side.

Poor sensitivity of mp-MRI for ECE, SVI, and LNI

Of the 60 patients with histopathologically organ-confined disease, 56 (93.3 %) were correctly diagnosed as such on MRI, whereas four (6.7 %) were considered to have cT3 disease and constituted false positives. Among the 30 patients with pT3 disease, MRI correctly predicted 9 (30.0 %), whereas 21 (70.0 %) were incorrectly considered to be organ-confined. The MRI reports of two patients in each group did not supply any information about the T status which had therefore to be excluded from analysis. This results in an accuracy of 72.2 %, with an overall sensitivity and specificity for diagnosing pT3 disease of 30.0 and 93.3 %, respectively. The positive predictive value of mp-MRI in this setting is 69.2 % with a negative predictive value of 72.7 % (Table 1). The sensitivity and specificity of MRI to diagnose positive SVI were 63.6 and 92.9 %, respectively. The sensitivity and specificity of MRI to diagnose positive LNI were 66.7 and 92.1 %, respectively.

Endorectal coil and 3 T imaging do not provide higher accuracy than 1.5 T imaging without endorectal coil

A total of 55 (59.1 %) preoperative MRIs were performed on 1.5 T scanners, while 38 patients (40.8 %) had 3 T images. The field force of one MRI examination could not be ascertained. Of the 55 1.5 T scans, 38 were performed with an endorectal coil (69.1 %), and for 32 of the 38 3 T MRIs, endorectal coils were used (84.2 %). For ECE, SVI, and LNI, 1.5 T MRI scanners showed sensitivities of 33, 75, and 71 %, respectively, and specificities of 93, 92, and 93 %, respectively. Of note, the accuracy of diagnosing ECE, SVI, or LNI on 3 T scanners was statistically not significant. On 1.5 T scans, the use of an endorectal coil did not enhance sensitivity or specificity for diagnosing ECE or SVI, but only LNI.

DWI enhances accuracy of SVI and LNI detection

A total of 59 MRIs were performed with and 34 without diffusion-weighted imaging, while 57 MRIs were carried out with and 34 without spectroscopy. There was no superior detection rate of ECE by either DWI or spectroscopy. However, DWI increased the accuracy of both SVI and LNI detection significantly (accuracy for SVI and LNI with DWI 92.9 and 92.6 %, without DWI 80.0 and 80 %, respectively). Statistical evaluation for spectroscopy was not possible as there were no patients with SVI or LNI in this group.

Preoperative MRI has an impact on the choice of RRP technique

In light of the relatively low accuracy of preoperative MRI staging, it was of interest whether or not the MRI result had an impact on the surgeon's choice of nerve sparing or LAD.

We identified 39 cases in which PSA level ($\leq$15 ng/ml), number of positive cores, and Gleason sum of the biopsy ($\leq$7) as well as intraoperative findings strongly suggested an organ-confined tumor: The surgeon was aware of the MRI in 27 of these cases; in 12, he was not. In all cases, MRI suggested organ-confined disease or could not detect any tumor.

Interestingly, in case of awareness of an existing MRI, there was a significantly higher percentage of nerve protection (left: 93 %; right: 89 % vs. left: 75 %; right: 75 %). The higher percentage of nerve sparing surgery did not result in a higher level of positive resection margins.

However, the number of LAD did not significantly differ between both groups (37 vs. 33 %) (Table 2).

Table 2 Percentage of nerve sparing (NS), lymphadenectomy (LAD), N0 and R0 resection in relation to awareness of preoperative MRI

CT2, PSA ≤15 ng/ml, Gleason ≤7, MRT ≤T2	LAD (%)	N0 (%)	Right NS (%)	Left NS (%)	R0 (%)
Surgeon knew …	37	90	89	93	86
… did not know about MRI	33	100	75	75	83

Discussion

The aim of this study was to assess the practical use of routinely performed preoperative mp-MRI of the prostate. The majority of these MRIs were not performed at academic centers, but in smaller local units and institutions where specialization in MRI of the genitourinary system is not always available. We evaluated the accuracy of mp-MRI predicting the absence or presence of ECE and SVI by correlation with preoperative biopsies and histopathologic findings on prostatectomy specimens. Further, we assessed whether or not this preoperative knowledge had an influence on the RRP technique.

The mp-MRI appears to be one of the most promising techniques for prostate cancer detection and staging as it is able to combine anatomic T2-weighted imaging with functional tissue analysis. In addition to morphology, provided by T2-weighted imaging [10, 11], DWI provides information about water molecule diffusion [12, 13] and DCE-MRI assesses microvascular properties [14]. MR spectroscopy measures the concentration metabolites in the prostate at a cellular level [15, 16]. Thus, mp-MRI provides additional information about altered vascularization, cellular metabolism, and diffusion [17].

However, the role of preoperative MRI staging is still controversial. Sensitivity and specificity for the detection of extracapsular growth are reported in the range from 13 to 95 % and 49 to 97 %. For the prediction of N + disease, sensitivity and specificity vary between 23 and 80 % and 81 and 99 %, respectively [18]. Our results are at the low end of these ranges, with a sensitivity of 30 % for the detection of ECE. Accordingly, the negative predictive value for predicting locally advanced disease was only 73 %. This means that if the MRI suggests organ-confined cancer, nerve sparing would be safe in not more than 73 % of the cases. For SVI and LNI, we found a better sensitivity of 64 and 67 %, compared with ECE, and a fairly good negative predictive value of 95 and 92 %, respectively.

According to our data, mp-MRI cannot be considered reliable enough to safely exclude ECE of prostate carcinoma. It is therefore questionable whether a surgeon should take a preoperative MRI into account for his approach to the NVB. As could be demonstrated in our study, however, existing mp-MRI results have a significant impact on the surgeon: The probability of nerve protection was significantly higher in cases the surgeon was aware of an MRI predicting organ-confined disease. Of note, this did not result in a higher rate of R1 resections.

These results are in accordance with the findings of Brajtbord et al. [19] who assessed the accuracy of a mixture of preoperative mp-MRI conducted at both academic and community radiology centers. They found the overall accuracy of mp-MRI to be 62 % for diagnosing pT3 disease, with a positive predictive value of 50 %, suggesting that pretreatment mp-MRI offers minimal clinical information. Most interestingly, they were unable to detect a significant difference in accuracy between mp-MRIs from community centers and those conducted in academic institutions. However, the study setup did not allow looking at a possible impact that the MRIs might have had on the surgeon's choice of nerve sparing.

According to our data, neither higher field force nor the use of an endorectal coil could enhance the accuracy of mp-MRI. Previous studies demonstrated the detection of ECE, SVI, and LNI to be improved by the use of the endorectal coil at 1.5 T and at 3 T [11, 20]. The staging accuracy at 1.5 T with an endorectal coil was found to be comparable to the accuracy at 3 T without an endorectal coil [21, 22]. Thus, the use of the endorectal coil is recommended at 1.5 T, whereas it is considered optional at 3 T [23]. However, some recent studies suggest that field strength and the use of an endorectal coil have only little impact on staging accuracy compared with other factors such as Gleason score or tumor extension inside the gland [24, 25].

In general, € 460–1100 are charged for an mp-MRI in Germany. Sedation is required for claustrophobic patients. Further, patients often complain about the discomfort associated with the use of an endorectal coil. In light of the low sensitivity and negative predictive value for ECE that we obtained, it seems hard to justify the expenses of the procedure as well as the patient's discomfort.

Limitations of this study are that other studies are larger [9, 26] and data were collected retrospectively. We did not standardize the patients who underwent mp-MRI; by definition, this results in selection bias. Additionally, we were unable to obtain the training and experience profiles of the radiologists who conducted the MRIs. Further, none of the MRIs were evaluated using the standardized

PI-RAD system as recommended by the guidelines of the ESUR [6].

Conclusion

In routine clinical practice, routine mp-MRI has very limited clinical value in predicting ECE and SVI. Even a negative mp-MRI ("no cancer detected") does not reliably rule out the presence of extraprostatic disease. The accuracy of detecting T3 disease did not improve by use of higher field force (3 T) or endorectal coils.

Our data support the current recommendations against the widespread preoperative use of mp-MRI at non-academic centers because it is not adding reliable predictive information on the extent of prostate cancer.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard This retrospective study was performed in accordance with the standards of the ethics committee.

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6. Zweite Veröffentlichung:

Poor standard mp-MRI and routine biopsy fail to precisely predict intraprostatic tumor localization

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ORIGINAL ARTICLE

Poor standard mp-MRI and routine biopsy fail to precisely predict intraprostatic tumor localization

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Abstract
Purpose To evaluate the localization accuracy of routinely performed preoperative multiparametric MRI (mp-MRI), not being assessed according to PI-RADS criteria.
Methods One hundred and six patients underwent radical retropubic prostatectomy (January 2011–June 2012) with preoperative MRI. Intraprostatic tumor localization suggested by mp-MRI was correlated to both biopsy and histopathology results.
Results Sensitivity and specificity were as low as 25–62 and 60–94 %, respectively. Neither higher field force nor the use of an endorectal coil could enhance accuracy. There was no statistically significant concordance in any sextant. The mean number of correctly identified sextants was between 3.11 and 4.00 and, thus, insignificantly above the value of 3 that one would obtain by tossing the coin. For transrectal biopsies, sensitivity and specificity of tumor localization were 52–63 and 46–80 %, respectively.
Conclusions Neither routinely performed "non-PI-RADS" MRI nor transrectal biopsy can accurately localize prostate cancer. Focal therapy concepts rely on a precise intraprostatic tumor detection and therefore inevitably require PI-RADS assessment by radiologists with genitourinary specialization. Regarding patient discomfort and costs, "non-PI-RADS" MRIs of the prostate are not justified.

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Keywords Prostate cancer · Multiparametric MRI · Transrectal biopsy · Localization accuracy · Radical retropubic prostatectomy

Introduction

A growing number of studies suggest the feasibility of a focal therapy of localized prostate carcinoma. Ideally, focal therapy is targeted to maximize the elimination of the tumor foci without treating the whole gland, while minimizing side effects [1, 2]. However, all focal therapies for prostate cancer inevitably rely on an accurate preoperative localization of the intraprostatic cancer lesion. In this context, the multiparametric MRI (mp-MRI) approach that combines anatomic T2-weighted imaging with functional data, such as altered vascularization, cellular metabolism, and diffusion, appears to be one of the most promising techniques for prostate cancer detection [3–8]. Reports about the accuracy of mp-MRI are at variance, some suggesting a sensitivity and specificity as well as a negative predictive value for identifying a cancer lesion within a defined region (sextant) of the prostate of >90 % [9–11]. Standardization with PI-RADS resulted in both increased reporting quality and reduced interobserver variability (pre-PI-RADS: kappa 0.39–0.55; with PI-RADS 0.46–0.80) [12, 13]. However, such trials were performed by academic radiologists specialized in genitourinary MRI as well as trained in the PI-RADS classification and reflect the best diagnostic performance of mp-MRI. Those specialists are rare in non-academic institutions where still the majority of MRIs of the prostate are being conducted.

Nevertheless, an increasing number of patients routinely undergo MRI in these "non-PI-RADS institutions" prior to radical prostatectomy—independent of their clinical

stage or biopsy Gleason sum. For these patients, we evaluated the accuracy of mp-MRI in localizing intraprostatic cancer lesions by correlation with preoperative biopsies and histopathologic findings on prostatectomy specimens. The aim of our study was to evaluate the practical value of routinely performed "non-PI-RADS" mp-MRI for cancer localization.

Materials and methods

Patient demographic, radiographic, and clinicopathologic data

We retrospectively identified 106 patients who underwent open retropubic radical prostatectomy (RRP; from January 2011 to June 2012) by a single surgeon and had preoperative MRI staging data available for review.

All MRIs were conducted as preoperative staging investigation at referring, non-academic institutions and assessed by board-certified radiologists with experience in genitourinary tract imaging. However, none of those MRI reports used PI-RADS classification. All MRIs were multiparametric and consisted at least of T2-weighted imaging combined with diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI). 60 % of the MRIs were performed on 1.5 T scanners and 40 % on 3 T scanners; 75 % were conducted with an endorectal coil.

Radiology reports were reviewed for visibility, localization and extension of the carcinoma within the gland, extracapsular extension (ECE), seminal vesical invasion (SVI,), and lymph node involvement (LNI). Pathologic reports were reviewed for pathologic Gleason score, extension and localization of tumor within the gland, ECE status, seminal vesicle invasion, surgical margin status and location if positive, and lymph node status. Positive surgical margins were defined as any evidence for cancer extending to the inked margin of the prostatectomy specimen. Pathologic examination was always performed by a board-certified pathologist in a high-volume center.

Statistical methods

Data were analyzed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to compare categorical variables as SVI, ECE, and LNI and to determine the statistical coherence between MRI stage and technique of radical prostatectomy. Sensitivity, specificity, and likelihood ratios (positive and negative) were calculated.

$P < 0.05$ was considered statistically significant for all statistical analyses two-tailed tests.

For graphical illustration histograms, boxplots and bar diagrams were applied.

To evaluate the accuracy of localization by either MRI or biopsy, prostate was divided into six regions, and findings were always allocated to the sextants: right apical, medial, and basal; left apical, medial, and basal. For each patient, we compared the sextants positive on MRI or biopsy to the sextants identified as positive by the definitive pathologic report.

The probability p to obtain an exact match only by guessing is a binomial distribution as a sequence of independent yes/no (Bernoulli) trials:

$$P = \binom{n}{k} \times p^k \times (1-p)^{n-k}$$
$$= \binom{6}{6} \times 0.5^6 \times (1-0.5)^0 = \left(\frac{1}{2}\right)^6 = 1.56\ \%.$$

The expected value $E[X]$ indicates the number of matching sextants that one would obtain by tossing the coin:

$$E[X] = np = 6 \times 0.5 = 3.$$

In other words, one would on average guess three sextants right for each single patient.

Standard deviation amounts to:

$$\sigma = \sqrt{np(1-p)} = \sqrt{np^2} = \sqrt{6 \times \frac{1}{4}} = \sqrt{1.5} \approx 1.22.$$

i.e., 68 % of guessed results would lie within a range between 1.8 and 4.2. One would expect a modality that reliably localizes the tumor within the gland to achieve an average of matching sextants of more than 4.2.

Results

Preoperative and postoperative histopathologic characteristics

Twelve patients had to be excluded from the study because of previous radiation or transurethral resection therapy, missing consent or insufficient MRI data. Ninety-four patients remained in the study.

The patients had a mean age of 65.5 years (range 43–80 years) and a mean preoperative PSA value of 11.7 ng/ml (range 1.1–87.9 ng/ml). The mean number of performed biopsies per patient was 13.0 (2–26). The number of positive biopsies averaged 5.0 (0–22), and the Gleason sum was four, five, six, seven, eight, nine, and 10 in one, one, 30, 48, three, 10, and one patient, respectively.

The pathologic stage of the RRP specimen was T1a, T2a, T2b, T2c, T3a, T3b, and T4 in one, three, two, 55, 16, 15, and two patients, respectively. The Gleason sum

averaged 7.2 (6–10). The mean number of prostate sextants with cancer detected was 3.3 (0–6).

Extracapsular extension (ECE) was detected in 32 patients (34.0 %), while 62 carcinomas (66.0 %) did not cross the prostatic capsule. Seventeen patients (18.9 %) had seminal vesicle invasion (SVI). In 54 of 94 patients (57.4 %), lymph node dissection (LND) was performed, while 40 patients (42.6 %) were operated without LAD. Of the 54 patients with LND, 11 had positive lymph nodes (20.4 %).

Seventy patients (74.5 %) had negative surgical margins (R0), while 24 (25.5 %) showed positive margins (R1).

Poor localization of prostate carcinoma inside the gland by MRI

Of all 94 patients, MRI detected prostate cancer in only 84 % of the cases.

For each sextant, sensitivity and specificity of correct cancer detection by MRI amount to 25–62 and 60–94 %, respectively. There was no statistically significant concordance in any sextant. The sensitivities and specificities for localizing prostate cancer correctly are depicted in Table 1. The number of matching sextants is 3.30 for MRI.

Twenty-three patients were allocated to low-risk group (preoperative PSA < 10 ng/ml and Gleason Score $\leq$ 6), 28 to intermediate-risk group (preoperative PSA < 10 ng/ml and Gleason Score = 7), and 41 to high-risk group (preoperative PSA $\geq$ 10 ng/ml or Gleason Score $\geq$ 8). The numbers of matching sextants in the MRI are 3.82 for the low-risk group, and 3.11 and 3.25 for the intermediate- and high-risk groups, respectively.

Poor localization of prostate carcinoma inside the gland by transrectal biopsy

Of all 94 patients, transrectal biopsies identify prostate cancer in 97 %.

Table 1 Accuracy of tumor allocation to sextants by MRI and transrectal biopsy

Sextant	MRI		Transrectal biopsy	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Right apical	49	79	63	80
Right central	50	71	62	64
Right basal	25	94	61	73
Left apical	35	80	52	46
Left central	62	60	63	50
Left basal	46	73	56	57

For each sextant, sensitivity and specificity of correct cancer detection by transrectal biopsy amount to 52–63 and 46–80 %, respectively.

The number of matching sextants is 3.64 for biopsy. Except for one (right apical), there was no statistically significant concordance in any sextant.

Per sextant, sensitivity was generally higher for biopsy while MRI gained a higher specificity.

No increased accuracy by 3 T field force or endorectal coil

Fifty-five (59.1 %) preoperative MRIs were performed on 1.5 T scanners, while 38 patients (40.8 %) had 3 T images. The field force of one MRI examination could not be ascertained. 3 T MRIs identified prostate cancer in 82 %, whereas 1.5 T MRIs detected a tumor in 86 %. For each sextant, sensitivity and specificity of correct cancer detection by 3 T are 22–78 and 73–100 %, and for 1.5 T MRI, they are 22–61 and 67–100 %, respectively. There was no statistically significant concordance in any sextant. The number of matching sextants is 3.55 for 3 T and 3.7 for 1.5 T MRIs.

Seventy (74.5 %) MRI examinations were performed with and 24 (25.5 %) without an endorectal coil. MRIs with endorectal coils identify a malignant tumor of the prostate in 86 % and MRIs without endorectal coils in 79 %. By the use of an endorectal coil, sensitivity and specificity of correct cancer detection for each sextant amount to 20–62 and 53–93 %, without endorectal coils 33–83 and 67–100 %, respectively. There was no statistically significant concordance in any sextant. With endorectal coils, the number of matching sextants is 3.55 and 4.00 without.

Even the use of both the field force of 3 T and an endorectal coil does not enhance the results. Sensitivity and specificity were 13–75 and 56–100 %, respectively. There was no statistically significant concordance in any sextant. The number of matching sextants was 3.41.

The sensitivities and specificities for localizing prostate cancer with or without endorectal coil and with different field forces correctly are depicted in Table 2.

Discussion

In our retrospective study of routinely performed "non-PI-RADS" MRIs of the prostate, the mean number of correctly identified sextants was between 3.11 and 4.00. This is within the standard deviation and, thus, insignificantly above the value of 3 that one would obtain by tossing the coin. Most notably, localization by transrectal 12 core biopsy was not better with a value of 3.64. A modality that reliably and reproducibly localizes an intraprostatic lesion would achieve an average of matching sextants of more than 4.2.

Table 2 Accuracy of tumor allocation to sextants by MRI related to the field force and use of an endorectal coil

	Correct allocation to each sextant (%)
3 Tesla	
Sensitivity	22–78
Specificity	73–100
1.5 Tesla	
Sensitivity	22–61
Specificity	67–100
With endorectal coil	
Sensitivity	20–62
Specificity	53–93
Without endorectal coil	
Sensitivity	33–83
Specificity	67–100
3 Tesla and endorectal coil	
Sensitivity	13–75
Specificity	56–100

However, all focal therapies for prostate cancer inevitably rely on an accurate preoperative localization of the intraprostatic cancer lesion. In general, this can be achieved by two means: imaging and biopsy.

As for prostate biopsy, standard practice is to use TRUS guidance to take 10–12 transrectal needle biopsies in a systematic fashion. However, TRUS-guided biopsy has a substantial false-negative rate, with cancer being found in ≈20 % of repeat biopsies [14] and, thus, significant cancers going undetected during the initial biopsy [15]. This is why many authors in the field of focal therapy advocate 3D transperineal template mapping (3D TPM) biopsies for accurate localization of clinically significant cancers and claim both a sensitivity and a negative predictive value of 95 % [16, 17]. However, it places a heavy burden on resources, commonly requiring general anesthesia and significant pathologist time.

Although 3D TPM biopsy is a reliable and detailed method of mapping individual prostate tumors, it may be a temporary step in our quest for image-guided diagnosis and treatment, as it has several disadvantages that may limit its long-term use. The prostate can change in shape as a result of distortion (from the US probe), rotate, and swell (as a result of the needle, edema, and hemorrhage), compromising the 3D spatial information. Morbidity can include temporary erectile dysfunction, perineal ecchymoses, and acute urinary retention.

Advances in MRI technique show potential for improving the diagnostic accuracy of MRI for prostate cancer detection. A recently developed multiparametric MRI approach that combines anatomic T2-weighted imaging with functional data appears to be one of the most promising techniques for prostate cancer detection [3–8]. The addition of functional MRI techniques can provide metabolic information, display altered cellularity, and aid in noninvasive characterization of tissue and tumor vascularity. Although these techniques have not been implemented broadly in daily clinical practice yet, they are increasingly mentioned in prostate cancer guidelines [18]. The latest diagnostic consensus statement by the European Society of Urogenital Radiology (ESUR) recommends anatomic T2-weighted imaging combined with at least three functional techniques: diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), and optionally MR spectroscopy.

In this context, the introduction of PI-RADS resulted in both increased reporting quality and reduced interobserver variability (pre-PI-RADS: kappa 0.39–0.55; with PI-RADS 0.46–0.80) [12, 13]. Additionally, PI-RADS seems to provide thresholds able to discriminate between significant and insignificant cancers [13, 19, 20]. However, this standard is usually only available at academic centers specialized in genitourinary MRI and routinely applying the PI-RADS classification. This expertise is rare in non-academic institutions where still the vast majority of MRIs of the prostate are being conducted. Our results indicate the necessity to promote a widespread introduction and use of the PI-RADS classification if focal therapy of prostate carcinoma should ever become a substantial option of treatment.

The comparably low localization accuracy of transrectal 12 core ultrasound-guided biopsy might be surprising at first glance; however, it is in line with other reports [21–23]. TRUS-guided biopsy is generally acknowledged as carrying multiple random and systematic errors. Our study reveals that not even the tumor-carrying site can reliably be predicted.

According to our data, neither higher field force nor the use of an endorectal coil could enhance the accuracy of mp-MRI. Previous studies demonstrated the detection of ECE, SVI, and LNI to be improved by the use of the endorectal coil at 1.5 T and at 3 T [20, 24]. The staging accuracy at 1.5 T with an endorectal coil was found to be comparable to the accuracy at 3 T without an endorectal coil [24, 25]. Thus, the use of the endorectal coil is recommended at 1.5 T, whereas it is considered optional at 3 T [26]. However, some recent studies suggest that field strength and the use of an endorectal coil have only little impact on diagnostic accuracy compared with other factors such as Gleason score or tumor extension inside the gland [22, 27]. There is general agreement that protocol (sequences), radiologist, and manufacturer's settings have greater impact on the diagnostic value of mp-MRI than field force or the use of an endorectal coil. Surprisingly, we found a higher

sensitivity in low-risk than in high-risk tumors, indicating the low reliability of MRI not being evaluated according to PI-RADS standards by genitourinary experts.

In general, € 460–1100 is charged for an mp-MRI in Germany. Sedation is required for claustrophobic patients. Further, patients often complain about the discomfort associated with the use of an endorectal coil. In light of the low localization accuracy that we obtained, it seems hard to justify the expenses of the procedure as well as the patient's discomfort if the MRI is not conducted according to the highest standards including PI-RADS classification.

Limitations of this study are that other studies are larger [23, 28] and data were collected retrospectively. We did not standardize the patients who underwent mp-MRI; by definition, this results in selection bias.

Further, this series consists of a mix of different MR techniques. The majority of these MRIs were not performed at academic centers, but in smaller local units and institutions where specialization in MRI of the genitourinary system is not always available—the training and experience profiles of the radiologists who conducted the MRIs could not be obtained. Thus, we showed that the MR accuracy is poor, but the study does not allow identifying a specific cause for the inaccuracy of intraprostatic cancer localization: bad reporting (no PI-RADS), lack of training, insufficient MR technique or a combination of all three factors. However, aim of this investigation was explicitly not to assess the diagnostic potential of MRI under best possible study conditions, but to reflect the current clinical practice of prostate cancer diagnostic work-up.

Conclusion

"Routine staging" MRI without PI-RADS classification is generally not able to accurately localize the tumor within the gland, although advances in MRI techniques and standardization of evaluation show potential for improving the diagnostic accuracy of MRI for prostate cancer localization. Focal therapies for prostate cancer inevitably rely on an accurate preoperative localization of the intraprostatic cancer lesion. Regarding patient discomfort and costs, "poor standard" MRIs of the prostate are not justified.

Our data support the recommendations against the widespread preoperative use of mp-MRI at non-academic centers and without standardization of evaluation because it is not adding reliable predictive information.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This retrospective study was performed in accordance with the standards of the ethics committee.

Authors' contribution A. Billing collected, managed, and analyzed the data, and wrote and edited the manuscript. A. Buchner analyzed the data. C. Stief involved in protocol and project development. A. Roosen involved in protocol and project development, managed the data, and wrote and edited the manuscript.

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