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Detection of Local Recurrence with 3-Tesla MRI After Radical Prostatectomy: A Useful Method for Radiation Treatment Planning?

DANIEL BUERGY[1], METIN SERTDEMIR[2], ANJA WEIDNER[3], MOHAMED SHELAN[4], FRANK LOHR[1], FREDERIK WENZ[1], STEFAN O. SCHOENBERG[3] and ULRIKE I. ATTENBERGER[3]

[1]*Department of Radiation Oncology, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany;*
[2]*Medical Care Center Radiology Karlsruhe West, Karlsruhe, Germany;*
[3]*Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany;*
[4]*Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*

Abstract. *Background/Aim: Salvage radiotherapy improves biochemical control in patients with recurrence of prostate cancer after prostatectomy. Radiotherapy target volumes of the prostatic fossa are based on empirical data and differ between different guidelines. Localization of recurrence with multiparametric magnetic resonance imaging (MRI) might be a feasible approach to localize recurrent lesions. Patients and Methods: Twenty-one patients with biochemical recurrence after radical prostatectomy were included (median prostate-specific antigen (PSA) =0.17 ng/ml). Multi-parametric MRI was performed using a 3-T MR system. Results: Lesions were detected in seven patients with a median PSA of 0.86 ng/ml (minimum= 0.31 ng/ml). Patients without detectable recurrence had a median PSA of 0.12 ng/ml. All patients with detectable lesions responded to radiotherapy. Eleven out of 14 patients without detectable recurrence also responded. Plasma flow in suspicious lesions was correlated with PSA level. Conclusion: Detection of recurrence at the prostatic fossa with our approach was possible in a minority of patients with a low PSA level. Clinical relevance of plasma flow in suspicious lesions should be further investigated.*

Correspondence to: Daniel Buergy, Department of Radiation Oncology, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. E-mail: daniel.buergy@umm.de

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Prostate carcinoma is the second most common cancer in males (1) and although mortality rates have decreased in European countries and the United States (US), it still accounts for more than 258,000 deaths worldwide (2). According to the US-population-based Surveillance, Epidemiology, and End Results Program database, ~80% of men with newly diagnosed prostate carcinoma had localized disease at the time of diagnosis (3). Most of these patients selected radical prostatectomy or external beam radiotherapy as their primary treatment option (4, 5). Recurrence rates after radical prostatectomy differ widely between around 10% of patients and more than 30% within 5 years (6-8), depending on Gleason score and other risk factors (6). In patients with positive surgical margins, it can be estimated that 20-40% of tumors recur (9, 10) and the majority of patients with biochemical relapse are diagnosed as having local recurrence (11). Radiotherapy as salvage treatment has been shown to improve biochemical control in patients with residual disease or biochemical relapse (12, 13). Stephenson *et al*. estimated that biochemical control can be achieved by radiotherapy in 48% of patients when salvage treatment starts before the prostate-specific antigen (PSA) level reaches 0.5 ng/ml; if administered at a PSA level of 0.5 ng/ml and above, only 26% of patients treated were free from (further) relapse (14). These results have been confirmed by modern series which additionally showed a clinical benefit in terms of distant metastasis-free survival, disease-specific mortality, and all-cause mortality (15). Furthermore, modern series indicated early salvage radiotherapy, initiated at the earliest sign of measurable PSA, to be beneficial in terms of biochemical and clinical endpoints (15, 16). Severe toxicity of salvage radiotherapy is generally reported to be low (17) but even in modern series, there is a residual risk of grade 3/4 bowel or urinary toxicity (18).

Timing of salvage treatment in patients who have not received adjuvant radiotherapy remains controversial. According to National Comprehensive Cancer Network (NCCN) guidelines (19) "treatment is most effective when pre-treatment PSA level is below 0.5 ng/ml"; however, the indication for salvage radiotherapy also includes "an undetectable PSA that becomes detectable and then increases on 2 subsequent measurements" (19). European guidelines propose salvage radiation before the PSA level increases to 0.5 ng/ml (20), and the American Society for Radiation Oncology/American Urological Association guidelines at earliest sign of PSA recurrence after undetectable PSA has been achieved (17). The latter approach is in line with aforementioned studies by Stish *et al*. (15), as well as that of Tendulkar *et al*. (16), published in 2016.

Local relapses are located at the urethro-vesical anastomosis in most cases (21-23). There are, however considerable differences in target volume definition between the four published consensus guidelines of the European Organisation for Research and Treatment of Cancer (24), the Radiation Therapy Oncology Group (25), the Australian and New Zealand Radiation Oncology Genito-Urinary Group (26), and the Princess Margaret Hospital (27)] in terms of size and prostate bed coverage (28, 29). In a comparative study (29), radiotherapy plans contoured according to consensus guidelines failed to meet QUANTEC (30), and RADICALS (31) trial dose constraints in 75%, and 40% of cases, respectively. These inconsistencies indicate that our current approaches to salvage treatment of prostate carcinoma after radical prostatectomy should be reassessed. Improvement of therapeutic efficacy could be achieved by reducing geographical miss and side-effects by accurate detection of residual disease.

Detection of residual prostate carcinoma is possible by magnetic resonance imaging (MRI) and positron-emission tomography–computed tomography (PET-CT). Evidence on restaging of biochemically relapsed patients with PET-CT was recently reviewed by Umbehr *et al*. (32). The authors analyzed 12 studies and found a pooled sensitivity and specificity of 85%, and 88%, respectively (mean PSA=7.9 ng/ml). In patients with early relapse (PSA <1 ng/ml), however, the authors found no convincing evidence for the use of PET-CT.

MRI with (33-35) and without (36) endorectal coil represents an alternative for detecting local recurrence after radical prostatectomy. Most studies have been performed on 1.5-T MR systems (33-36) and local recurrence was in some cases detected in patients with PSA levels of 1-2 ng/ml or less (35-38). Despite these results, it remains controversial, if local recurrence may be detected by 1.5-T MRI before PSA levels rise above 1 ng/ml (20). This would facilitate early targeted salvage radiation before a PSA level is reached of which probability for biochemical control is impaired (14, 39).

Table I. *Characteristics of 21 patients after radical prostatectomy for prostate carcinoma.*

Characteristic	Value
Gleason score, n	
6	1
7	14
8	3
9	3
T-Stage, n	
pT2	11
pT3	10
N-Stage, n	
N0/pN0	18
pN1	2
pNx	1
M-Stage, n	
M0	21
Resection status, n	
R0	11
R1	8
R2	1
Rx	1
Age, years	
Min-Max	49-75
Median	64
PSA at time of MRI, ng/ml	
Min-Max	0.03-4.3
Median	0.17

MRI, Magnetic resonance imaging; PSA, prostate-specific antigen.

We assumed that with 3-T MRI protocols (40-42), detection of local recurrence after radical prostatectomy is feasible at early stages when the PSA value is still below 1 ng/ml. Accurate detection would further reduce geographical miss and most probably enhance therapeutic ratio, by dose escalation to small residual volumes (18) or reduction of treated volumes. In addition, visualization of tumor vasculature with quantification of plasma flow (PF) and mean transit time (MTT) might further add functional information for improved target definition.

Patients and Methods

Patients. From September 2008 to November 2012, 28 patients with suspected local recurrence after radical prostatectomy were scanned by MRI. Seven patients were excluded from analysis because of identification of metastatic disease at MRI in two, refusal of radiotherapy in one, missing PSA test between surgery and radiotherapy in one, technical problems in one and artifacts due to foreign material in the bladder, and MRI appointment after start of radiotherapy in two. The majority of the remaining 21 patients presented because of PSA persistence or progression after R0 surgery in 14, biochemical progression after R1 surgery in five, and R1 surgery with residual PSA level in two.

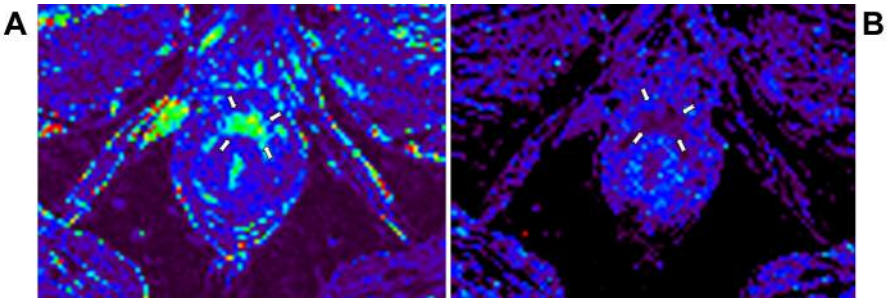

Figure 1. *Suspected local recurrence after radical prostatectomy in magnetic resonance imaging (MRI). Dynamic contrast-enhanced MRI (quantitative color-coded maps) demonstrates nodular lesion with increased plasma flow (PF) (a) and decreased mean transit time (MTT) values (b) in comparison to the surrounding tissue (PF=159.3 ml/100 ml/min; MTT=65.32 s).*

All patients included in the analysis received radiotherapy to the prostatic fossa. Target volume dose was 70 Gy (five fractions per week, 2 Gy per fraction); patients with identifiable localization of residual disease (either by MRI or by positive surgical margins) received an integrated boost up to 75 Gy targeted at the recurrent tumor volume. Irradiation of pelvic lymph nodes was performed to a dose of 44 Gy if positive nodes were found at surgery or if lymph node resection was deemed insufficient, and the preoperative risk of lymph node involvement was >15% based on the Roach-Formula. Detailed results of the radiotherapy regimens applied have been reported elsewhere (18). Further patient characteristics are detailed in Table I. This retrospective study was approved by the Ethics Committee of Heidelberg University, Medical Faculty Mannheim (2008-338N-MA).

MRI protocol. MRI was performed on a 3-T MR system (Magnetom TimTrio; Siemens Healthineers, Erlangen, Germany) utilizing a 12-channel body coil. To suppress bowel motion, up to 40 mg N-butylscopolaminium (Buscopan®; Boehringer Ingelheim GmbH, Ingelheim, Germany) was injected intravenously. All patients were examined in feet-first supine position. Imaging protocols consisted of a high-resolution, T2-weighted triplanar turbo spin echo sequence, an axial, fat-suppressed, single-shot, echo-planar diffusion-weighted imaging (DWI) sequence and an axial, 2D, T1-weighted dynamic contrast-enhanced DCE scan using a spoiled gradient echo saturation recovery TurboFLASH sequence. The DCE MRI examination was performed after bolus injection of 0.1 mmol/kg body weight of gadolinium chelate (Dotarem®; Guerbet, Roissy, France) with a bolus velocity of 2.5 ml/s using a power injector (Medrad Inc., Pittsburgh, PA, USA) followed by a saline flush of 40 ml. Imaging parameters of the T2w, DCE and DWI sequence MRI are summarized in detail in Table II.

Table II. *Scan parameters of the T2-weighted, dynamic contrast-enhanced (DCE) and diffusion-weighted imaging (DWI) magnetic resonance imaging sequences.*

Parameter	T2w	DCE	DWI
TR/TE (ms)	4,000/101	3.85/1.42	4,900/88
Sequence type	TSE	TWIST	EPI
FOV (mm × mm)	200×200	260×260	204×204
Matrix	320×320	160×160	136×136
Number of slices	19/23/19	20	20
Slice thickness (mm)	3	3.6	3
Interslice gap (mm)	0.3	0	0
Spatial resolution (mm^3)	0.6×0.6×3.0	1.6×1.6×3.6	1.5×1.5×3.0
b Values (s/mm^2)	-	-	0, 50, 500, 800
Flip angle (°)	137/150/150	12	-
Parallel imaging factor	Grappa (2)	Grappa (2)	Grappa (2)
Temporal resolution (s)	-	4.22	-
Averages (n)	4	-	8
Acquisition time (min)	4.26/4.1/3.38	5.02	5.4

TSE, Turbo-spin-echo; TWIST, time-resolved angiography with interleaved stochastic trajectories; EPI, single-shot echo-planar imaging; TR, repetition time; TE, echo time; FOV, field of view.

Post-processing and data analysis. A radiologist (M.S.) with 5 years' experience in prostate MRI post-processed the DCE MRI data using open source software tool towards quantitative MRI perfusion analysis (UMM Perfusion, OsiriX DICOM viewer, Version 3.9.4; The OsiriX Foundation, Geneva, Switzerland) (43). For each patient, nodules with focally altered perfusion parameters in the prostate bed were considered suspicious. DCE and T2-weighted images were also taken into account for differential diagnosis between nodules and artifacts such as clips or bowel movements. Contrast enhancement curves were analyzed with a model-free deconvolution analysis as described elsewhere (40, 41, 44). The arterial input function was measured in a plane with clear delineation of the common femoral artery at arrival of contrast agent. Quantitative color-coded maps of PF and MTT were calculated by de-convolving pixel-based concentration-time curves with the AIF as published previously (40-42). On the quantitative color-coded PF and MTT maps, nodular lesions with increased PF and decreased MTT values in comparison to the surrounding structures were defined as suspicious for recurrence, and one region of interest (ROI) was drawn in the area with suspicious increased PF and decreased MTT values in the prostatic fossa. For all ROIs, PF and MTT values were measured as the mean of pixel values. A defined ROI volume of 0.2×0.2 cm^2 was delineated for all detectable lesions.

Statistical analysis. Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Significance was defined as

$p \leq 0.05$. Differences of quantitative variables between independent groups were tested using the Mann-Whitney *U*-test. The two-sample paired Wilcoxon test was used to compared quantitative variables between corresponding samples (pre-therapeutic *vs.* post-therapeutic). Correlations among continuous variables were computed by Spearman's rank-order correlation.

Results

Two independent radiologists who were blinded to PSA levels identified suspicious nodular lesions with increased PF and decreased MTT values in seven out of 21 cases (an example is depicted in Figure 1).

The median PSA level in patients whose local recurrence was identified in MRI was 0.86 ng/ml [mean=1.65 ng/ml; standard deviation (SD)=1.67 ng/ml]). The minimum PSA level in a patient whose tumor was suspected by MRI was 0.31 ng/ml. Of seven patients with suspicious findings in MRI, five had a PSA level of less than 1 ng/ml (three of these patients had a PSA level less than 0.5 ng/ml).

In patients without detectable recurrence, the median PSA was 0.12 ng/ml (mean=0.168 ng/ml; SD=0.174 ng/ml). Two out of 14 patients whose recurrence was not detected by MRI had a PSA value greater than 0.21 ng/ml (0.33 and 0.71 ng/ml, respectively; see Figure 2). The difference between PSA levels in patients with suspected lesion in MRI *versus* those without localizable tumor was significant ($p=0.001$; Mann-Whitney *U*-test; Figure 2).

In the group of patients with lesions deemed as suspicious by MRI, PF at the suspect lesion (ROI=0.2×0.2 cm) was associated with increased PSA level ($p=0.014$; r=0.857; Spearman's rank correlation coefficient), MTT was not associated with PSA ($p=0.383$; r=–0.393) or PF ($p=0.253$; r=–0.5) in the analyzed group of patients.

In the first follow-up examination after radiotherapy (6-12 weeks after irradiation), the median PSA level was reduced as compared to the pre-radiotherapy level in all patients whose recurrent tumor had been detected by MRI (0.04 ng/ml after radiotherapy *vs.* 0.86 ng/ml before radiotherapy; $p=0.018$; Wilcoxon test). In patients whose tumors was not detected by MRI, the median PSA level in the first follow-up after radiotherapy was also lower as compared to the pre-therapeutic level (0.085 ng/ml after radiotherapy *vs.* 0.12 ng/ml before radiotherapy; $p=0.039$; Wilcoxon test). In two patients of the group with undetectable recurrence, the PSA level after radiotherapy had risen, and in one patient, PSA was unchanged as compared to the level before radiotherapy, consistent with suspected distant disease.

Discussion

Optimal timing of salvage radiotherapy is still the subject of discussion. Subanalyses of the SWOG8974 trial demonstrated improved metastasis-free survival in patients with all PSA

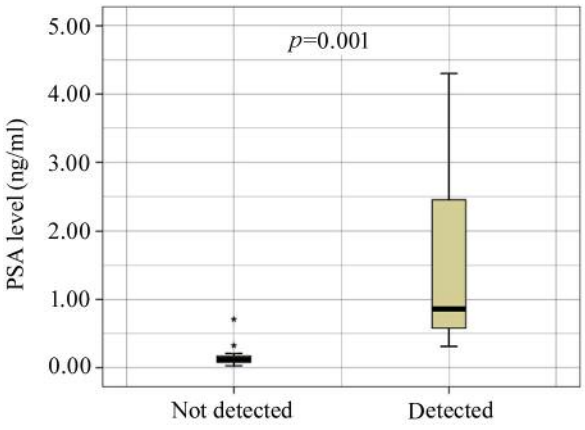

Figure 2. *Comparison of prostate-specific antigen (PSA) levels in patients whose tumor could not be detected by magnetic resonance imaging versus patients who had tumors that was detected. The bottom and top of each box represent the first and third quartiles, respectively. The band shows the median of each group. Outliers were defined as values beyond the 1.5-fold interquartile range (bars) and are marked with an asterisk. The difference between groups was calculated using the Mann-Whitney U-test.*

levels (<0.2 ng/ml, 0.2-1.0 ng/ml, >1.0 ng/ml) after prostatectomy when salvage radiotherapy was applied (11). Nevertheless, accumulating evidence indicates that treatment should be initiated early after the detection of biochemical recurrence at a PSA level of 0.2 ng/ml. In a systematic review encompassing 5597 patients, King estimated that each further PSA increment of 0.1 ng/ml is associated with an average 2.6% loss of biochemical relapse-free survival (39). Given these findings and the need to further improve the therapeutic ratio in salvage radiotherapy, we should aim for early detection of local recurrence by modern imaging techniques. As discussed above, there is currently no convincing evidence for the use of PET-CT in this clinical setting (32).

In our series reported here, we were able to detect areas highly suspicious for local recurrence at PSA values below 0.5 ng/ml at a minimum level of 0.31 ng/ml, indicating that some tumors in patients with a PSA value of 0.2-0.5 ng/ml can be detected by our method. We were not able to detect any local recurrence in patients with a PSA level below 0.3 ng/ml and we failed to identify local relapse in three patients with PSA levels of 0.2 ng/ml and greater (0.209, 0.33, and 0.71 ng/ml), although these patients responded to local therapy, indicating that local relapse not visible by MRI was present.

Recent literature on the topic shows that local recurrence was detected in larger series at a PSA level of around 0.8-1.3 ng/ml (45, 46). Cirillo and coworkers estimated sensitivity of 84% and specificity of 89% in patients with a PSA level of ~1.2 ng/ml (35). The authors were not able to detect local recurrence in patients with PSA values below 0.45 ng/ml with 1.5-T MRI.

These results concur with those provided by Silverman and coworkers, who reported the range where recurrent disease was suspected to be 0.4-11 ng/ml (38). Three studies reported that detection of local failure may be possible in patients with a PSA level below 0.4 ng/ml but one study was performed under systemic treatment for prostate cancer (37), therefore the results do not apply to the typical situation in which salvage radiation therapy is initiated. Rischke *et al*. were able to detect suspicious lesions in 66% of patients with a median PSA level of 0.51 ng/ml (range=0.11-2.38 ng/ml; 1.5-T MRI) (36). Another small series was reported by Roy *et al*., who estimated a sensitivity of 97% using T2-weighted MRI plus DCE-MRI (mean PSA=0.98 ng/ml, range=0.3-2.8 ng/ml) (47). Taken together, evidence on early detection of recurrence after radical prostatectomy at a PSA level below 0.5 ng/ml is inconsistent. Our data are in line with the studies performed with 1.5-T MRI, indicating that improvements by 3-T MRI are not sufficient for an earlier detection of local recurrence. Additionally, our data showed an association between PSA level and PF, but not with MTT. These observations must be confirmed in larger series. It has been shown that PF is a marker for angiogenesis (48); however, larger studies are needed to show if its quantification has a clinical or prognostic significance.

The weakness of this study is its small sample size. Additionally, as in most other studies on this issue, local recurrence was not confirmed by biopsy, only by treatment outcome (in terms of PSA response). It was not possible to improve detection cut-off compared to the best reported results using 1.5-T MRI with our approach. Reported studies on the subject are not yet sufficient to estimate the sensitivity and specificity in patients with a PSA level below 0.5 ng/ml. Potentially, the ongoing MRI-Mapped Dose-Escalated Salvage Radiotherapy Post-Prostatectomy-trial (49) will provide further insight. Furthermore, contrast agents such as superparamagnetic iron oxides (50) may lower detection limits in future studies.

Conclusion

Detection of gross recurrence by MRI of the prostatic fossa might improve tumor control if radiation doses could be escalated without compromising side-effect profiles. Our data indicate that high field strength alone is not sufficient to reliably detect recurrence in the prostatic fossa at PSA values below 0.5 ng/ml. This is in line with most published studies reporting on 1.5-T MRI application and indicates an unmet need for better imaging of the prostatic fossa after radical prostatectomy.

Declarations

Ethics approval and consent to participate: The study was approved by the ethics committee of Heidelberg University, Medical Faculty Mannheim (2008-338N-MA). Written informed consent for study participation was obtained from all patients.

Availability of data and material: The dataset generated and analyzed during the current study are available from the corresponding author on reasonable request.

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None.

Consent for Publication

All patients gave their written informed consent on anonymized publication of individual patient data.

Conflicts of Interest

DB reports personal fees from Siemens AG, personal fees from NB Capital Research GmbH, personal fees from NB Capital ApS, outside the submitted work.

FL reports grants and personal fees from Elekta AB, grants and personal fees from IBA, personal fees from C-RAD, during the conduct of the study.

FW reports grants and personal fees from Elekta, during the conduct of the study.

SOS reports the department of Clinical Radiology and Nuclear Medicine Mannheim has research agreements with Siemens Healthineers

UIA, M Sertdemir, AW and M Shelan have nothing to disclose.

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