MR images of prostate cancer site and normal prostate after radical radiotherapy

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Aims and objectives

Radiotherapy is one of the major treatment methods for prostate cancer. Radiation results in a number of changes that make the gland difficult to assess in MRI examination.

Histopathological examination of normal prostate after radiotherapy reveals grand atrophy, a significant increase in the number of stromal relative glands, atrophy of the secretory epithelium and prominence of basal cells. Moreover, there may be variable amounts of stromal fibrosis along with marked vascular changes, including luminal narrowing and fibrous obliteration. Furthermore, these changes may even be visible for over five years after treatment. Evans et al. in a report of 2011 assessed histologically material obtained in the core needle biopsy 18-24 months after the completion of radiotherapy. In their study focus of cancer after radiotherapy may present variously from no treatment effect until such a histopathological image in which cancer cannot be recognised [1]. Severe atrophy and fibrotic changes predominate in the prostate after radiation. The prostate shrinks and no proper zonal image of the gland is observed [2,3,4,5].

Approximately 30-50% of patients show the characteristics typical of active neoplastic infiltration within 5 years after treatment [2]. Typically, PSA level in blood plasma is measured to control the prostate gland. The increase in PSA level may be due to local recurrence, metastasis, but it may also be the result of inflammation and radiation [2]. The best study to confirm or rule out local recurrence of prostate cancer is multiparametric MRI (mpMR). Whereas it is relatively easy to identify neoplastic infiltration in the untreated prostate in the MR examination, the assessment of cancer foci as well as the rest of the prostate tissue may be extremely difficult after radical radiotherapy.

The aim of the study is the assessment of cancer site evolution and normal prostate tissue (both in peripheral and central zones) using mpMRI technique in patients after radical radiotherapy without biochemical signs of cancer recurrence for a minimum of three years after the treatment completion.
Methods and materials

Multiparametric MRI examinations of 33 patients (aged 65 +/- 8 years) were assessed before and after radical radiotherapy due to prostate cancer. In all cases prostate cancer was histopathologically confirmed. MRI was performed using magnetic induction 3T with a surface coil. MRI image parameters:

- T2ax TR 3231; TE 90; FOV 160x160x95, thickness 3 mm,
- T2sag TR 2536; TE 90; FOV 190x190x95, thickness 3 mm,
- T2cor FS TR 2800, TE 700, FOV 210x210x109, thickness 3 mm,
- DWI ax using 6 b-values 0, 50, 500, 750, 1000, 1200 s/mm², thickness 3 mm
- DCE T1FS ax after intravenous administration of a paramagnetic contrast agent at a dose of 0.1 mmol/kg at a velocity of V = 3 ml/sec.

Time of single DCE T1FS acquisition: approx. 55-60s.
The number of acquisitions: 8 (DCE total time of approx. 6-7 minutes), thickness 2mm.
The mean age of patients was 65 years (+/- 8 years) (figure 1).

MR examinations were performed between 2006 and 2011. The first examination was performed approximately 4 weeks before treatment. The second MRI was done mean 23 months after radiotherapy (from 5 to 30 months); only 2 patients underwent MRI assessment earlier i.e. approximately 5 months after radiotherapy.

The mean level of PSA in blood serum before treatment was 16.5 ng/ml (3.4-58.1 ng/ml). Most patients 13/33 (40%) were diagnosed with Gleason score of 6 (3+3).

Figure 2 presents the other data.

None of the patients had lymph node, bone or other organ metastases. 22 patients (67%) were treated with external-beam radioteraphy (EBRT) (mean dose of 73 Gy), 1 patient was treated with brachytherapy only (3%) (3x11 Gy dose) and 10 patients (30%) were treated with combined radiotherapy and brachytherapy. Biochemical recurrence was not found during the long-term follow-up (minimum 3 years after treatment).

The prostate cancer site was evaluated before and after treatment using PI-RADS scale (Prostate Imaging Reporting and Data System by the European Society of Urogenital Radiology- ESUR). The normal peripheral zone and the "central" zone (central and transitional) of the gland were also assessed in T2-weighted, DWI and DCE images [6,7,8].
We assessed the changes in the entire gland volume and the volume of cancer site as well as the change in ADC values of cancer infiltration site and normal peripheral and central zones of the prostate before and after radiotherapy.

The Wilcoxon test was used for the analyses. However, student’s t-test was used when the distribution of measurement differences was consistent with normal distribution. The level of statistical significance was set at \( \# = 0.05 \).
Fig. 1: Distribution of patients age.

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**Fig. 2:** Additional clinical information of all patients (n=33).

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**Results**

A statistically significant decrease in the prostate volume and in tumour infiltration site (p <0.0001) was observed in patients after radical radiotherapy. The median value of tumor volume before treatment was 2.32cm$^3$ and 0.22cm$^3$ after treatment (figure 3). The median value of prostate volume before radiotherapy was 37.53cm$^3$ and 29.05 cm$^3$ after therapy (figure 4).

1. Neoplastic infiltration:

Total PI-RADS (T2 + DWI + DCE).
We observed a decrease in total PI-RADS from 13/15 to 5/15 points, and a decrease in all components of PI-RADS after radiotherapy in the area of cancer infiltration (figure 5). In 17/33 patients (52%) total PI-RADS in the infiltration site was 3-5 points. Only in 1 patient total PI-RADS was slightly decreased from 15 to 13 points (the study was performed 30 months after treatment). That patient showed low-grade cancer at baseline (PSA 5 ng/ml, Gleason score 3 + 4) and no biochemical recurrence was noted in a 7-year follow-up.

T2 PI-RADS

Cancer sites before treatment in T2-weighted images in 26/33 patients (79%) were well margined and with a low SI (PI-RADS 4 and 5 points) and after treatment SI was still low in 39% of lesions (PI-RADS 4 and 5), and in 17/33 patients (51%) a low SI of cancer sites was indistinguishable from the rest of normal prostate (PI-RADS 3). Median PI-RADS T2 score value of the tumour before treatment was 4/5 points and 3/5 points (p = 0.0002) after treatment (figure 6).

DWI PI-RADS

Before treatment in 21/33 (64%) patients tumour site showed focal diffusion restriction with PI-RADS 5, 4/33 (12%) had a low ADC value (lower than normal prostate) but without diffusion restriction with PI-RADS 4. After treatment none of cancer lesions showed diffusion restriction, only 8/33 (24%) had a low ADC value - PI RADS 4. The rest of cancer sites (76%) had normal diffusion of PI-RADS1.

PI-RADS of tumour sites in DWI scored 5 points before treatment and 1point after treatment (p <0.0001) (figure 7).

DCE PI-RADS
42% (14/33) of patients (PI-RADS 3 and 4) showed plateau-type enhancement curves and 21% (7/33) wash-out type curves before treatment. After radiotherapy in 5/33 patients (85%) persistent curves were found (PI-RADS 1).

ADC

In the cancer infiltration site a significant increase in the median ADC value from 0.84 to $1.3 \times 10^{-3}$ mm$^2$/s was revealed after treatment ($p < 0.0001$) (figure 9).

2. NORMAL PROSTATE

Normal central and peripheral zones of the prostate before radiotherapy in T2-weighted images showed no significant changes. However, after treatment we observed diffuse non-focal areas with a significant SI decrease covering part of the gland or the whole prostate.

No signs of diffusion restriction in the normal prostate before and after radiotherapy were noted.

In the normal peripheral zone before radiotherapy persistent curves were found in 22/33 patients (67%) and in 90% of patients after treatment. Similar results were obtained for the normal central zone of the prostate before treatment in 24/33 patients (73%) - steady growth curves and after treatment in 94% of patients (31/33). No wash-out curves were found in patients before and after treatment in the normal peripheral and central zones.

The ADC value of the normal peripheral zone of the prostate did not change (before treatment $1.56 \times 10^{-3}$ mm$^2$ and after treatment $1.52 \times 10^{-3}$ mm$^2$) (figure 10).

In the normal central zone the ADC value increased from 1.3 to $1.5 \times 10^{-3}$ mm$^2$/s after treatment ($p = 0.001$) (figure 11).
**Fig. 3:** Comparison between the median values of tumor volume measured before RT and after RT.

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Fig. 4: Comparison between the median values of prostate volume measured before RT and after RT.

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Fig. 5: Comparison between the median values of PI-RADS score measured before RT and after RT.

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Fig. 6: Comparison between the median values of T2 score (PI-RADS) measured before RT and after RT.

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Fig. 7: Comparison between the median values of DWI score (PI-RADS) measured before RT and after RT.

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Fig. 8: Comparison between the median values of DCE score (PI-RADS) measured before RT and after RT.

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Fig. 9: Comparison between the ADC median values measured in tumor before RT and after RT.

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Fig. 10: Comparison between the ADC median values measured in normal peripheral zone before RT and after RT.

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**Fig. 11:** Comparison between the ADC median values measured in normal central zone before RT and after RT.

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Conclusion

Discussion:

Radical radiotherapy results in a significant change in the MR image of both prostate cancer site and normal prostate tissue [3,4,5]. PIRADS scale recommended by ESUR has been introduced for the purpose of easier and more systematic evaluation of suspicious lesions in the prostate. However, it is primarily dedicated to the evaluation of previously untreated prostate [6,7,8,9,10,11,12]. The aim of the study was the assessment of the evolution of prostate cancer site and normal prostate after radical radiotherapy in patients without biochemical recurrence. The evaluation of the prostate after radiotherapy is difficult. The results obtained in this study describe the prostate after radical radiotherapy.

After radiotherapy both the normal central zone and the peripheral zone are characterised by diffuse non-focal areas with decreased SI in T2-weighted images [3,4,5] (figure 12 a, b / 13 a, b).

Cancer site before treatment in T2-weighted images in 26/33 patients (79%) was well marginated with low SI (PI-RADS 4 and 5 points) and after treatment SI was still decreased in 39% of the lesions (PI-RADS 4 and 5) and in 17/33 patients (51%) low SI was indistinguishable from the rest of normal prostate (PI-RADS 3). Such an image of the prostate in T2 images is confirmed by other studies and it is related to the low usefulness of T2-weighted images for differentiation of recurrence and changes after radiotherapy [2,3,4,5].

We observed a significant increase in the ADC value of the irradiated cancer from 0.84 to 1.3 x10^{-3} \text{mm}^2/\text{s}. It is compatible with normal response to treatment. Similar results were also obtained by Decker [3,13]. No significant changes in the ADC value of the peripheral zone of the normal gland was observed, which is consistent with the results obtained by Decker [3]. However, we showed a significant increase in the ADC value of the central zone of the normal gland, contrary to the study of Decker. The difference, however, may be due to the period of MR examination after radiotherapy (in the study of Decker the last MRI examination was performed 3 months after treatment).

21/33 (64%) cancer sites showed focal diffusion restriction - PI-RADS 5 before treatment, and after treatment none of the tumour sites had diffusion restriction. Only 8/33 (24%) had low ADC value but without diffusion restriction - PI RADS 4. The rest of normal gland tissue (76%) had normal diffusion of PI-RADS1 (figure 12 and 13).
No diffusion restriction was found in the normal prostate before and after radiotherapy. In malignant tumours limitations to the mobility of water molecules and diffusion restriction are observed due to increased cell density, disorganised tissue structure and an increase in the irregularity of the extracellular space. Therefore such tissues are characterised by high signal intensity in DWI images with a high b value and low ADC values. Diffusion acceleration is caused by the decrease in the number of cells per unit volume or an increase in the number of cells with damaged cell membrane in effectively treated tumour [13,14,15].

Types of contrast enhancement curves both in the focus of cancer and in the normal prostate can be varied, as demonstrated by the study results. In the study group, wash-out type curves were not found in any patient in the normal gland area of the peripheral and central zones (before and after radiotherapy). Persistent type curves predominate in the cancer site and in the normal prostate after radiotherapy. However, according to the literature, enhancement curves in the prostate do not always correlate with the nature of changes, and their usefulness is limited in the assessment of the nature of changes [2,3,4,5] (figure 14 and 15).

Conclusion:

Most frequently the site after the invasion of prostate cancer after radiotherapy in patients without biochemical recurrence is not isolated from the rest of the prostate in T2-weighted images, does not show diffusion restriction and is characterised by persistent type curves.
Fig. 12: A 63 years old patient at time of diagnosis, with maximum PSA level before EBRT: 33.8 ng/ml and Gleason 3+3. PI-RADS score 14/15. a) hypointense lesion in right periheral zone (white arrow) in T2-WI before EBRT b) hyperintense signal area in DWI b=1200 before EBRT c) ADC map 0.51x10^-3 mm²/s before EBRT d) equally hypointense prostate with no evident lesion in T2-WI after 12 months from EBRT e) DWI b=1200 after EBRT f) ADC map 1.52x10^-3 mm²/s in tumor bed

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**Fig. 13:** A 67 years old patient at time of diagnosis, with maximum PSA level before EBRT: 21.0 ng/ml and Gleason 3+3. PI-RADS score 15/15. a) Hypointense lesion bilateral in peripheral zone (white arrow) in T2-WI before EBRT b) Hyperintense signal area in DWI b=1200 before EBRT c) ADC map 0.73x10^-3 mm^2/s before EBRT d) Equally hypointense prostate with no evident lesion in T2-WI after 18 months from EBRT e) DWI b=1200 after EBRT f) ADC map 1.24x10^-3 mm^2/s in tumor bed

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Fig. 14: a) focal asymmetric enhancement in right peripheral zone with washout on dynamic contrast-enhanced perfusion imaging (DCE) before EBRT (red curve) b) prostate after EBRT with normal perfusion on DCE

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Fig. 15: a) focal asymmetric enhancement in left peripheral zone with washout on dynamic contrast-enhanced perfusion imaging (DCE) before EBRT (red curve) b) prostate after EBRT with normal perfusion on DCE

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