International Consensus Statement on Prostate Imaging for Recurrence Reporting (PIRR) after Radiation Therapy and Radical Prostatectomy

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Abstract

Context: The role of imaging and the optimal means of integrating the different modalities for detection of prostate cancer recurrence still needs to be clarified. According to the available evidence, its use is essential for the identification of local recurrence for salvage therapy and to exclude distant progression that should be addressed with systemic therapy. However, there is as yet no agreement on imaging protocols that should be applied consistently for the management of men with biochemical recurrence.

Objective: To propose a standardized method for image acquisition and evaluation of prostate cancer recurrence after whole gland therapy: Prostate Imaging for Recurrence Reporting (PIRR).

Evidence Acquisition: Prostate Imaging for Recurrence Reporting was formulated through consensus using existing literature and clinical experience.

Evidence Synthesis: PIRR is a 5-point category scale for MRI of the prostate that allows the Radiologist to assign numerical categories to post-treatment prostate evaluation after radiation therapy and radical prostatectomy. Reporting criteria are based on anatomical and functional

imaging findings, that identifies the likelihood of prostate cancer recurrence with specific management implications.

Conclusions: PIRR is designed for stratifying the risk of having malignant tumor recurrence in men undergoing MRI of the prostate gland/prostatic bed after whole gland therapy.

Patient Summary: PIRR is designed for guiding clinical care, to promote standardization and diminish variations in the acquisition, interpretation, and reporting of MRI for prostate cancer recurrence.

1. Background

1.1 Rising PSA values after therapy: Biochemical Failure

Active treatment for selected men diagnosed with localized prostate cancer has been whole-gland focused, based either on prostatectomy (RP) or radiotherapy (RT) with/without neoadjuvant/adjuvant androgen deprivation therapy (ADT). More recently, there has been a shift towards focal ablation therapy, for well selected patients. After whole gland therapy, patients are serially evaluated using serum PSA and digital rectal examination (DRE) [1]. When there are persistent or rising serum PSA levels after primary therapy, the first distinction that needs to be made is between biochemical persistence and recurrence, recognized by Urologists as distinct entities.

1.1.1 PSA persistence. The definition of PSA persistence strictly depends on the primary treatment. After radical surgery, patients might experience PSA persistence due to residual benign prostate tissue, persistent local prostate cancer, or undiagnosed/untreated pre-existing nodal disease or distant metastases. PSA persistence is defined as persistently detectable PSA levels and, in most studies, it is defined as a PSA > 0.1 ng/mL 4-8 weeks after surgery [2–5]**.** According to the National Comprehensive Cancer Network (NCCN) updated in 2019, PSA persistence after surgery is defined as a failure of PSA to fall to undetectable levels. Currently, there is no agreed definition on PSA persistence after radiation therapy and focal therapy.

1.1.2 Biochemical Recurrence. When serum PSA levels are elevated and rising beyond the period of PSA persistence, biochemical recurrence (BCR) can be suspected. In 2006, the RTOG-ASTRO Phoenix Consensus Conference defined PSA relapse after radiotherapy as any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir. This definition, with an accuracy of > 80% for clinical failure, has been widely adopted for BCR after radiotherapy, although it was designed as a trial endpoint [6]. The BCR definition after radical prostatectomy changed in the 2020 EAU guidelines, with no specific

PSA cut-off to define its presence nor a threshold to initiate salvage therapy. Instead, rising PSA levels now need to be judged according to patients' risk for developing harms [1], with consideration given to PSA value kinetics rather than absolute values [7–11]. Supplementary Table 1 describes EAU risk groups. The American Urological Association (AUA) biochemical recurrence definition is unchanged and is defined as PSA >0.2 ng/mL measured 6–13 weeks after surgery, followed by a confirmatory test showing a persistently elevated PSA above 0.2 ng/mL [12,13]. The threshold that best predicts the development of clinical harms including metastatic spread and prostate specific mortality is a serum PSA >0.4 ng/mL [14,15] after prostatectomy, therefore this represents the threshold for the institution of salvage therapy. For the 2020 EAU definitions, high-risk BCR is the only group that benefits from pelvic salvage therapy [16]. After focal therapy, currently there is no consensus on the definition of BCR recurrence/PSA relapse [1,12]. Recently, a group of experts defined a standardized nomenclature to define a follow-up guideline after FT and prostate ablation for localized prostate cancer [17]. Supplementary Table 2 summarized BCR definitions according to guidelines.

Physicians should be aware and inform patients that BCR is common (about 30%) and that BCR may not necessarily lead to clinical harms, which occur in a minority of patients [1]. Imaging has become an important tool in determining presence of recurrent disease, but there is, as yet, no agreement on imaging techniques and timing that should be applied consistently for the management of men with BCR. On the other hand, the timetable of clinical evaluations using PSA and DRE is well established for men BCR after prostatectomy, allre recommended at three, six and twelve months post-operatively, every six months thereafter until three years, and then annually [1].

1.2 Role of Imaging in the follow up of suspected prostate cancer recurrence

There are a number of clinical requirements that need to be met in patients with suspected BCR. These include: (1) identify high-risk men and those who will likely to benefit from local salvage therapy; (2) to detect the location of pelvic recurrence in order to plan biopsies before local salvage is done, particularly for men who have had primary radiotherapy; (3) exclude polymetastatic disease before local pelvic salvage therapy is undertaken; and (4) guide how salvage therapy should be delivered in men with oligometastatic disease, in order to postpone the onset of androgen deprivation therapy (ADT), without compromising overall survival.

In order to meet these clinical needs, it is important to realize that salvage pelvic radiotherapy after RP is often decided on the basis of BCR alone without imaging, because of the known poor imaging sensitivity when PSA levels are low, recognising that the relevant treatment PSA threshold is 0.4 ng/mL and rising. Therefore, in the presence of high PSA after RP the clinical priority is to 'rule-out' systematic recurrence rather than to 'rule-in' local recurrence. On the other hand, for patients with BCR after RT, the detection of localized recurrence and biopsy status is a major predictor of long-term outcome. Given the greater morbidity of local salvage after RT, it is necessary to obtain histologic proof of the local recurrence before initiating retreatments. Here there is a different imaging role including biopsy targeting and the guidance of treatments. Therefore, after RT the clinical priority is to both 'rule-in' local recurrence disease and to 'rule-out' systematic recurrence.

Imaging should provide a stepwise multimodal approach that allows both systemic and local restaging, according to clinical priorities and primary therapy, when applicable. The choice of imaging modality depends on the technique's sensitivity for clinically relevant PSA levels (0.2 ng/mL (definition of BCR after RP) and 0.4ng/mL (higher likelihood of patient harms and clinical progression). Clinical guidelines indicate the need to perform both nuclear medicine imaging (specifically PET/CT scans with a variety of tracers) for systemic evaluations and MRI for the prostate gland or post-operative bed, itself. Prostate Imaging for Recurrence Reporting

(PIRR) was developed for the detection of local prostate cancer recurrence using a standardized method for MR image acquisition and evaluation. It combines predefined imaging criteria, in order to provide a likelihood of recurrence and to guide subsequent management. It currently does not address the use of other nuclear medicine investigations indicated for the BCR setting.

2. Evidence Acquisition

PIRR was formulated through consensus using existing literature and clinical experience. A non-systematic literature review using Medline, PubMed, and Web of Science sources was performed by an international panel of experts of different Working Groups from ESUR, ESUI, PI-RADS Steering Committee to draft this position statement on the systematic evaluation of MRI in the setting of prostate cancer recurrence. Final PIRR consensus was achieved through a combination of electronic and face-to-face exchanges.

3. Evidence Synthesis

3.1 Multiparametric MRI Requirements

PIRR recommends using the same patient preparation, MRI equipment, and imaging protocol outlined in PI-RADS v2.1[18]. However, after radical prostatectomy, T2W images should be acquired in three orthogonal planes (axial, coronal and sagittal) to properly include and evaluate the vesicourethral anastomosis, the residual seminal vesicles and the full posterior wall of the urinary bladder, as these are primary site of recurrence. Acquisition of at least one pulse sequence with a large field-of-view (FOV) is also recommended to evaluate pelvic nodes up to the aortic bifurcation [18] and the presence of bone metastases using either T1W, or DWI sequences (b 900/1000).

3.2 *Scoring and reporting of mpMRI in suspected prostate cancer recurrence*

PIRR for recurrence utilizes a 5-point categorization scoring system that summarizes the level of suspicion of prostate cancer recurrence based on mpMRI findings. Categories 1 or 2 are

assigned to lesions with a very low and low likelihood of recurrence, respectively. A final category of 3 is assigned when there is equivocal likelihood of recurrence. Categories 4 and 5 is assigned when there is a high and very high likelihood of recurrence, respectively.

Reporting criteria are based on anatomical and functional imaging findings. (1) anatomical: size, location, and shape noting that local recurrence after RT most commonly appears in the gland at the site of the original primary tumor, with only 4% - 9% of local recurrent disease appearing elsewhere [19–21], and (2) functional criteria based on DWI and DCE which assess the tissue cellularity and vascularity.

3.2.1 After Radiation Treatment

T2WI. Treatments consist of a variety of methods to deliver RT to the prostate gland, such a EBRT, IMRT or Brachytherapy. Guidance implants may be used for EBRT to reduce radiation toxicity, neoadjuvant and adjuvant ADT. Identification of recurrence can be difficult due to changes in signal intensity, morphology of the prostate and morphological distortions after treatments. The normal anatomy of the treated prostate consists of a smaller, T2W hypointense gland without a clear zonal distinction. This is due to inflammation, glandular atrophy and fibrosis [22,23]. This hypointensity on T2W imaging, diminishes the prostatic zonal differentiation decreasing contrast and the distinction between benign versus malignant tissue [24].

Post-EBRT local recurrence appears as a mass-like abnormality that may exhibit a capsular bulge, and that is relatively hypointense compared with treated prostatic tissue due to the rapid growth of tumor relative to the atrophic tissue [25]. However, a focal signal change on T2WI may not always represent cancer recurrence [26]. Recurrent disease is most often seen at the site of prior tumor [19].

After low-dose rate (LDR) brachytherapy, post-treatment changes are similar to those after EBRT, with the visualization of the radioactive sources which appear as small ellipsoid signal voids scattered throughout the gland. After LDR brachytherapy, the prostate gland becomes progressively more atrophic and shrinks in size, often with caudal sources migration [27]. It can lead to a significant degradation in dose coverage of the prostate and inadequate spacing of specific areas that should be more carefully evaluated for local failure [28]. Due to these changes in the background signal within the prostate, T2WI alone is of limited diagnostic accuracy [29].

DWI MRI and ADC Map. After RT, the DWI signal intensity of local recurrence is similar to that of the primary tumor. Local recurrence can therefore be expected as a focal hyperintensity on high b-value images corresponding to an hypointense area on the ADC map, that may or may not correspond to a nodular area visualized on T2W imaging. On the other hand, DWI can be less useful in detecting local recurrence after LDR brachytherapy, because the retained seed implants cause susceptibility artifacts, thus limiting the diagnostic accuracy of DWI [30]. In this circumstance, DCE is of particular importance in detecting potential recurrence [31]. These artifacts are not present in high dose rate (HDR) brachytherapy where no metal is retained within the gland after treatment completion. DWI should not be performed during and shortly after radiation therapy (at least after 6 weeks), due to the changes in signal in the prostate caused by early inflammatory effect of RT, that might reflet low ADC values of benign tissue [32,33].

DCE MRI. Post-radiation glandular fibrosis is characterized by reduced cellularity and diminished vascularity compared to pre-treatment normal glandular tissue. Conversely, recurrent tumors retain their highly vascular network [34,35], so local recurrence will appears as a hypervascular, early enhancing homogeneous nodule, contrasting well with the nonenhancing, or only minimally, slowly homogeneously enhancing surrounding/background

fibrotic tissue [36]. The drawback of DCE is that it should be performed not earlier than 3 months after the completion of radiation treatment, because the inflammatory reaction of prostate tissues after RT can cause increases in perfusion and blood volume, leading to false positive and false negative interpretations [30,37].

MRI evaluations should be performed using appearances on T2W images, DWI, and DCE to arrive at an overall risk assessment on the likelihood of local recurrence (Tables 1-3)

Overall risk assessments. A five-point PIRR score for recurrence is generated using the DWI, and DCE MRI categories and suggests the probability of local recurrence (Figure 1-2) for tumor originating from both transitional and peripheral zone. The T2W sequence is helpful for recognizing BPH, to localize the suspicious foci and compare them to the preoperative imaging when available and/or histopathologically defined location. Note that table descripitors for T2WI is not part of the final overall score. The risk estimates after RT are assessed by both DWI and DCE [37–46] . The likelihood of recurrence increases when DCE demonstrates highly vascularized focal lesions and DWI highly cellular tissue. The definitive category is determined by the sequence with the highest score among the two, use figure 1a) when the highest score is determined by DWI, and figure 1b) when determined by DCE. The up-grading from PIRR 4 to PIRR 5 applies when the site of the diffusion restriction and enhancement match. When there is any discordance on lesion location between DWI and DCE sequences, morphologic T2W sequence can be helpful.

3.2.2 After Radical Prostatectomy

T2WI. Local recurrence after RP should be suspected in the presence of asymmetric perianastomotic soft tissue thickening that shows signal intensity (SI) intermediate to that of pelvic muscle and surrounding fat tissue, on T2W images [47]. Recurrent tissue can assume various shapes including lobulated, semi-circumferential, nodular- or plaque-like masses. In most cases, local recurrence is different from normal postoperative fibrosis, which shows SI

similar to muscle [30]. The presence of residual seminal vesicle remnants resembling normal seminal vesicles, should not always raise suspicion of PCa recurrence by themselves.

Evaluation of any man suspected of recurrence after surgey must be informed with a full review of the whole gland pathology whenever possible. Local recurrence after RP can be found anywhere within the surgical bed. Pathology data from surgical specimen are valuable, if available, for localization of recurrence, key features to look for are all tumor locations and any positive surgical margin (high-risk group) and its location. The most common sites of recurrence are the peri-anastomotic areas (around the bladder neck or the membranous urethra), the retro-vesical space (between bladder and rectum) and seminal vesicles remnants [48]. Other frequent sites of recurrence include the anterior or lateral surgical margins of the prostatic bed (e.g., abutting the levator ani muscles) [49,50]. Local recurrence localization should be described based on the clock position, with the center of the clock being the vesico-urethral anastomosis (12 o'clock position -head of the patient and 6 o'clock – foot of the patient):

***DWI MRI and ADC map*.** DWI has a good diagnostic accuracy in detecting local recurrence after RP when combined with other sequences [51], although it can often be markedly distorted by the presence of surgical clips and susceptibility artifacts. Local recurrence after RP, like primary tumors, shows high signal intensity on high b-value DWI and low ADC values (impeded diffusion), especially in focal or mass-like areas >1 cm in size. DWI can help clarify recurrence from slowly enhancing benign tissue on DCE-MRI [52].

DCE MRI. DCE imaging plays the dominant role in detection of PCa recurrence after surgery. It significantly increases the sensitivity and specificity for detection of local recurrence [53–55]. Even small foci of local recurrence, that may not be visible on T2W imaging, tend to show a significant enhancement in the early arterial phase often with contrast wash-out [39]. Tumor recurrence enhances earlier in time and more avidly than normal postoperative changes [56]. The kinetics of prostate cancer recurrence enhancement is usually similar to primary cancers,

with brisk enhancement in the early phase with variable wash-out patterns. On the other hand, post-operative changes will either not enhance or enhance very slowly and uniformly, as expected for fibrotic/granulation tissue.

MRI scoring should be performed using appearances in T2W images, DWI, and DCE to create an overall risk assessment of local recurrence (Tables 4-6).

***Overall risk assessments*.** A five-point score for recurrence is generated using the individual, DWI, and DCE MRI categories and suggests the likelihood of local recurrence (Figure 3). The dominant sequence for risk estimation of recurrence following surgery is DCE MRI. The T2WI sequence is helpful to localize the suspicious foci and compare them to the preoperative imaging when available and/or histopathologically defined location of positive surgical margins. The table for T2WI is not part of the final overall score, however it serves a "descriptive" function. The presence of local recurrence is firstly decided by DCE MRI that demonstrates highly vascularized focal lesions. Whenever there is any discordance between T2WI and DWI sequences on recurrence detection, the morphologic T2W sequence findings can be taken into account.

3.3 Implication of Scoring for recurrence assessment categories

PIRR is a 5-point category scale for MRI of the prostate that allows the Radiologist to assign numerical categories to post-treatment prostate evaluation after whole gland treatments, that identifies the likelihood of prostate cancer recurrence with specific management implications. After any type of treatment, a score 1 and 2 effectively excludes the presence of loco-regional recurrence, and patients are further investigated and managed according to clinical guidelines including assessments for regional or distant metastases.

After radiation therapy a PIRR assessment score of 3 is an indication for the need to perform biopsy before focal salvage therapy is undertaken. Based on consensus, it may be possible, for

PIRR 4-5 lesions to undergo salvage therapy without biopsy in the setting of BCR after prostatectomy (because the histopathology is known), and biopsy avoidance may be considered after radiotherapy although many oncologist would require biopsy confirmation before undertaking potentially morbid salvage treatments. In all cases where salvage therapy is being considered, distant re-staging using next generation imaging should be performed in accordance to clinical guidelines [1,57].

4. Limitations

There are several limitations that need addressing for PIRR: (1) The risk assessment scores evaluate prostate cancer recurrence are exclusively limited to the prostate gland or prostatic bed in men who have undergone whole gland therapy. For a comprehensive assessment of BCR, additional nodal and distant organ evaluations with other imaging modalities are recommended, according to clinical risk groups (See supplementary material); (2) PIRR categories are based on expert consensus and the actual frequency of recurrence in individual PIRR categories is currently unknown; biopsy or correlation with other imaging modalities and clinical validation is needed; (3) These assessment scores do not apply to recurrence or new disease after focal therapy, as there is yet no consensus nor robust evidence on the topic; (4) Interobserver and intraobserver variability need to be investigated; (5) criteria for assigning scores to lesions identified by each technique are not yet generally accepted, and re-definition might be necessary after validation studies.

5. Summary

Prostate Imaging for Rrporting Recurrence (PIRR) is designed for stratifying the risk of having malignant tumor recurrence in men undergoing MRI of the prostate gland/prostatectomy bed after whole gland therapy. PIRR provides a comprehensive categorization of abnormal findings, in order to facilitate the management of patients according to the risk of recurrence. PIRR recommendations are likely to fulfill the need to promote standardization and diminish

variations in the acquisition, interpretation, and reporting of prostate MRI for recurrence. This system is designed for guiding clinical care, but has potential for incorporation into clinical trials, where reproducibility of prospective assessments and comparisons of results obtained in different centers can be undertaken. PIRR is based on expert consensus and it requires validation including assessments of reproducibility of observations and integration with other biomarkers including PSA kinetics in the setting of biochemical recurrence after whole gland therapy.

Endorsement of PIRR:

Data Sharing Policy : Preparation of this paper did not involve analysis of data.

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7. Tables and Figures

Recurrence after RT	SCORE	PATTERN CHANGES
T2W	1	No abnormal signal intensity compared to the background
	2	Linear, wedge-shaped or diffuse moderate hypointensity or residual BPH-nodules
	3	Focal or mass-like mild hypointensity not at the primary tumor site; includes others that do not qualify as 2, 4 or 5
	4	Focal or mass-like moderate hypointensity not at the same site of the primary tumor, or location of primary tumor not known
	5	Focal or mass-like marked hypointensity at the same site of the primary tumor

Table 1. T2WI Assessment Categories after Radiation Therapy

Recurrence after RT	SCORE	PATTERN CHANGES
DWI	1	No abnormality on high b-value DWI and ADC map
	2	Diffuse moderate hyperintensity on high b-value DWI and/or diffuse moderate hypointensity on ADC map
	3	Focal marked hypointensity on ADC map or focal marked hyperintensity on high b-value DWI, but not on both
	4	Focal marked hyperintensity on high b-value DWI and marked hypointensity on ADC map not at the same site of the primary tumor, or site of primary tumor not known
	5	Focal marked hyperintensity on high b-value DWI and marked hypointensity on ADC map at the same site of the primary tumor

Table 2. DWI Assessment Categories after Radiation Therapy

Recurrence after RT	SCORE	PATTERN CHANGES
DCE	1	No enhancement
	2	Diffuse or heterogeneous enhancement
	3	Focal or mass-like late enhancement
	4	Focal or mass-like early enhancement not at the same site of the primary tumor, or tumor site not known

	5	Focal area with early enhancement at the same site of the primary tumor

549 **Table 3**. DCE Assessment Categories after Radiation Therapy

Recurrence after RP	**Score**	**Pattern Changes**
T2WI	1	Normal hypointense vesicourethral anastomosis and seminal vesicle beds-remnants.
	2	Diffuse thickening of the vesicourethral anastomosis and/or thick-walled seminal vesicle remnants and/or course scar tissue within the seminal vesicle beds
	3	Symmetric focal or mass-like of any signal intensity in the perianastomotic area or seminal vesicle bed(s)
	4	Asymmetric focal or mass-like iso/hyperintensity in the perianastomotic area or seminal vesicle bed(s) not at the same side of primary tumor, or tumor side not known
	5	Asymmetric focal or mass-like iso/hyperintensity in the perianastomotic area or seminal vesicle bed(s) at the same side of primary tumor

550 **Table 4.** T2WI Assessment Categories after Radical Prostatectomy

Recurrence after RP	**SCORE**	**PATTERN CHANGES**
DWI	1	No signal abnormality on high b-value DWI and ADC map
	2	Diffuse moderate hyperintensity on high b-value DWI and diffuse moderate hypointensity on ADC map
	3	Focal marked hypointensity on ADC map or focal marked hyperintensity on high b-value DWI, but not on both
	4	Focal marked hyperintensity on high b-value DWI and marked hypointensity on ADC map not at the same site of the primary tumor, or site of primary tumor not known
	5	Focal marked hyperintensity on high b-value DWI and marked hypointensity on ADC map at the same site of the primary tumor

551 **Table 5**. DWI Assessment Categories after Radical Prostatectomy

Recurrence after RP	**SCORE**	**PATTERN CHANGES**
DCE	1	No enhancement
	2	Diffuse or heterogeneous enhancement

	3	Focal or mass-like late enhancement
	4	Focal or mass-like early enhancement not at the same site of the primary tumor, or tumor site not known
	5	Focal or mass-like with early enhancement at the same site of the primary tumor

552 **Table 6.** DCE Assessment Categories after Radical Prostatectomy

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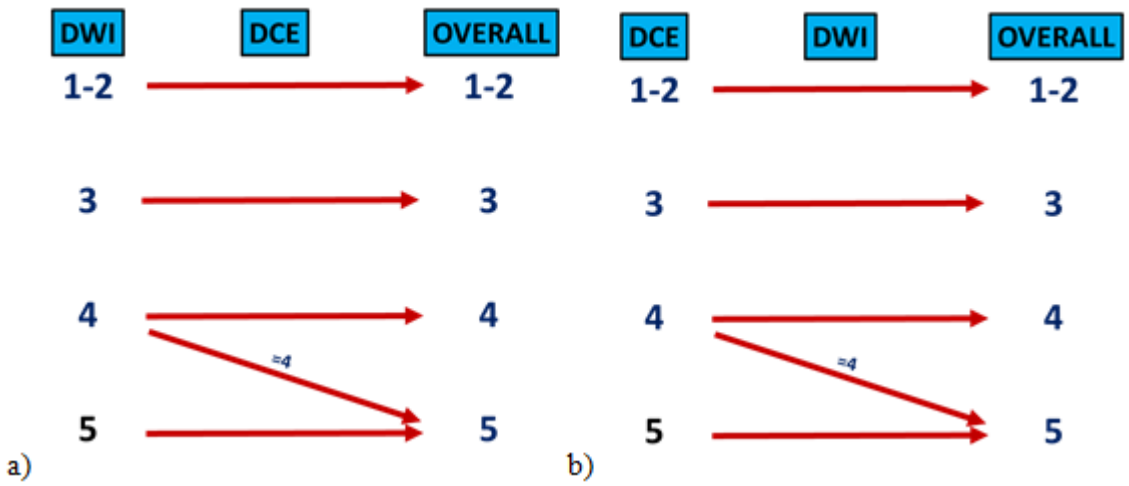

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555 **Figure 1.** Overall PIRR assessment score for local recurrence after Radiation Therapy. The

556 definitive category is determined by the sequence with the highest score. Use figure 1a) when

557 the highest score is determined by DWI, and figure 1b) when determined by DCE.

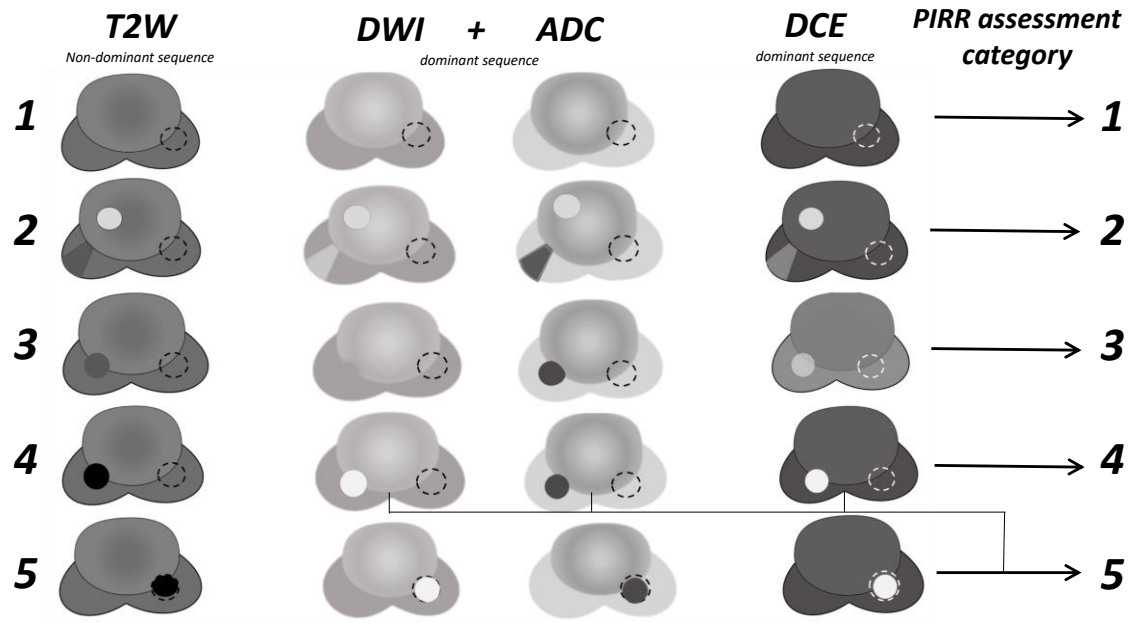

Figure 2. Schematic diagram of PIRR assessment categories for prostate cancer recurrence after radiation therapy. Note: in dashed line the location of the primary tumor; in filled circle the location of the recurrence.

Figure 3. Overall assessment score for local recurrence after Radical Prostatectomy