European Journal of Radiology 85 (2016) 2231–2237

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Can multiparametric MRI replace Roach equations in staging prostate cancer before external beam radiation therapy?

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ARTICLE INFO

Article history:
Received 21 July 2016
Received in revised form
27 September 2016
Accepted 21 October 2016

Keywords:
Prostate cancer
External beam radiation therapy
Roach equations
Magnetic resonance imaging
T stage

ABSTRACT

Purpose: To investigate the agreement between Roach equations (RE) and multiparametric magnetic resonance imaging (mpMRI) in assessing the T-stage of prostate cancer (PCa).
Materials and methods: Seventy-three patients with biopsy-proven PCa and previous RE assessment prospectively underwent mpMRI on a 3.0T magnet before external beam radiation therapy (EBRT). Using Cohen's kappa statistic, we assessed the agreement between RE and mpMRI in defining the T-stage (≥T3 vs.T ≤ 2) and risk category according to the National comprehensive cancer network criteria (≤intermediate vs. ≥high). We also calculated sensitivity and specificity for ≥T3 stage in an additional group of thirty-seven patients with post-prostatectomy histological examination (mpMRI validation group).
Results: The agreement between RE and mpMRI in assessing the T stage and risk category was moderate (k = 0.53 and 0.56, respectively). mpMRI changed the T stage and risk category in 21.9% (95%C.I. 13.4–33-4) and 20.5% (95%C.I. 12.3–31.9), respectively, prevalently downstaging PCa compared to RE. Sensitivity and specificity for ≥T3 stage in the mpMRI validation group were 81.8% (95%C.I. 65.1–91.9) and 88.5% (72.8–96.1).
Conclusion: RE and mpMRI show moderate agreement only in assessing the T-stage of PCa, translating into an mpMRI-induced change in risk assessment in about one fifth of patients. As supported by high sensitivity/specificity for ≥T3 stage in the validation group, the discrepancy we found is in favour of mpMRI as a tool to stage PCa before ERBT.

1. Introduction

External beam radiation therapy (EBRT) has gained widespread acceptance as definitive treatment for prostate cancer (PCa). EBRT is indicated in all patients with non-metastatic disease, using intensity-modulated radiation therapy (IMRT) as the technical standard to deliver highly conformal treatments [1].

Most influencing factors affecting EBRT planning are cancer T stage, prostatic specific antigen (PSA) level and Gleason score (GS) after biopsy, which in turn are combined to stratify patients for the risk of PCa recurrence after therapy [1,2]. In accordance with risk categories, EBRT regimens can be modulated in terms of dose, volume, fractionation and duration of concomitant androgen deprivation therapy (ADT) [2,3]. However, clinical determination of the T stage is still a major challenge [1,2], leading to widespread use of nomograms as a tool to increase the sensitivity in predicting organ-confined (stages T1-T2) vs. extraprostatic disease (stages T3-T4) [4]. Roach equations (RE) combine Gleason Score (GS) and the PSA level to estimate the individual risk of extracapsular extension (ECE) (stage T3a) and seminal vesicle invasion (SVI) (stage T3 b) [5–7] and in turn to take a "go or no-go" decision on how extended the clinical target volume should be [8].

In patients with PCa addressed to EBRT, final pathological proof will lack by definition, thus emphasizing the need for planning the treatment based on the most objective available evidence of disease extension. Despite the limited capability of mpMRI in assessing microscopic T3a stage, this technique is regarded as the method of

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http://dx.doi.org/10.1016/j.ejrad.2016.10.023
0720-048X/

Table 1
Acquisition parameters of multiparametric magnetic resonance imaging of the prostate. T1-w = T1-weighted imaging; T2-w = T2-weighted imaging; DWI = Diffusion-weighted imaging; DCE = Dynamic contrast-enhancement imaging; TSE = Turbo-spin-echo; EPI = Echo-planar imaging; 3D-FFE = Fast-field-echo 3D sequence; TR = Repetition time; TE = Time to echo; FOV = Field-of view; PI = Parallel imaging.

	T1-w	T2-w	DWI[a]	DCE
Sequence	TSE	TSE	EPI	3D-FFE
Acquisition plane	Transverse	Transverse, sagittal, coronal	Transverse	Transverse
Type of acquisition	Free breathing	Free breathing	Free breathing	Free breathing
TR (ms)	605	3691	5129	3.4
TE (ms)	10	80	63	1.75
Flip angle	90	90	90	15
FOV (mm)	200 × 200	200 × 200	200 × 200	240 × 240
In-plane resolution (mm)	0.46 × 0.46	0.46 × 0.46	1.39 × 1.39	0.68 × 0.68
Slice thickness (mm)	3	3	3	4
Number of slices	24	24	20	20
PI	No	SENSE (x 1)	No	SENSE (x 2)
Acquisition time (min)	4.30	5.0	8.0	5.0[b]

[a] For b-values see the text.
[b] 34 acquisitions after contrast injection (acquisition time 8.8 sec each).

choice for staging PCa [1]. However, there is still intense debate on the systematic use of mpMRI as a staging tool, given costs, limited availability and uncertain effectiveness in patients at lower risk [1]. Not surprisingly, nomograms such as RE are still widely used in clinical practice. To our knowledge, little is known about the agreement between RE and mpMRI in assessing the T stage of PCa, and whether such an agreement is high enough to use RE and mpMRI interchangeably. We hypothesized that a significant rate of discrepancies in this setting would suggest to prefer mpMRI for staging, since functional and high-resolution images are reasonably more objective than RE in assessing PCa.

The purpose of our study was to investigate the agreement between RE and mpMRI in assessing the T stage of PCa in patients addressed to EBRT.

2. Materials and methods

2.1. Study populations

This study was performed as a part of an ethical committee-approved trial investigating the impact of 3.0T mpMRI on the management of PCa. Patients expressed informed consent for participation.

Between January 2013 and August 2015, we prospectively enrolled all subjects with biopsy-proven PCa who underwent staging mpMRI before EBRT (study target group). Indication to EBRT was established by a referring radiation therapy oncologist (20 years of experience) following National comprehensive cancer network (NCCN) recommendations [2]. On a per-patient basis, clinical T-stage was defined by our referring clinician by applying RE to predict the percentage risk of ECE (stage T3a) and SVI (stage T3b). In particular, risk of ECE and SVI was calculated as a percentage (%) using the following formulas [7]:

$$\mathrm{ECE} = (3/2\,\mathrm{xPSA}) + (10\,\mathrm{x(GS\text{-}3)}) \quad (1)$$

and

$$\mathrm{SVI} = (\mathrm{PSA} + (10\,\mathrm{x(GS\text{-}6)}) \quad (2)$$

respectively. Thresholds for ECE and SVI were >50% and >20%, lying in a range of observed incidence of 46.7% and 37% [5,6], respectively.

A second study group was prospectively enrolled during the period September 2015–March 2016, including all patients who underwent mpMRI for staging biopsy-proven PCa before radical prostatectomy (mpMRI validation group). In this group, the standard of reference was represented by histological examination performed by referring pathologists.

2.2. mpMRI protocol

In both study groups, examinations were performed on a 3.0T system (Achieva, Philips Medical Systems, Best, the Netherlands) with a 32-channel surface coil. Patients underwent cleansing enema to void the rectum from air one hour before mpMRI. Examination was performed with the bladder in mild repletion state, after i.m. administration of 20 mg hyoscine butylbromide (Buscopan, Boehringer Ingelheim GmbH, Ingelheim, Germany) as a spasmolytic agent.

Study protocol is illustrated in Table 1. The dynamic contrast-enhanced sequence (acquisition time = 8.8 s) was acquired 34 consecutive times after i.v. administration of 0.1 mmol/kg of gadobenate-dimeglumine (Multihance, Bracco, Milan, Italy), at an injection rate of 2–3 mL/s. Contrast administration was avoided in two patients with previous, severe allergic reaction. In the case of diffusion-weighted imaging (DWI), we used spectrally adiabatic inversion recovery (SPAIR) for fat saturation, with b-values of 0, 800 and 1200 s/mm^2 (before 2015) or 0, 1000, 1500 and 2000 s/mm^2 (from 2015). The ADC map was generated by the vendor's software (Extended MR WorkSpace, Philips Medical Systems, The Netherlands), using linear regression of signal intensity vs. b-values.

2.3. Image analysis

Two radiologists (3 and 13 years of experience) performed image analysis *in consensus* on the vendor's workstation (Extended MR WorkSpace, Philips Medical Systems, The Netherlands). Readers were blinded to clinical T stage and RE assessment. Diagnosis of cancer was performed in accordance with the Prostate Imaging Reporting and Data System (PI-RADS) version 1 criteria [9], using the sum of individual T2-weighted imaging, DWI and DCE scores equal or larger than 10 (PI-RADS 4) and 13 (PI-RADS 5), respectively, as detailed elsewhere [10]. Since PI-RADS was upgraded to version 2 [11] during the study conduction, we performed a post-hoc analysis to revise initial categorization. No discrepancies in PI-RADS ≥4 categories were found between the two versions. Patients of the mpMRI validation group who performed the examination after the introduction of PI-RADS 2 were analyzed with this system only.

PI-RADS ≥4 lesions were then staged using the following score [9]: a) for ECE (stage T3a), we attributed 1 point to abutment, 3 points to irregularity of the capsule profile, 4 points to neurovascular bundle thickening and/or bulge with loss of capsule, and 5 points to measurable extra-capsular extension; b) for SVI (stage T3b), we attributed 1 point to expansion, 2 points to low T2 signal, 3 points to filling of an angle and 4 points to enhancement and impended