mpMRI vs nomograms in the risk assessment of prostate cancer: a study in patients addressed to external beam radiation therapy

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Aims and objectives

Background

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].

Risk stratification is of pivotal importance in addressing patients with PCa of variable clinical significance to the most appropriate EBRT regimen (Tab. 1). Depending on the risk category, EBRT can be modulated in terms of dose, volume, fractionation and duration of concomitant androgen deprivation therapy (ADT) [2-3].

Available risk classification systems are based on the combination of prostatic specific antigen (PSA) level, Gleason score (GS) and clinical T stage (cT) as determined by digital rectal examination (DRE). One might suppose that, being more objective in nature, multiparametric magnetic resonance imaging (mpMRI) has the potential to replace DRE in providing the T stage within the risk stratification process. However, there is still concern about a more systematic use of mpMRI, given costs, limited availability, and uncertain effectiveness in patients at lower risk. Not surprisingly, popular nomograms such as Partin tables (PT)[10] and the Memorial Sloan Kettering Cancer Center nomogram (MSKCCn) [11] are still widely used to refine cT in terms of intra- or extraprostatic disease, and in turn to contribute to define patients' risk category [4, 5].

Purpose

We wondered whether mpMRI, PT and MSKCCn agree at a sufficient extent to be used interchangeably in the risk stratification process of patients referred to EBRT.
Table 1: Risk-group assessment with associated treatment options, according to the NCCN criteria.

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Methods and materials

Study populations
In the period January 2014 - July 2016 we prospectively addressed staging mpMRI all patients referred to IMRT by our institutional uro-oncological group because of biopsy-proven PCa (target group). Clinical risk stratification was performed according to the National comprehensive cancer network (NCCN) criteria [2], using the T stage as resulting from PT and MSKCCn, respectively (Tab. 2) [10-11]. In particular, the T stage was estimated as #T3 (extraprostatic disease) vs. #T2 (intraprostatic disease) according to the following equation

\[100 - \text{probability of organ-confined disease} > 50\% \ (1),\]

where the probability of organ-confined disease was that calculated by nomograms.

To validate mpMRI results, we prospectively enrolled also patients undergoing surgery in the period between January 2015 and July 2016 (validation group). Exclusion criteria were contraindications to MRI, incomplete or lacking information on post-mpMRI management and low image quality. mpMRI protocol mpMRI was performed on a 3.0T magnet (Achieva, Philips Medical Systems, Best, the Netherlands), using a 32-channel surface coil. Patients' preparation included a cleansing enema 1h before the examination and i.m. administration of 20 mg hyoscine butylbromide as an antiperistaltic agent (Buscopan, Boehringer Ingelheim GmbH, Ingelheim, Germany) before the scan start. During the acquisition, the bladder was in the state of mild repletion. The study protocol, which is illustrated in Table 3, included high-resolution multiplanar T2-weighted sequence, Diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE). The latter was acquired after a single i.v. 0.2 mL/Kg dose of gadobenate dimeglumine (Multihance, Bracco, Milan, Italy), administered with a remote injection system at a rate of 3 mL/s. High temporal resolution DCE sequence (acquisition time = 8.8 s) was acquired 34 times after contrast injection, with no temporal gap between the acquisitions. Concerning DWI, we used fat saturation with the spectrally adiabatic inversion recovery (SPAIR) approach, with a b-values set of 0, 800 and 1200s/mm2 before March 2015 and with a b-values set of 0, 1000, 1500 and 2000 s/mm2 after March 2015. Quantitative ADC map was calculated by a dedicated software by performing linear regression of signal intensity vs. b-values, using a dedicated workstation (Olea Sphere, Olea Medical, La Ciotat, France). Image analysis mpMRI images were analysed in consensus by two radiologists (3 and 10 years of experience) using a dedicated console (Olea Sphere, Olea Medical, La Ciotat, France). Readers were blinded to the PSA, GS and cT values, as well as to NCCN risk stratification categories. The prostatic
findings were classified as cancer if corresponding to classes 4 and 5 according to the first version (before December 2015) [8] or the second version (after December 2015) [7] of the Prostate imaging reporting and data system (PI-RADS). For the first version, PI-RADS 4-5 classes were attributed for a sum of the scores of individual sequences equal or greater than 10, as detailed elsewhere [8]. PI-RADS 4-5 lesions were then staged according to a slightly modified version of PI-RADS v1 criteria as shown in Tab. 4, including broad capsular-tumour contact. Extracapsular extension (ECE) and seminal vesicle invasion (SVI) were considered to be present for a staging score equal or greater than 4 or in the case of clear invasion of adjacent pelvic structures. 

Data analysis In the target group, we used Cohen’s kappa statistic to calculate the agreement (i) between mpMRI and each nomogram and (ii) between nomograms in defining: 1) first, extraprostatic vs. intraprostatic disease; 2) NCCN risk categories (#low vs. intermediate vs. # high) obtained by combining PSA, GS and the T stage resulting from PT, MSKCCn and mpMRI, respectively. In the validation group we calculated sensitivity and specificity for extraprostatic disease using histology as a reference. Analysis was performed on a per-patient basis.
**Table 2:** clinical factor required for T staging with PT and MSKCCn

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**Table 3:** mpMRI protocol.

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Table 4: attribution’s criteria of stage # T3 in mpMRI.

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Results

Study population

Descriptive characteristics of the target group (patients addressed to EBRT) and validation group (surgical patients) are shown in Tab. 5. Patients showed well-balanced clinical characteristics and a comparable detection rate of extraprostatic disease of mpMRI.

In the validation group, sensitivity and specificity for pathological T#3 stage were 86.3% (95% C.I. 77.3-95.4) and 93.9% (95% C.I. 86.8-99.9), respectively. In particular, mpMRI missed three microscopic pT3a cancers and induced 2 false-positives.

Agreement in defining the T stage

The T stage was changed by mpMRI in about 40-45% of cases compared to nomograms, translating into a very low agreement (k = 0.13-0.18) (Tab. 6-8). On the contrary, there was moderate agreement between the nomograms (k = 0.53).

The main effect of mpMRI was to downstage extraprostatic into intraprostatic disease, especially when compared to the MSKCCn.

Agreement in risk group assignment

Based on the shift in T stage, mpMRI changed risk group assignment in 40% of patients compared to PT and 41% of cases compared to MSKCCn, corresponding to fair agreement in both cases (k = 0.32-0.38) (Tab. 9-11).

Compared to PT, mpMRI determined a balanced number of risk downgrading (n= 13) and upgrading (n= 15), whereas the prevalent effect compared to MSKCCn was to downgrade the risk (18 downgrading vs. 7 upgrading) (Tab. 9-11) (Fig. 1-2). In the majority of cases, there was a downgrading from high risk to intermediate risk.
Table 5: General characteristics of study population. Numbers near ratio represent C.I. 95%.

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Table 6: mpMRI vs. PT in assessing the T stage of Pca. Compared to PT, mpMRI determined a downstaging in 17 patients and an upstaging in 13 cases. The rate of change of T stage induced by mpMRI was 30/70 cases (42.8%; 95% C.I. 31.21-54.39), corresponding to a poor agreement between the two methods (kappa = 0.13).

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Table 7: mpMRI vs. MSKCCn in assessing the T stage of Pca. Compared to MSKCCn, mpMRI determined a downstaging in 26 patients and an upstaging in 5 cases. The rate of change of T stage induced by mpMRI was 31/70 cases (44.3%; 95%C.I. 32.66-55.94) corresponding to a poor agreement (kappa = 0.18).

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Table 8: PT vs. MSKCCn in assessing the T stage. The agreement between the two nomograms is moderate (kappa = 0.53), with upstaging in 17/70 cases (24.3%, 95% C.I. 14.25-34.35).

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Table 9: mpMRI vs. PT in risk stratification. mpMRI led to a downgrading of the risk in 13 patients and an upgrading in 15 cases. The rate of risk-induced change mpMRI was 28/70 cases (40.0%; 95%C.I. 28.52-51.48), corresponding to a fair agreement (kappa = 0.38).

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Table 10: mpMRI vs. MSKCCn in risk stratification. mpMRI led to a downgrading of the risk in 22 patients and an upgrading in 7 cases. The rate of risk-induced change mpMRI was 29/70 cases (41.4%; 95%CI. 29.86-52.94) corresponding to a fair agreement (kappa = 0.32).

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**Table 11:** PT vs. MSKCCn in risk stratification. The rate of risk-induced change mpMRI was 16/70 cases (22.9% %; 95%C.I. 13.06-32.74) corresponding to a substantial agreement (kappa = 0.61).

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**Fig. 1:** mpMRI staging of prostate cancer in a 74 years-old patient with a Gleason score 7 (4+3) cancer (3/10 positive cores) and PSA level 7.20 ng/ml. After prostate cancer staging (# T3 stage) and assignment of risk group, respectively, with Partin Tables (58%, high risk) and with Memorial Sloan Kettering Cancer Center nomograms (MSKCC) (62%, high risk), we performed the multiparametric MRI. It showed a lesion of about 11x7 mm of left middle peripheral zone, characterized by restriction of DWI (hyperintense signal at b-value 2000 (a) and its low signal ADC map (b) and hypointensity on T2WI(c, e, f) (PI-RADS 4). It does not appear hypervascular, after contrast agent administration as is observed in the subtracted images in (d). In the T2 weighted images in the axial (c), coronal (d) and sagittal plane (f) the capsular profile is preserved (stage T2 on mpMRI). mpMRI led a downgrading from initial "high risk" to "intermediate" one, with reduction of ADT timing associated with the RT (from 2-3 years at 4-6 months).

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**Fig. 2:** mpMRI staging of prostate cancer in a 79 years-old patient with a Gleason score 7 (4+3) cancer (7/12 positive cores) and PSA level 10.57 ng/ml. After prostate cancer staging (# T3 stage) and assignment of risk group, respectively, with Partin Tables (88%, high risk) and with Memorial Sloan Ketterin Cancer Center nomograms (MSKCC) (76%, high risk), we performed the multiparametric MRI. It showed a lesion of about 11x19 mm of right middle peripheral zone, characterized by restriction of DWI (hyperintense signal at b-value 2000 (a) and its low signal ADC map (b) and hypointensity on T2WI(c, d, e) (PI-RADS 5). It shows an early and intense contrast enhancement as is observed in the subtracted images in (f). In T2 weighted images in the axial (c), coronal (d) and sagittal plane (e) the capsular profile is preserved (stage T2 on mpMRI) with a downgrading from initial "high risk" to "intermediate risk".
Conclusion

· We observed no substantial agreement between mpMRI and PT or MSKCCn in stratifying patients' risk, with about 40% of changes in risk assignment.

· Changes in risk assignment have potential impact on EBRT, e.g. in terms of dose, clinical target volume, fractionation, and duration of ADT.

· As supported by high sensitivity/specificity in the surgical validation group, disagreement should be considered in favour of mpMRI as a risk stratification tool, at least in patients at higher risk.
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