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ROLE OF MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN PROSTATE CANCER ASSESSMENT

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SUMMARY – Multiparametric magnetic resonance is assuming an increasingly important role in the diagnosis, initial assessment and monitoring of patients with prostate cancer. This paper offers a more complex insight into the application of magnetic resonance imaging with prostate cancer, with a current literature overview. The focus is on the problem of initial prostate cancer evaluation which strongly affects further decision-making and therapeutic interventions. Clinical suggestions based on the current guidelines are also offered.

Key words: *Cancer staging; Diagnostic imaging; Guidelines; Magnetic resonance; Prostate cancer; Radical prostatectomy*

Introduction

The primary goal of prostate cancer (PC) assessment is disease characterization and the evaluation of disease extent (local and distant) and aggressiveness. Conventional strategies in the disease stage determination, and therefore the choice of therapy, have so far been based on the digital rectal examination (DRE), prostate specific antigen (PSA), quantitative and qualitative parameters of systemic biopsy, computerized tomography (CT), pelvic lymphadenectomy and bone scintigraphy (99mTc-MDP). Accompanied by risk stratification tools, these diagnostic examinations help the decision-making process regarding patient treatment. Unfortunately, such a paradigm underestimates the character, as well as the localization of the disease in 20-30% of cases[1].

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Discussion

What is the importance of determining the precise stage of the disease?

Precise determination of prostate cancer stage is essential for treatment planning. Digital rectal examination (DRE) still serves as a benchmark for clinical stage assessment, although it is known that it is highly inaccurate. The cancer spreading out of the prostate - extracapsular extension (ECE) and/or involvement of the seminal vesicles (SVI) - are the criteria of non-localized disease, classified as T3 according to TNM classification. Traditionally, such patients have been treated with radiation (EBRT) with or without hormone therapy. Today, there is a rising number of patients being treated surgically at this stage as part of the multimodal therapy approach, but there is also an increased need for more sensitive methods in detecting T3 disease.

Improper staging leads to:

a) Lack of confidence in the selection of active surveillance;

b) Insufficient treatment (undertreatment) and relapse in patients initially considered low-risk patients with favorable prognosis and localized disease;
c) Poor choice of patients for new focal treatment methods (HIFU, radiofrequency ablation, cryotherapy, etc.);
d) Poor choice of patients for nerve-sparing radical prostatectomy;
e) Poor selection of patients for extensive pelvic lymphadenectomy[2].

Precise stage determination is therefore crucial in conservative therapeutic approaches such as active surveillance, as well as in radical surgical treatments, especially regarding patient selection, choice of treatment method and the extent of therapy. It is clear that in the case of reliable determination of low risk and/or localized disease it is easier to decide and recommend active surveillance, HIFU or any of the other methods of focal therapy that are now in the research focus. On the other hand, in the case of reliable preoperative T3 disease findings, more radical surgical procedures can be planned, including extensive pelvic lymphadenectomy and avoiding nerve-sparing technique (at least on the side of the extraprostatic spread).

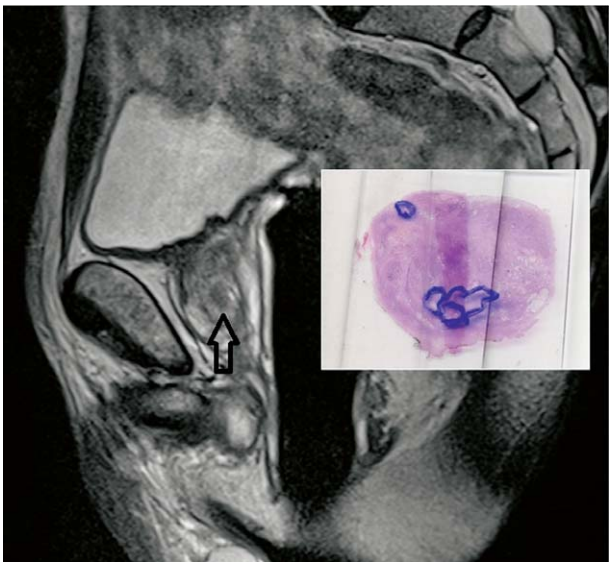

Fig. 1. Multiparametric magnet shows a localized index lesion limited within the prostate. Pathological finding after radical prostatectomy confirms localized cancer (index lesion), Gleason score 3+4, (cT2 stage) and one smaller, peripheral indolent lesion.

(Courtesy of: Assist. Prof. Monika Ulamec, MD and Karolina Bolanča, MD, Sestre milosrdnice University Hospital Center Zagreb).

Magnetic resonance and multiparametric magnetic resonance in prostate cancer staging

The role of multiparametric magnetic resonance imaging (mpMRI) today is extensively studied in patients:

- With an indication for biopsy,
- With an indication for repeated biopsy,
- With confirmed prostate cancer before treatment selection (staging purpose),
- During active surveillance to determine disease progression,
- After active treatment to detect recurrence[3,4,5].

Guidelines of the European Urology Association (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines do not give definite indications for the application of magnetic resonance imaging (MRI). On the other hand, both guidelines rather hypothesize on the role of this technique, especially in the high-risk disease[5,6].

Over the past decade, MRI has shown promising results for prostate cancer detection (Fig. 1). However, stage determination and detection of T3 disease are still a challenge, with the sensitivity and specificity range from 23 to 90% and 30 to 95%, respectively, which highly depends on patient selection and applied methods[7,8].

Although T2-weighted imaging was the main base for prostate MRI, it is known that this method is unspecific for cancer because low signal lesions in the peripheral zone can be the result of prostatitis, scarring or hyperplasia. Using additional MR recording techniques such as diffusion-weighted MR imaging, MR spectroscopy and dynamic contrast-enhanced MR imaging improve the overall specificity of the method. Such specialized sequences require time and experience. However, the results are better with 3-Tesla devices [9]. Recent meta-analysis concluded that MRI has good specificity for T staging, while the sensitivity is positioned within a very wide range[10].

A total of 75 studies (9796 patients) were analyzed. In the ECE group (45 studies, 5681 patients), SVI (34 studies, 5677 patients) and the complete detection of T3 stage (38 studies, 4001 patients) showed sensitivity and specificity of 0.57 (95% confidence interval [CI] 0.49-0.64) and 0.91 (95% CI 0.88-0.93), 0.58 (95%

CI 0.47-0.68) and 0.96 (95% CI 0.95-0.97) and 0.61 (95% CI 0.54-0.67) and 0.88 (95% CI 0.85-0.91), sequentially. Functional T2-weighted imaging and the use of higher field strength (3T) improved sensitivity for ECE and SVI, but even then the sensitivity is not greater than 0.63. ECE sensitivity did not improve with the use of endorectal coil[10]. Accordingly, it can be concluded that the MRI is not sensitive enough to detect all tumors with extraprostatic spread and as such, leaves a high level of clinical insecurity regarding the potential of exact local stage determination, especially compared to the usual clinical based classification models. Criticism of this meta-analysis stands in the fact that the analysis has taken into account all of the MR imaging techniques, while experiences with adding functional imaging are relatively new with a limited number of studies.

Individual studies with mpMRI have showed that its diagnostic accuracy overcomes nomograms. Gupta *et al*. showed that 3T mpMRI is superior to Partin's tables in small series (n = 60), low and medium risk patients (area under curve [AUC] 0.82 versus 0.62, P=0.04). mpMRI shows high quality in detecting localized (T2) disease (sensitivity 81.6%, specificity 86.4%, positive predictive value [PPV] 91.2%, negative predictive value [NPV] 73.1%) and ECE (sensitivity 77.8%, specificity 83.4%, PPV66.7%, NPV 89.7%)[11]. mpMRI consistently improves clinical models (Partin's table, Cancer of Prostate Risk Assessment [CAPRA] score, Memorial Sloan Kettering Cancer Center [MSKCC] nomogram) for ECE and SVI suggesting that a combination of clinical and radiological findings, at this point, gives the optimal diagnostic accuracy[12]. Feng *et al*. showed that the AUC for ECE increases when 3T mpMRI is added to Partin's tables (AUC 0.93 vs. 0.85, P=0.017) and MSKCC nomogram (AUC 0.94 vs. 0.85, P=0.023)[12]. Clinical applicability of mpMRI for preoperative staging varies depending on initial disease risk. In low risk patients, a high NPV is sufficient to exclude ECE, and due to the low probability of an unfavorable pathological finding, nerve-sparing prostatectomy or active surveillance would be a suitable choice. A relatively high proportion of false-negative mpMRI findings in intermediate-risk patients suggests that even without ECE at mpMRI, there is a significant risk (around 40%) of ECE in the final pathology finding after the surgery. Therefore, the NPV of 57.7% is not convincing enough and the burden of the decision-making falls on the surgeon, to avoid positive surgical margins during resection[13].

Focal and multifocal ECE

The ECE finding on mpMRI shows "an established ECE" with high reliability. This is defined as multifocal ECE or > 5 extracapsular glands. On the other hand, mpMRI cannot reliably detect focal ECE, which is associated with better prognosis and is not, or does not have to be, clinically significant. Detection of ECE also depends on tumor localization and prostate anatomy. Sensitivity for ECE detection is lowest on the apex (30%) and largest on the base (70.4%)[12].

Tay *et al*. emphasized the importance of specialized radiologist (uro-radiologist) for the mpMRI findings interpretation. Sensitivity and specificity of standard interpretation (77% and 44%) are significantly inferior to those observed by the uro-radiologist (86% and 81%) [14].

Influence of mpMRI findings on surgical plan

McClure *et al*. analyzed the changes of surgeons' decisions based on mpMRI findings. After the inspection of mpMRI findings surgical plans were changed in 27% of cases; 61% of these changes went from non-nerve-sparing towards nerve-sparing techniques, while 39% of the changes went from neurovascular bundle preservation to non-nerve-sparing technique. Positive surgical margins were found in only one patient, as a possible result of a false negative mpMRI. The authors concluded that expert mpMRI interpretation can reduce the morbidity of radical prostatectomy (nerve-sparing technique) with the preservation of oncological outcomes and a low positive surgical margins rate[15].

Tumors invisible on mpMRI

The clinical significance of MRI-invisible lesions remains unclear. It is comforting that 75% of missed Gleason 3+4 lesions had <10% of Gleason's grade 4[16]. De Visschere *et al*. reported 391 patients with elevated PSA and negative mpMRI. In 124 patients (31.7%) prostate cancer was diagnosed within 2 years. Most of these cases were Gleason 3+3 (67.7%); Gleason 3+4 (17.7%) and primary Gleason ≥4 (14.5%). High grade tumors (Gleason ≥4) that were missed were dominantly smaller in size (66.6% of 18 tumors <1 cm). About

96% of all missed tumors and 83.3% missed Gleason ≥4 were T2 (prostate restricted)[17]. The same authors also analyzed the causes of negative lesions on mpMRI and found that additional revision detected only 5 cases of truly invisible lesion in 18 missed findings and over half was technically insufficient.

Pathological interpretation of ECE

Beside the radiological T-stage disease determination, there is a problem with pathological findings. Even after radical prostatectomy, which is often considered the gold standard for pathological findings, the final pathology report is susceptible to a variety of interpretations. There are published interobserver kappa values for extracapsular spread detection among various pathologists that analyze prostate tissue which range from 0.33 to 0.63, and the results are approximately the same as the kappa values of 0.59 to 0.67 for different radiologists describing ECE on MRI[18,19].

Conclusion

In the light of the growing enthusiasm for the role of mpMRI in detection, staging and prostate cancer follow-up, we are exposed to a great amount of publications with offer contradictory findings. That is why the American Urology Association (AUA) Working Group 2017 published the Guidelines on mpMRI use [20]. In short, their conclusions related to the application of mpMRI for staging purposes are as follows:

- mpMRI results can be integrated with currently existing clinical staging systems of risk stratification;
- Therapeutic options, including surgical techniques, radiation planning and hormone treatment, can be modified according to improved radiological staging in relationship to clinical staging;
- The evaluation of lymph node involvement using MRI can be considered in selected patients (T3/T4 and T1/T2) combined with the risk predicting nomograms for lymph node involvement >10%. In that sense, MRI is considered to be equivalent to CT and positron emission tomography (PET);
- mpMRI/TRUS can present valuable information about the stage, when done before definitive local treatment. However, current accuracy in the staging did not show ability to exclude microscopic ECE or positive surgical margins [20].

In conclusion, it is important to be aware of the potential role of mpMRI in clinical practice, but also of the limitations of the technique in prostate cancer imaging, which can sometimes challenge the decision-making process. Further technological development in functional imaging, combined with molecular and genomic markers, as well as wider experience and expertise will continue to improve the treatment of prostate cancer.

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Sažetak

MULTIPARAMETRIJSKA MAGNETSKA REZONANCIJA U PROCJENI KARCINOMA PROSTATE

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Multiparametrijska magnetska rezonancija preuzima sve značajniju ulogu u dijagnostici, inicijalnoj procjeni, kao i praćenju pacijenata s karcinomom prostate. Ovaj rad nudi složeniji uvid u pitanje primjene magnetske rezonancije kod karcinoma prostate, uz pregled trenutne literature iz područja. Posebno težište je stavljeno na problem inicijalne procjene karcinoma prostate koje uvelike determinira daljnje odlučivanje i terapijsko postupanje. Ponuđene su i preporuke temeljene na trenutnim smjernicama.

Ključne riječi: *Dijagnostika; Magnetska rezonanca; Karcinom prostate; Radikalna prostatektomija; Smjernice; Stadij tumora*