REVIEW

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VESICAL IMAGING REPORTING AND DATA SYSTEM (VI-RADS), A NEW MODALITY IN BLADDER CANCER TREATMENT

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Summary

Bladder carcinoma incidence is on the rise making it the tenth most common and thirteenth deadliest carcinoma in the world. Transurethral resection of bladder tumor (TURBT) following a cystoscopy is the golden standard for diagnosis and treatment, despite it missing about 25% of muscle invasion of the bladder wall. This leads to understaging and increase of bladder carcinomas with unfavorable prognosis and elevating mortality. To avoid understaging a new and complementary method is needed. A new system called Vesical imaging reporting and data system (VI-RADS), based on multi-parametric magnetic resonance imaging (mpMRI) which suggests the probability of muscle invasion, could greatly improve diagnosis and treatment of bladder cancer.

KEYWORDS: *urinary bladder cancer, transurethral resection of a bladder tumor, Vesical imaging reporting and data system, multi-parametric magnetic resonance imaging*

BLADDER ANATOMY

The urinary bladder is a triangle-shaped, hollow organ, located in the lower abdomen. It is held in place by ligaments attached to other organs and the back of a pelvic bone. Its function is to store urine excreted by the kidneys via the ureters until micturition. It comprises the trigone (triangle shaped region near the junction of the urethra and the bladder), right and left lateral walls of the body, superiorly located apex or dome and posteriorly located fundus. The bladder wall includes three basic layers: mucosa, muscularis propria and perivesical fatty tissue. Mucosa incorporates urothelial cells and subepithelial connective tissue(1,2). Urothelial cells or specialized transitional epithelium up to seven cells thick, lay atop subepithelial connective tissue or lamina propria containing muscularis mucosae (thin, wavy smooth muscle fascicles associated with large, thin walled blood vessels). Underneath lays the muscularis propria, composed of two perpendicularly oriented inner and outer smooth muscle layers innervated by sympathetic and parasympathetic fibers to control voluntary urination. Muscularis propria contains aggregates of adipose tissue which merges with perivesical adipose tissue without a clear transition line between the two layers(2).

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BLADDER CANCER

Transitional epithelial cells are in contact with urine and therefore constantly exposed to potentially mutagenic agents filtered into urine through kidneys. This leads to the fact that 90% of all urinary bladder carcinoma originate from transitional epithelial cells and only 10% from squamous cells(3). Histologically, urothelial cell carcinomas are stratified into cancers with low and high-grade. Furthermore, high grade urothelial

cell carcinomas are then subdivided into ones that invade and do not invade the muscle. Non-muscle-invasive bladder cancers (NMIBCs) make only about one third of high-grade lesions, but they can progress into muscle invasive and metastatic type in about 20-25% of cases. Treatment of NMIBCs is aimed at reducing stage progression while maintaining close surveillance in order to detect muscle invasion and to preserve the quality of life. Muscle-invasive bladder cancers (MIBCs) are aggressive tumors whose prognosis depends on TNM staging system (2017, 8th ed)(2). Despite new modalities and the use of systemic treatment, overall survival rates from bladder cancer have not improved significantly over the last three decades. Average 5-year survival rate with bladder cancer is around 77% and is highly dependent on the stage at the time of diagnosis, since metastatic disease has a 5-year survival rate of less than 5%(3).

EPIDEMIOLOGY AND RISK FACTORS

Prevalence is on the rise, making it the tenth most common cancer on a global scale, with an estimated 550,000 cases diagnosed in 2018., with the absolute prevalence more significant in developed countries. This is possibly due to increased exposure to tobacco usage and industrial chemicals in more developed countries(3). Cigarette smoking as the most common risk factor is held responsible for more than half of all cases, with an average lag time of 20-30 years(4,5). Other risk factors include exposure to chemicals in paint, rubber and petroleum processing, fungicides, pelvic radiation and cyclophosphamide. A protozoal urinary tract infection (UTI), schistosomiasis, which promotes chronic inflammation, is linked to squamous cell carcinoma(3,6). Some recent studies show a less distinctive correlation between chronic cystitis caused by common bacterial pathogens and bladder cancer. They suggest an increased risk of transitional epithelial cells blader cancer in people with regular cystitis, but a protective effect on bladder cancer risk in people with a small number (<5) of UTI episodes treated with antibiotics. Possible explanation for this protective effect of antibiotics is in mediating the role of nitric oxide and its part in promoting tumour growth and proliferation(7,8). These findings furthermore highlight the important role of antibiotics in groups prone to chronic UTI such as postmenopausal women, elderly man and patients with ureteric stents and the use of JJ stents immersed in and coated with antibiotics(8,9). It is estimated that 80% of bladder cancers can be attributed to preventable risk factors(3,10). As smoking is more common in males, the incidence of urinary bladder cancer is about three to four times greater in male than female population. This trend is also observable in Croatia, with 752 new cases in male and only 267 in female patients in 2018(11). Although bladder carcinoma is the tenth most common type of cancer, it is only the thirteenth deadliest with an estimated 200,000 deaths from bladder carcinoma in 2018. Over ninety percent of all new bladder carcinomas in the United States are in people over 55 years, with the average age of diagnosis of 73(3,12). According to the WHO, the number of bladder cancer cases and deaths are anticipated to almost double in the near future owing to increased life expectancy over time(4,13). There are no national screening programs for bladder cancer.

CLINICAL PRESENTATION

In most cases bladder cancer is diagnosed after asymptomatic hematuria, causing 2 - 5% of microscopic and 10-20% macroscopic hematuria. Nonspecific symptoms, such as pollakiuria and dysuria, are associated with CIS (carcinoma in situ) of the bladder(14).

VESICAL IMAGING REPORTING AND DATA SYSTEM (VI-RADS)

The aim of this paper is to overview and try to quantify the role of Vesical Imaging Reporting And Data System (VI-RADS) in the bladder cancer diagnosis, staging and therapeutic response. Transurethral resection of bladder tumor (TURBT) following a cystoscopy is currently the golden standard in diagnosis and even definitive treatment method for most NMIBCs. Determining the presence of histological muscle invasion in bladder cancer gives us essential data for treatment planning and remains the cornerstone of bladder carcinoma diagnosis. The problem arises when TURBT serves as a sole diagnostic procedure for MIBC, as it is operator dependent and may miss up to 25% of muscle infiltrating cancers, leading to

understaging(2,15). This accentuates the use of multimodal approach in staging, employing TURBT and multi-parametric magnetic resonance imaging (mpMRI), as it reduces the risk of oversight and staging errors through better anatomical visualization of cancer invasion. Given its lack of radiation, MRI also provides us with numerous imaging opportunities of the same patient – prior, during and following treatment(2,16). mpMRI combines advanced imaging sequences including T2-weighted imaging (T2WI), diffusion weighted imaging (DWI) and dynamic contrast enhancement (DCE) which display different signal intensities from particular layers of the bladder enabling better differentiation potential and to assess overall risk of invasion score. T2WI sequence has high spatial resolution, which is useful in evaluation of the structural integrity of the detrusor muscle (muscularis propria layer). Detrusor muscle gives low signal intensity (SI) on T2WI, with intermediate SI on DWI and no early enhancement on DCE. Interruption of the low SI of the muscular line on T2WI could suggest muscle invasion (Fig 1). On DCE sequence the tumor and inner layer enhance early, sometimes at the same time and grade, simultaneously the muscularis propria layer remains as a low SI layer with no enhancement beneath the tumor(2,17). DWI shows hyperintense tumor SI with corresponding hypointense SI on ADC map (Fig 2). Muscluaris propria may give intermediate SI, while the stalk and inner layer have low SI on DWI. On the basis of different SI images on structural (T2WI), contrast enhancing (DCE) and DWI, categories with 5 grades, were formed(2,16,17). Combination of different grades of combined categories is then used to form a five point VI-RADS score. This score suggests the probability of muscle invasion. VI-RADS 1 and 2 categories have an unlikely muscle invasion, in VI-RADS 3 the presence of muscle invasion is equivocal, in VI-RADS 4 muscle invasion is likely and in VI-RADS 5 invasion of muscle and tissues beyond the bladder is very likely. The final score is primarily based on T2WI because of high spatial resolution in the evaluation of integrity of muscularis propria. Definitive muscular invasion

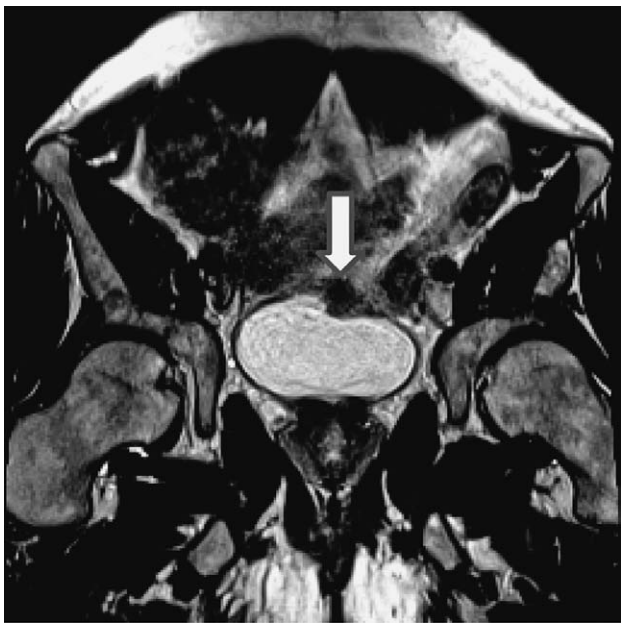

Figure 1. T2W image. Arrow points to the tumor which is of low intensity. Spread of the tumor through the muscular layer is clearly visible

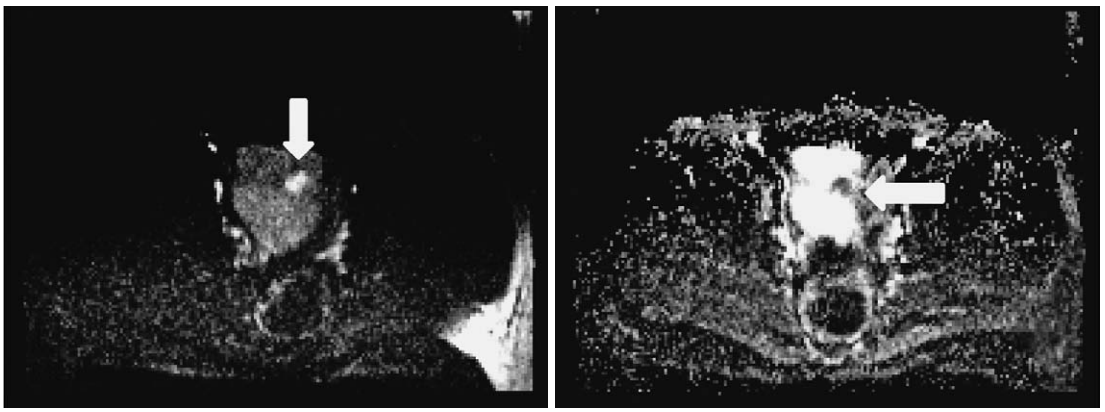

Figure 2. DWI (on the left) and ADC map (on the right). Urinary bladder tumor (arrows) of high intensity on DWI and of low intensity on ADC map depicting diffusion restriction characteristic for malignant lesions.

in ambiguous cases can be resolved by using DCE and DWI MRI sequences(2). In order for VI-RADS to be used universally it is necessary to standardize imaging conditions. High resolution scans of ≥3 Tesla with standardized protocols are necessary, also a number of considerations such as endpoint bladder distention or pharmacotherapy to address visceral motion artifact must be taken into account. In patients with post-neoadjuvant chemotherapy treatment, inflammation can cause fibrosis and irregular bladder wall thickening adding complexity in recognizing tumorous tissue(16). Use of artificial intelligence (AI) is more and more present in assessment of radiologic images due to tremendous progress in image-recognition tasks, recognizing complex patterns in imaging data and providing quantitative assessments of radiographic characteristics(18). Although mpMRI sequences are acquired in one go, image deformation on DW images with registration errors between different DCE volumes can occur due to patient movement potentially causing extreme changes in enhancement and influencing parameter estimation. Use of computer aided diagnosis systems (CAD), radiomics and AI can align each contrast enhanced frame to T2WI, which already led to its successful application in prostate cancer evaluation and in future is likely to be implemented in mpMRI evaluation of bladder cancers(18,19).

CONCLUSION

TURBT still remains the golden standard in diagnosis and treatment of bladder cancer. Given that about 25% of bladder carcinoma invasion of the muscle wall is missed by TURBT, an additional modality in diagnosis is needed. VI-RADS represents a very promising diagnostic tool using different MRI sequences to try and differentiate NMIBCs from MIBCs. At the moment its value lies predominantly in analysis of pre-TURB and pre-inflammatory changed walls of the bladder. Additionally, it gives us a very important complimentary method, improving diagnosis of MIBC while reducing radiation-based imaging. For MRI to claim a more important role in bladder carcinoma diagnosis and treatment in future years it has to be reproducible and feasible in the general hospital setting. For this reason authors of VI-RADS system ask for it to be tested, validated and refined where necessary in future years(2).

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Sažetak

VESICAL IMAGING REPORTING AND DATA SYSTEM (VI-RADS), NOVI MODALITET U LIJEČENJU KARCINOMA MOKRAĆNOG MJEHURA

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Incidencija karcinoma mjehura je u porastu te je danas deseti najčešći I trinaesti najsmrtonosniji karcinom na svijetu. Cistoskopska transureteralna resekcija tumora mjehura (TURBT) je zlatni standard u dijagnozi I liječenju, unatoč činjenici da ne detektira 25% slučajeva invazija mišića stjenke mjehura. To vodi do neadekvatnog *staging-a* tumora te povećanog broja karcinoma s nepovoljnom prognozom i povećanom smrtnošću. Kako bi se ovo izbjeglo nova i komplementarna metoda je potrebna. Novi sistem nazvan *Vesical imaging reporting and data system (VI-RADS*), koji se temelji na multi-parametrijskoj magnetskoj rezonanci (mpMRI) te procjenjuje vjerojatnost invazije mišića, mogao bi uvelike poboljšati dijagnozu i liječenje karcinoma mjehura.

KLJUČNE RIJEČI: *karcinom mokraćnog mjehura, transureteralna resekcija tumora mjehura, Vesical imaging reporting and data system, multi-parametrijska magnetska rezonanca*