Editorial Commentary

Bladder cancer under staging: still unavoidable?

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Magnitude of the issue

Under staging of locally advanced bladder urothelial cancer (BUC) is an important issue as far as it impacts the treatment and may hamper eventually the prognosis. It is particularly true for cT1 BUC as far as guidelines (1) provide also conservative treatment, which is indeed unfit to treat invasive cancer, leading to an impaired chance of surviving. Overall, under staging is not a rare phenomenon. It ranges up to 25% in specimen of second transurethral resection (2) and up to 50% in specimen of radical cystectomy (1,3) without significant improvement in the last decades.

How to deal with under staging

How may we overcome the issue? Basically, there is a consensus on performing always a restaging as indicated by guidelines (TUR) (1). About 10% of cT1 BUC harbour invasive cancer after a second TUR is performed, independently from operator experience and technicalities adopted during the first procedure (2). Contrast computed tomography (CT) scan and magnetic resonance (MR) are reliable tools for the detection of nodal or distant metastasis when muscle invasive or metastatic cancer is suspected (1). Indeed, MR is gaining an increasing role in the local staging of BUC. In 2018, the VI-RADS score has been implemented (4). VI-RADS is a five-point scoring system linked to likelihood of up staging to muscle invasive disease. A validation study showed promising results. Area under the receiver operating characteristic curve was 0.94, with a 95% CI of 0.9–0.98, whereas a VI-RADS score of 3 or greater had a sensitivity of 87.1% (95% CI: 78–93%) and specificity of 96.5% (95% CI: 93–98%), respectively (5). Clinical predictive factors of up staging may be also useful. Hydronephrosis at clinical presentation or lymphovascular invasion on TUR specimen are significantly linked with upstaging (3,6) as well as variant urothelial histology (micropapillary, nested, plasmacytoid, sarcomatoid) and prostatic urethral involvement (7) and should be considered when assessing a cT1 BUC.

Molecular staging and bladder cancer

Molecular staging is a relatively new approach, based on pattern of genes expression in specimen of BUC tumours, which may be encompassed in the general concept of the precision medicine. Up to date, basically, two main subtypes of BUC have been identified, luminal and basal, the latter associated with a worse prognosis (8,9). An alternative classification, based also on cell cycle alteration and markers of differentiation, includes the subsequent subtypes: urothelial-like (luminal), genomically unstable, basal-squamous, mesenchymal-like, and neuroendocrine-like subtype with most of the tumours belonging to the first three categories (10). As a matter of fact, BUCs are characterized by a discrete heterogeneity (10). Therefore, specimen used for subtyping analyses may only express one of the patterns which compose the entire tumour. Maybe this is the reason why, so far, concerns have been raised about usefulness of molecular subtyping at the present point of our knowledge (8). Its clinical impact has been retrospectively tested in patients with BUC. Basal BUC seemed linked with a

better response to neoadjuvant chemotherapy (11) whereas no association has been found between subtyping and radiation response in a population submitted to trimodal therapy for invasive BUC (12). The study of Lotan and colleagues is original as far as they investigated the link between upstaging after radical cystectomy and molecular subtyping (13). They retrospectively reviewed a cohort of patients submitted to radical cystectomy without prior neoadjuvant therapy. Overall 206 patients with cT1–2 patients were included in their analysis. One hundred had luminal subtype cancer and 106 non luminal. Non luminal patients had a significantly higher risk of up staging to pT3–4 disease (47% versus 24%). Moreover, adding molecular subtyping to clinical staging increased the area under the curve of their predictive model from 0.67 to 0.72. Probably, those findings may be translated to the subgroup of cT1 stage patients (87 subjects had a cT1 stage BUC and 31 were up staged to pT2–4 disease), making them extremely interesting.

Conclusions

Under staging of cT1 BUC is yet a relevant issue. It may occur frequently even using the best of our knowledge. The combination of different modalities may at least reduce significantly the likelihood of under staging, which may have catastrophic consequences, due to improper allocation of the patient to the wrong treatment. Molecular subtyping as well as VI-RAD score of a dedicated MRI, if confirmed in larger, prospective cohorts, may be the missing piece of the puzzle

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Alfred Witjes J, Lebret T, Compérat EM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol 2017;71:462-75.
2. Naselli A, Hurle R, Paparella S, et al. Role of Restaging Transurethral Resection for T1 Non-muscle invasive Bladder Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus 2018;4:558-67.
3. Turker P, Bostrom PJ, Wroclawski ML, et al. Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome. BJU Int 2012;110:804-11.
4. Panebianco V, Narumi Y, Altun E, et al. Multiparametric Magnetic Resonance Imaging for Bladder Cancer: Development of VI-RADS (Vesical Imaging-Reporting And Data System). Eur Urol 2018;74:294-306.
5. Wang H, Luo C, Zhang F, et al. Multiparametric MRI for Bladder Cancer: Validation of VI-RADS for the Detection of Detrusor Muscle Invasion. Radiology 2019;291:668-74.
6. Mitra AP, Skinner EC, Miranda G, et al. A precystectomy decision model to predict pathological upstaging and oncological outcomes in clinical stage T2 bladder cancer. BJU Int 2013;111:240-8.
7. Klaassen Z, Kamat AM, Kassouf W, et al. Treatment Strategy for Newly Diagnosed T1 High-grade Bladder Urothelial Carcinoma: New Insights and Updated Recommendations. Eur Urol 2018;74:597-608.
8. Satyal U, Sikder RK, McConkey D, et al. Clinical implications of molecular subtyping in bladder cancer. Curr Opin Urol 2019;29:350-6.
9. Seiler R, Ashab HAD, Erho N, et al. Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy. Eur Urol 2017;72:544-54.
10. Warrick JI, Sjödahl G, Kaag M, et al. Intratumoral Heterogeneity of Bladder Cancer by Molecular Subtypes and Histologic Variants. Eur Urol 2019;75:18-22.
11. Seiler R, Gibb EA, Wang NQ, et al. Divergent Biological Response to Neoadjuvant Chemotherapy in Muscle-invasive Bladder Cancer. Clin Cancer Res 2019;25:5082-93.
12. Kool R, João Mansure J, Kassouf W. Molecular subtyping, tumor infiltration, and trimodal therapy for muscle-invasive bladder cancer: more questions than answers. Transl Androl Urol 2019;8:S325-8.
13. Lotan Y, Boorjian SA, Zhang J, et al. Molecular Subtyping of Clinically Localized Urothelial Carcinoma Reveals Lower Rates of Pathological Upstaging at Radical Cystectomy Among Luminal Tumors. Eur Urol 2019;76:200-6.

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