Red patches during bladder cancer surveillance: to biopsy or not to biopsy?

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Editorial for *Translational Andrology and Urology* regarding:

Isolated Red Patches Seen During Endoscopic Surveillance of Bladder Cancer: Incidence of Malignancy and When Should We Biopsy?

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The causes of "red patches" (RPs) in the bladder are many and varied, ranging from minor cystoscope trauma and inflammatory lesions to carcinoma in situ (CIS). The diagnosis of the latter is crucial since CIS is a highly malignant lesion both molecularly and clinically [1], and is the single most important risk factor for progression to muscle-invasive disease in the EORTC non-muscle-invasive bladder cancer (NMIBC) risk tables [2]. Thus, in the context of NMIBC, urologists face a dilemma when red patches are observed during endoscopic surveillance: to biopsy or not to biopsy. This dilemma is magnified when one considers that previous data show a pick-up rate for malignancy of only 11.9% (although CIS was diagnosed in 78.3% of these malignant biopsies) [3], and that in the presence of concomitant tumour, there is a risk of tumour cell reimplantation at the biopsy site [4], thus potentially augmenting the risk of multifocal disease. Notwithstanding, the EAU guidelines for NMIBC recommend taking cold-cup biopsies from abnormal urothelium identified during transurethral resection (TURBT) [5]; the use of intravesical chemotherapy mitigates the potential risk of tumour cell reimplantation [6]. However, in the flexible cystoscopy surveillance setting the dilemma remains.

In a study recently published in the *Journal of Endourology*, Nkwam et al retrospectively reviewed 4,805 white light imaging (WLI) flexible cystoscopy reports to identify 241 episodes where solitary RPs had been identified in 183 NMIBC surveillance patients; 120 such RP episodes (49.8%) occurred in patients previously-treated with intravesical BCG [7]. Overall, 85 RPs (35.3%) were biopsied, and malignancy was found in 20 biopsies (23.5%). All positive biopsies were identified in patients previously-diagnosed with intermediate- or high-risk NMIBC; no low-risk NMIBC surveillance

patients, nor patients under the age of 67 years, had malignant histology following the biopsy of a RP. Importantly, 11 of the 20 malignant biopsies (55%, or 12.9% of all RPs biopsied) diagnosed CIS. Biopsies were undertaken by rigid cystoscopy under general/regional anaesthesia on 53 occasions (62.4%), and immediately at flexible cystoscopy on 32 occasions (37.6%). In the former, urothelial carcinoma (UC) and CIS were identified in 30.4% of biopsies, and for the latter in 18.8% of biopsies. It would be interesting to know if there was a department policy in determining the method of biopsy; for example, did prior intravesical BCG treatment or prior negative flexible cystoscopy biopsy increase the likelihood of biopsy by rigid cystoscopy? Or was rigid cystoscopy routine as first follow-up after BCG treatment for CIS, whereas flexible cystoscopy was undertaken later in the surveillance of recurrence-free patients where the likelihood of CIS per se was lower? Furthermore, urine cytology was not undertaken in any patient, as per the unit's policy; this is understandable, since the benefit of routine urine cytology is questionable [8;9], but it would have been informative to observe the relationship between malignant RPs and abnormal urine cytology. Other units operate a similar policy, but still collect a whole void urine sample pre-cystoscopy and subsequently request urine cytology if suspicious findings emerge from the cystoscopy (if not, the sample is disposed of). In intermediate- and high-risk NMIBC patients one should always be aware that the source of abnormal or malignant cytology could be WLI-invisible CIS or upper tract urothelial carcinoma (UTUC). In the future, DNA-based urine tests may improve diagnosis [10].

However, the comparison of the yield of malignant disease between rigid and flexible cystoscopic biopsy of RPs is probably the most interesting aspect of the study, with almost double the yield of malignant disease with rigid cystoscopic biopsy. The interpretation of the small biopsies achievable with flexible cystoscopes is challenging for histopathologists and so these findings are not unexpected, and there are inherent risks to spontaneous outpatient bladder biopsies due to the prevalence of concurrent diseases and antiplatelet or anticoagulant medication in the predominantly elderly UC population. Thus, in the WLI setting, should one surmise that RPs should only be biopsied

electively by rigid cystoscopy in the operating theatre? As a counterpoint, in Nkwam et al's study some NMIBC patients with RPs were scheduled for earlier follow-up flexible cystoscopy (4-6 weeks later) if biopsy was not undertaken; some of these patients did not undergo biopsy at this episode either, others did not return, and some no longer had an identifiable RP [7]. There is thus potential value in all patients with RPs being biopsied when the RP is first seen in the outpatient clinic.

Importantly, urologists now have access to optical image enhancement technologies (e.g. narrow band imaging, NBI, and photodynamic diagnosis, PDD, etc [11]). In the TURBT setting, evidence suggests that NBI and PDD are more sensitive than WLI for detecting CIS [12;13]. However, in the outpatient flexible cystoscopy setting, does the enhanced optical diagnosis of CIS by NBI or PDD outweigh the shortcomings of the small biopsy? Limited data would suggest that biopsies obtained during PDD-guided flexible cystoscopy are adequate for the diagnosis of Ta, T1a and CIS in 90-97% of cases [14;15]. Notwithstanding, the use of PDD in the surveillance setting with outpatient flexible cystoscopy is sparsely investigated. Feasibility studies have been successful [14], but the clinical relevance and benefits have not yet been thoroughly investigated. An ongoing Danish randomised controlled trial is currently investigating PDD-guided flexible cystoscopy NMIBC surveillance in the outpatient setting (DaBlaCa11) [abstract 1140 EAU2018], and the results are eagerly awaited. However, there are a number of potential limitations to PDD (e.g. catheterisation and instillation of the PDD agent, photo-bleaching and time limitations, inter-surgeon variability, cost, etc) that may mean its adoption in the outpatient setting is restricted to specialised centres or centres with a specific interest in PDD. NBI does not possess the same limitations, and its adoption in the outpatient NMIBC surveillance setting has been more rapid [16]. Furthermore, the utilisation of high definition (HD) cameras also appears to improve the diagnosis of abnormal lesions when compared to standard definition (SD) [17].

In summary, Nkwam et al have demonstrated that the incidence of malignancy in RPs identified during NMIBC surveillance in their study is higher than previously described, 23.5% [7] vs. 11.9% [3]. Could the use of HD WLI in the more recent study partly explain this considerable difference? The use of HD or SD is not specified in the publication. Malignancy was only identified in patients with previous intermediate- or high-risk NMIBC and in patients 67 years or older; the diagnosis of malignancy was considerably higher if biopsy was undertaken by rigid cystoscopy in the operating theatre (30.4% vs 18.8%). Other studies would suggest that if image enhancement technologies were to be used, then the diagnosis of malignancy from a suspicious RP would be higher [12;13], and that adequate biopsies can be obtained at flexible cystoscopy [14;15]. Thus, should we now conclude that when RPs are identified by WLI flexible cystoscopy in intermediate- and high-risk NMIBC surveillance patients then they should be biopsied by rigid cystoscopy in the operating theatre, but if PDD or NBI flexible cystoscopy are utilised then outpatient biopsy is appropriate and adequate? In favour of flexible cystoscopic biopsy is the omission of the time and cost of general or regional anaesthesia, especially if the patient has RPs and no tumour whereby, in the absence of a malignant cause, the RPs might have disappeared at the time of rigid cystoscopy. One can only recommend that urologists discuss the utility of flexible cystoscopy biopsies with their histopathology colleagues to reach a consensus on a unit-by-unit basis, and dependent upon the local availability of PDD or NBI.

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