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

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11

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13

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15

16 **Conflicts of interest:** JB Jensen and RT Bryan have contributed to advisory boards for Olympus
17 Medical Systems.

18

19

20 **Editorial for *Translational Andrology and Urology* regarding:**

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

23 Nkwam N et al. *J Endourol.* 2018 Feb 1. doi: 10.1089/end.2017.0744

24

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

39

40 In a study recently published in the *Journal of Endourology*, Nkwam et al retrospectively reviewed
41 4,805 white light imaging (WLI) flexible cystoscopy reports to identify 241 episodes where solitary
42 RPs had been identified in 183 NMIBC surveillance patients; 120 such RP episodes (49.8%) occurred
43 in patients previously-treated with intravesical BCG [7]. Overall, 85 RPs (35.3%) were biopsied, and
44 malignancy was found in 20 biopsies (23.5%). All positive biopsies were identified in patients
45 previously-diagnosed with intermediate- or high-risk NMIBC; no low-risk NMIBC surveillance

46 patients, nor patients under the age of 67 years, had malignant histology following the biopsy of a
47 RP. Importantly, 11 of the 20 malignant biopsies (55%, or 12.9% of all RPs biopsied) diagnosed CIS.
48 Biopsies were undertaken by rigid cystoscopy under general/regional anaesthesia on 53 occasions
49 (62.4%), and immediately at flexible cystoscopy on 32 occasions (37.6%). In the former, urothelial
50 carcinoma (UC) and CIS were identified in 30.4% of biopsies, and for the latter in 18.8% of biopsies. It
51 would be interesting to know if there was a department policy in determining the method of biopsy;
52 for example, did prior intravesical BCG treatment or prior negative flexible cystoscopy biopsy
53 increase the likelihood of biopsy by rigid cystoscopy? Or was rigid cystoscopy routine as first follow-
54 up after BCG treatment for CIS, whereas flexible cystoscopy was undertaken later in the surveillance
55 of recurrence-free patients where the likelihood of CIS per se was lower? Furthermore, urine
56 cytology was not undertaken in any patient, as per the unit's policy; this is understandable, since the
57 benefit of routine urine cytology is questionable [8;9], but it would have been informative to observe
58 the relationship between malignant RPs and abnormal urine cytology. Other units operate a similar
59 policy, but still collect a whole void urine sample pre-cystoscopy and subsequently request urine
60 cytology if suspicious findings emerge from the cystoscopy (if not, the sample is disposed of). In
61 intermediate- and high-risk NMIBC patients one should always be aware that the source of abnormal
62 or malignant cytology could be WLI-invisible CIS or upper tract urothelial carcinoma (UTUC). In the
63 future, DNA-based urine tests may improve diagnosis [10].

64

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

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

77

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

96

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

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