

## Determination of Bladder Cancer Risk in Long-term Catheterized Patients and Management of Diagnostic Process

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### Abstract

Bladder cancer is a rare but potentially lethal occurrence in long-term catheterized patients. When examining bladder cancer among long-term catheterized patients, physicians use the tools such as urinalysis, urine cytology, cystoscopy and random bladder biopsies to detect bladder cancer in this population, and to determine whether there is a role for screening and/or surveillance with any of these investigations. Although bladder cancer is a significant oncologic complication in this patient population, it is still controversial whether routine screening and/or surveillance of these patients is necessary. In this review, we will discuss how to determinate the risk of bladder cancer in long-term catheterized patients and how to manage the diagnostic process in these patients by the guidance of literature.

**Keywords:** Bladder cancer, Long-term catheterization, Neurogenic lower urinary tract dysfunction, Screening, Surveillance

### 1. INTRODUCTION

Bladder cancer (BC) is the 11th most commonly diagnosed cancer worldwide(1).Major risk factors are defined as tobacco smoking, occupational exposure to chemicals such as aromatic amines, pelvic radiotherapy, dietary intake of flavonols and lignans, bladder schistosomiasis, chronic urinary tract infection (UTI) and male gender(2).Also history of chronic indwelling foreign bodies like urethral and suprapubic catheters is accepted as another risk factor for urinary tract malignancies (3).Previous studies showed that usage of chronic indwelling catheters due to a neurological or non-neurological condition is associated with the increased risk of BC. In early literature the reported incidence of BC associated with a long-term indwelling catheter is 2.3 to 10%(4–9).These studies have suggested that the relative risk of a BC is 16–28 times that of a normal population but most of these studies were descriptive or cross-sectional studies(5,7,8). Recently, large series of BC diagnosis among spinal cord injury(SCI) patients estimate an incidence of 0.1–2.4%(8,10–14). Although patients with SCI are known as a high-risk group for BC, no

controlled prospective study has ever been published due to its low incidence rate (9).

Urinary retention and urinary incontinence are the two main indications for long-term catheters (15). SCI patients constitute the majority of long-term catheterized patients. Although clean intermittent catheterization (CIC) remains the gold standard for bladder drainage, it is not always possible. Poor hand function, aversion to being catheterized by others, impaired cognitive function, difficulty and trauma during catheterization and noncompliance are some limiting factors (16).Prior studies found that BC develops in patients with SCI earlier than normal, at a mean age of 48 to 61 years, and about 24% were diagnosed at less than 40 years old (10,14,17,18). Also, death ratio of the BC is shown to be increased in SCI patients. A previous study demonstrated that given the same age, gender and race/ethnicity, patients with SCI were approximately 6.7 times (95% CI 5.4-8.1) more likely to die of BC than the general population (19). Another study showed that the BC in SCI patients tended to be aggressive with 58.4% of the tumors presenting in Stage III or IV and 43% of the patients died of their tumor at a mean of 2.4 years after diagnosis (12).

There is consensus that SCI patients benefit from urological surveillance(20). Screening of SCI patients for BC is routinely recommended in many SCI management guidelines and by expert consensus; however, evidence for screening tools and protocols is lacking(10,21–23).Also, there is a lack of specific recommendations in the guidelines of the American Urological Association (AUA) and European Association of Urology (EAU) to address this issue.

On the other hand not only SCI patients, but also long-term catheterized non-SCI patients are shown to be at increased risk of developing BC (9). But there is lack of further studies investigating long-term catheterized non-SCI patients among the risk of BC. Large amount of studies on this topic have been done on SCI patients. Therefore, most of the recommendations related to urological surveillance are directed at SCI patients.

In this review we will discuss whether screening and/or surveillance of BC is necessary for long-term catheterized patients by the guidance of literature.

## **2. DISCUSSION**

Life expectancy for SCI patients is increasing due to innovations in management of this patient group. Therefore, the risk of developing BC is gaining importance. Since long-term catheterization and associated complications are major risk factors for BC, the same sensitivity should be observed in long-term catheterized non-SCI patients(8–12,14,24–26).

Multiple studies have been published examining the association between BC and SCI patients. These studies reported the incidences of 2.3–10% (4–9). However, reported incidence of most recent studies is 0.1–2.4% (8,10–14).In a large retrospective cohort involving 43651 SCI patients showed the incidence of BC estimated to be 0.11% (11). In another population-based study including 33565 SCI patients showed an incidence of 0.39% (14).According to the results of these recent studies, although the incidence of bladder cancer is not as high as in previous studies, it still has a remarkably high incidence and required attention should be given to this issue.

It has been shown that BC occurs at a younger age in SCI patients. In general population, the mean age at diagnosis of BC is 60–70 years (27). However, in SCI patients the mean age at BC

diagnosis is reported to be between 48 and 61 years (8,10,13,14,17,18,28,29).Also, squamous cell carcinoma (SCC) subtype is more common in these patients. In a study Bejany et al. reported a ratio of 81% for SCC subtype(7). In another study Stone hill et al. reported the prevalence of SCC as 59% (26). Similarly Subramonian et al. reported this prevalence as 50% (13). Although there are other studies reporting that transitional cell carcinoma (TCC) subtype is more common, the accepted thought is that SCC is widespread (11,28,30,31). The majority of bladder SCCs are high grade, high stage tumors with most cancers having muscle invasion at the time of diagnosis (32). SCC has been recognized as an aggressive tumor with a relatively unfavorable prognosis. Compared to TCC it is a rapidly growing infiltrative tumor (4). Prognosis for patients with SCC of the bladder is poor, and most die from their disease within 1–3 years of diagnosis (33).BC is a rare and potentially lethal occurrence in SCI patients. Physicians need to have a high index of suspicion for BC, particularly among patients managed with long-term indwelling catheters (34). Since these tumors are not screened properly, most of them were thought to be diagnosed in advanced stages however it is still controversial whether screening these patients is necessary.

In the literature, the possible risk factors for BC among this patient group are listed as follows: Long-term indwelling catheterization, frequent UTIs, frequent bladder stones, CIC, smoking, increased urine contact time and altered immunological function (9,10,26,35,36).

Chronic mechanical irritation and increased epithelial proliferation caused by the catheter balloon are thought to be responsible for the histological changes observed in patients with long-term indwelling catheters (36,37). Epithelial proliferation may increase susceptibility to environmental carcinogens (38). Keratinizing squamous metaplasia is a significant risk factor for the development of SCC. It has also been reported in association with other conditions that may be additive, such as bladder stone, bladder outlet obstruction and neurogenic lower urinary tractdys function (NLUTD)(39–42). Keratinizing squamous metaplasia is characterized by a replacement of the urothelial layer with the stratified keratinizing squamous epithelium due to chronic inflammation and/or irritation of the bladder mucosa. This is postulated to be a pre-malignant

condition leading to a higher risk of the development of BC, especially if dysplasia and/or extensive keratinization is present (43). The risk of developing BC in patients with keratinizing squamous metaplasia is high as progression has been reported 27% with a variable period of latency between 4 and 28 years (39). Squamous metaplasia of the bladder was significantly greater in patients who had been catheterized for more than 10 years (80%), compared to those catheterized for less than 10 years (42%) and patients without catheters (20%) (5). The prevailing belief is that indwelling catheters, particularly when used for >10 years, are a risk factor for BC (44–46).

Regardless of etiology, all patients with NLUTD are at increased risk for recurrent UTI compared to the normal population with an annual incidence as high as 20 to 25% (47). Urinary stasis due to elevated post void residual volume, high pressure voiding, urinary stone disease, vesicoureteral reflux, bladder over distension and presence of long-term indwelling catheters are postulated for the increased susceptibility to UTI in these patients (25). Close to 60% of SCI patients develop bacteriuria or UTI within the first year post injury, while 80% experience at least one UTI by their 16th year postinjury (48). Several mechanisms have been proposed to explain the association between UTI and BC. Frequently recurring or chronic UTIs seem to have an impact on carcinogenesis. Moreover, prolonged contact time with urinary carcinogens is a possible pathologic mechanism. Urinary retention and stasis may increase exposure of the bladder to urinary carcinogens (11,49). In addition, chronic inflammation of the bladder mucosa may increase absorption of the urinary carcinogens. Also, bacterial flora in the urine may contribute to the production of nitrites that are converted to carcinogenic nitrosamines (50–52). Endogenous generation of nitrosamines by UTIs could predispose to BC in these patients (53). In a study conducted by Davies et al. significant amounts of nitrosamines were detected in urine samples of SCI patients (54). In addition N-nitrosamine contamination of rubber products and urinary catheters is well documented (55,56). These results support the hypothesis that chronic UTI may have a role in the etiology of BC in SCI patients.

History of bladder stone is shown as a significant risk factor for BC (8,14,26). The possible mechanism is thought to be chronic and focal irritation of the bladder developing

changes in bladder mucosa (12). Also, bladder stones and recurrent UTIs can be both a cause and a result of each other. It is difficult to tell which one is the cause and which one is the result. However, the main pathology that triggers the process is thought to be urinary stasis and the presence of long-term indwelling catheters (12,25,49).

The effect of CIC on BC formation is controversial. In some studies it is reported that CIC is more suitable than indwelling catheterization in patients who require long-term bladder drainage as a means of minimizing the histological changes that occur in the bladder mucosa that may predispose and lead to malignant transformation (37,57). On the other hand it has subsequently been hypothesized that CIC promotes progression to SCC through a combination of direct catheter trauma, persistent bacteriuria and keratinizing squamous metaplasia (35,36,58–61). The reason behind this hypothesis is that inflammation from chronic urinary tract irritation, either from bacterial or parasitic infections, foreign bodies and bladder calculi, or chronic bladder outlet obstruction is implicated in the pathogenesis of SCC (4). Therefore, not only long-term catheterization, but also CIC is considered to be an important risk factor in BC formation.

Apart from all these described possible risk factors, the nature of NLUTD is thought to be predisposed to BC. Kalisvaart et al. mentioned that NLUTD itself might be a risk factor for the development of BC. In their study relevant histological findings were present even in 15% of the patients with NLUTD who voided spontaneously. Also over 50% of patients diagnosed with BC in their population did not have an indwelling catheter. This suggests that the NLUTD, not the indwelling catheter, may be the risk factor for BC (12).

In the literature screening and surveillance of SCI patients for BC is recommended by using different screening tools and protocols. Hamid et al. mentioned that screening may be performed with yearly urine cytology or yearly screening cystoscopy (38). Hess et al. has implemented surveillance cystoscopies in patients with prolonged indwelling catheters and unexplained microscopic or gross hematuria (29). Manuta et al. recommended using yearly cystoscopy and urine cytology in patients with NLUTD after 10 years of indwelling catheters or CIC (33). Sammer et al. suggested that

surveillance cystoscopy might be warranted, but the ideal starting point and frequency was not specified. They concluded that screening cystoscopy and cytology should be performed in every patient with NLUTD after 5 years every 1–2 years(43). Pannek et al. suggested every patient with an indwelling catheter for at least 5 years, or any patient with NLUTD and hematuria or with suspicious finding in ultrasound of the bladder to undergo cystoscopy and cytology. They mentioned that the combination of the two techniques could improve detection rates and lower the number of unnecessary biopsies(62). Kalisvaart et al. attempted to perform a yearly screening cystoscopy on all patients with indwelling catheters for any length of time, especially those who have had one in place for >10 years. They also performed a cystoscopy on any patient with hematuria, recurrent UTIs, or any other urologic complaints indicating need for a cystoscopy (that is, frequency, change in bladder functioning, clogging of catheter, etc) (12). Locke et al. suggest screening with annual urine cytology and, when positive, a complete urological evaluation(4). Navon et al. recommend annual cystoscopy starting 10 years following SCI and in patients with recurrent or chronic UTI(44). Chao et al. recommend cystoscopy and cup biopsy after 10 years of indwelling catheter drainage(63). In the Clinical Practice Guideline of Bladder Management for Adults with SCI it is recommended to conduct more frequent cystoscopic evaluations for individuals with long-term indwelling catheters than for those with no indwelling methods of bladder management (Scientific evidence-III, Grade of recommendation-C, Strength of panel opinion-Strong). But the intervals of the cystoscopic evaluations was not specified (22). In Veterans Health Administration Handbook for SCI and Disorders System of Care, the annual evaluation of genitourinary system included cystoscopy, cytology, and random bladder biopsy to be performed on a regular basis (21). In AUA Guideline for Asymptomatic Microhematuria in Adults, history of chronic indwelling foreign body was defined as a common risk factor for urinary tract malignancy in patients with microhematuria and performing a cystoscopy was recommended for these patients (3).

As seen in the literature, many different screening and surveillance protocols have been

proposed and implemented. However, the question is whether screening and/or surveillance for BC is necessary for long-term catheterized patients. Screening involves one or more tests performed to identify the potential for disease early when it is easier to prevent and possibly cure. Surveillance involves testing people who previously have had BC or who are at increased risk of disease(64). The medical community are now well aware of the components necessary for an effective screening test. The cancer must be common. Obviously if the cancer is common, then more of the individuals undergoing the screening test stand to benefit and fewer people undergo an unnecessary test. Less obvious is that a high prevalence decreases the false-positive rate, meaning that fewer people undergo unnecessary confirmatory tests. In addition, the test must detect cancers earlier than would be detected through usual care. Finally, early detection should allow for more effective cancer treatment, meaning lower cancer death rates(24). The general SCI population is at an increased risk of BC and eventual death from the disease. However, this risk is not high enough to warrant screening (24). In a study Hamid et al. did not recommend routine surveillance cystoscopy and biopsy in patients with NLUTD and long-term indwelling catheters due to high screening costs with low detection rate and associated morbidity (19,38). In another study Yang et al. demonstrated that in 500 individuals with SCI who used an indwelling catheter or CIC and were at least 5 to 10 years after injury, no cancers were detected by screening cystoscopy and they concluded that cystoscopy was not a valid screening test (65). Differently in a recent study Pannek et al. mentioned that whereas a general screening for bladder cancer in patients with SCI did not seem to be justified, surveillance in certain risk groups might be feasible(62). The Guidance issued by the National Clinical Guideline Centre for National Institute for Health and Care Excellence (NICE) analyzed cost-effectiveness of three monitoring strategies namely regular eGFR measurements, ultrasound and cystoscopy in the management of lower urinary tract dysfunction (LUTD) in neurological disease. It concluded that the three monitoring strategies are likely to be cost-effective. Despite acknowledging cost-effectiveness, NICE does not recommend cystoscopic surveillance in individuals with NLUTD in general with no specific recommendation for the high-risk group

managed with long-term indwelling catheters (20,66).

Although early studies recommend various screening and surveillance protocols for long-term catheterized patients, recent studies reveal that screening or surveillance protocols are not cost-effective. However instead of routine screening or surveillance protocols, near follow-up of selected patients with high risk factors for BC might be useful. As the first step high-risk patients should be well identified. Well established risk factors for BC in this population are indwelling catheters for >10 years, frequent UTIs, frequent bladder stones, smoking, male gender, purulent leakage around the catheter, macroscopic and/or microscopic hematuria (2,8,10,14,26,32,44,45). Evaluation of these high-risk patients with cystoscopy seems to be mandatory. Also, cytology and bladder biopsies might be added on cystoscopy if needed. In the presence of significant findings for BC, further diagnostic tools should be used and a complete urological evaluation should be done. However, in the presence of negative findings, surveillance with any diagnostic tool should not be recommended because of its cost. But patients should be well informed for the need of reevaluation.

### 3. CONCLUSION

Regardless of etiology, long-term catheterized patients are at high risk for BC. Although multiple screening and surveillance regimens have been described in the early literature, recent studies do not recommend routine screening and/or surveillance protocols for this patient group since they are not cost-effective. In this case, it might be more rational to select and evaluate high-risk patients for BC. Multicenter, prospective, randomized control trials should be instituted in earnest to define the high-risk factors in this patient population. Thus, usage of unnecessary cystoscopies and other diagnostic tools might be prevented and early diagnosis of high-risk patients might lead to a decrease in morbidity and mortality due to BC.

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