Spinal Cord Series and Cases (2020)6:55
https://doi.org/10.1038/s41394-020-0307-4

ARTICLE

Incidental bladder cancer at initial urological workup of spinal cord injury patients

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Received: 29 April 2020 / Revised: 13 June 2020 / Accepted: 16 June 2020

Abstract

Study design Retrospective descriptive study.

Objectives To compare histopathological findings and the long-term course of SCI patients with bladder cancer found incidentally at the initial urological workup to those diagnosed with bladder cancer many years after the onset of SCI.

Setting Spinal cord injury center in Germany.

Methods Data and follow-up of consecutive in- and out-patients with SCI admitted at a tertiary spinal cord injury center between January 1, 1998 and December 31, 2018 were screened retrospectively. All patients with acquired SCI were evaluated for pathological findings in the urinary bladder present at the time of SCI on the initial urological workup. Data of 37 long-term SCI patients from the same center with diagnosed bladder cancer and data of the general German population served as reference groups. Descriptive statistics were applied.

Results In total, four patients with bladder cancer at initial urological workup were assessed. They all had non-muscle invasive bladder cancer. Two of the patients were cystectomized 34 and 106 months after first bladder cancer diagnosis, due to relapsing tumor and progressive renal failure, respectively. In both cases no tumor was found in the resected bladder. All four patients are currently alive with no tumor and a mean follow-up of 105 months.

Conclusions In incidental bladder cancer observed at the initial urological workup after acquired SCI, the duration of SCI, at least in the first 5 years, does not noticeably contribute to a poor prognosis, i.e., progression to muscle invasive bladder cancer (≥T2) or a higher grading (G3).

Introduction

Bladder cancer is the tenth most common cancer worldwide and therefore not a very common disease [1]. Nevertheless, in recent years there has been growing evidence that spinal cord injury (SCI) patients are at higher risk of developing bladder cancer than the general population [2]. It is well documented that bladder cancer risk increases substantially after about 10 years of paralysis [3]. In addition, at the time of diagnosis, these SCI patients often already have a locally advanced bladder cancer, often with an unfavorable grading. This implies a considerably worse prognosis as compared with patients without SCI [4]. The mortality of SCI patients from bladder cancer increases considerably with the duration of paralysis [5]. Another important observation is that SCI patients are on average 20 years younger than patients in the normal population when bladder cancer occurs [6].

Nevertheless, bladder cancer in SCI patients is still a challenge for clinicians and basic scientists as well,

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Published online: 29 June 2020

although in the last years two remarkable observations were published: first, a study [7] which for the first time describes genetic differences (especially GATA3) in bladder cancer cases with and without neurogenic bladder dysfunction (mainly caused by SCI or spina bifida) and second a large study [6] of long-term SCI patients with bladder cancer treated without permanent indwelling or suprapubic catheterization but with the same poor outcome as SCI patients treated with permanent catheterization.

However, many questions remain open at present. Neither has the specific pathogenesis been sufficiently defined [8], nor have meaningful screening strategies been established [9, 10].

Therefore, the question of whether differences can be shown between SCI patients who already had bladder cancer at the onset of the SCI and bladder cancer in long-term SCI or the able-bodied population is clinically and with regard to basic research an important issue.

Methods

This is a retrospective descriptive study of SCI patients at the Centre for Spinal Cord Injuries at BG Klinikum Hamburg (BG Berufsgenossenschaftlich; Statutory Accident Insurance), a tertiary trauma hospital. The database, containing 7004 consecutive in- or outpatients between January 1, 1998 and December 31, 2018, was reviewed to identify SCI patients who presented with histopathological confirmed urinary bladder cancer at initial urological workup (i.e., commonly within the first eight weeks) after acquired SCI (details regarding the collected data and bladder cancer T category and grading see Table 1).

As part of the initial urological workup in SCI patients, a cystoscopy is performed to identify and, if necessary, to treat preexisting pathological findings in the urinary bladder like a diverticulum or strictures that could interfere with the therapy of neurogenic bladder dysfunction.

All SCI patients were regularly monitored in a system of "life-long surveillance" with neuro-urological check-up in risk-adapted intervals, at least every 2 years. Data were extracted from patient charts, entered into a database, and pseudonymized during entry. For reference, we used, first, recently published data of our database of 37 long-term SCI patients who developed confirmed urinary bladder cancer several years after SCI [6] and, second, urinary bladder cancer data of the general population in Germany in the years 1999–2016 provided by the German Centre for Cancer Registry Data at Robert Koch Institute in Berlin.

All bladder cancers were T categorized according to TNM classification as follows: CIS or Tis means very early, high grade cancer cells are only in the innermost layer of the bladder lining; Ta means the cancer is just in the innermost layer of the bladder lining; T1 means the cancer has started to grow into the connective tissue beneath the bladder lining; T2 means the cancer has grown through the connective tissue into the muscle; T3 means the cancer has grown through the muscle into the fat layer; T4 means the cancer has spread outside the bladder [11]. Grading of bladder cancers was performed as follows: Grade 1—The cancer cells look very like normal cells. They are called well differentiated. Grade 2—The cancer cells look less like normal cells (abnormal). They are called moderately differentiated. Grade 3—The cancer cells look very abnormal. They are called poorly differentiated. In recent years grading of bladder cancer has been also described as low grade or high grade. Low grade is the same as grade 1. High grade is the same as grade 3. Grade 2 can be split into either low or high grade. Carcinoma in situ (CIS) tumors are high grade [12].

Calculations regarding the frequency of the different T categories and gradings in the study group in comparison to the two reference groups ("long-term SCI patients with bladder cancer" and "bladder cancer data of the general population in Germany") as well as the Kaplan–Meier curves of these groups were performed using the statistical analysis software SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

All applicable institutional and governmental regulations concerning the ethical use of the data were observed. The ethics committee of the University of Lübeck (AZ 17-345A) and the Institutional Review Board (Institution for Statutory Accident Insurance and Prevention in the Health and Welfare Services, address: Pappelallee 33, 22089 Hamburg) both approved the study.

Results

Among 7004 SCI patients, 4 patients with histopathological proven bladder cancer, confirmed at the initial urological workup after acquired SCI, were identified. Therefore they were excluded from our previous study on bladder cancer as long-term sequela of SCI [6]. Demographic data, level of SCI, tumor category and grading, mode of bladder management, therapy, and long-term outcome as well as smoking habits and occupational bladder cancer risk factors of these four patients are summarized in Table 1.

Mean age at SCI and bladder cancer diagnosis was 65.5 years (median 64 years, range 52–82 years). All four patients had non-muscle invasive bladder cancer: 3 × pTa and 1 × pT1, all transitional cell carcinoma. The grading was 1 × G1 and 3 × G2. This differs considerably from our findings in SCI patients with bladder cancer after

Table 1 Data of four spinal cord injury patients with incidental bladder cancer at initial urological workup.

No.	Gender	Level of SCI, ASIA Scale	Age at SCI onset/tumor diagnosis (Years)	Weeks between SCI and tumor diagnosis	T category and grading	Bladder management	Therapy	Vital status	Follow-up (months)	Smoking (pack years)	Occupational bladder cancer risk	Notes
1	M	C4 D	82	4	pTaG2 low grade, TCC	Volitional	1. TUR-B 01/03/2014: pTaG2 low grade, 2. Re-TUR-B 02/17/2014: no tumor found	Alive	75	0	No	Subjective well-being, switched to permanent indwelling catheter 3 months ago
2	F	T12 C	64	4	pTaG2 low grade, TCC	Volitional, incontinence	1. TUR-B 05/11/14: pTaG2 low grade, 2. Re-TUR-B 03/05/2015: pTaG2 low grade, 3. Re-Re-TUR-B 06/08/2016: no tumor found	Alive	66	0	No	Double-J right, changes twice a year, subjective well-being
3	M	C5 A	52	6	pTaG1, TCC	IC-A (+CC) 5 years, Brindley (+CC) 4 years	1. TUR-B 10/16/2003: pTaG1, 2. Re-TUR-B 11/27/2003: no tumor found, CystE with IlCo 08/02/2012 (low compliance bladder, progressive kidney failure)	Alive	199	37	No	2012 CystE: no tumor found (106 months after first diagnosis), subjective well-being
4	M	C3 D	64	7	pT1G2 high grade + pTis, TCC	Volitional	1. TUR-B 08/30/2013 pT1G2: high grade + pTis, 2. Re-TUR-B 10/27/2014: pT1G2 high grade, 3. Re-Re-TUR-B 05/11/2016: pT1G2 high grade, prophylactic BCG instillation 12/2013–11/2015, rad. CystE with IlCo 06/16/2016	Alive	80	32	No	2016 rad. CystE: no tumor found (34 months after first diagnosis); subjective well-being

ASIA Scale American Spinal Injury Association impairment scale, *BCG* Bacillus Calmette–Guérin, *Brindley* sacral anterior root stimulation after sacral deafferentation, *CC* condom catheter, *CystE* cystectomy, *double-J* indwelling ureteral stent, *IC-A* intermittent catheterization by attendant, *IlCo* ileal conduit, *rad. CystE* radical cystectomy, *TCC* transitional cell carcinoma, *TUR-B* transurethral resection of bladder tumor.

long-term paralysis [6] and is comparable to the distribution of tumor categories and gradings in the general population (Fig. 1).

All four SCI patients with bladder cancer at acquired SCI survived without tumor progression with a mean follow-up of 105 months and are currently tumor free. This differs considerably from the poor prognosis in SCI patients with bladder cancer diagnosed after long-term paralysis but is comparable to bladder cancer cases in the general population (Fig. 2).

Two of the four study patients were cystectomized 34 and 106 months after first bladder cancer diagnosis. In one case, an increasing deterioration of renal function with low compliance of the bladder wall required cystectomy with application of an ileal conduit to establish a low-pressure drainage of the kidneys. In the other case, repeated transurethral resections showed several tumor recurrences and a prophylactic instillation treatment with Bacillus Calmette–Guérin was finally terminated due to intolerable adverse side effects. This patient underwent a radical cystectomy with urinary diversion via an ileal conduit. In both cases, the definitive histological examination of the resected bladder tissue showed no residual tumor.

The Kaplan–Meier curves of cystectomized patients with bladder cancer at acquired SCI and of cystectomized SCI patients with bladder cancer diagnosed after long-term paralysis illustrate the relevant survival advantage of SCI patients with bladder cancer diagnosis at initial urological workup of SCI patients (Fig. 3).

Discussion

To the best of our knowledge, this is the first presentation of a small series of SCI patients with bladder cancer diagnosed at the initial urological workup (i.e., commonly within the first 8 weeks after SCI). T category, grading of bladder cancer and course of four SCI patients are presented and compared with data from long-term SCI patients and the general population in Germany. Our findings are comparable to the general population in Germany, but in contrast to the unfavorable T category and grading, and consequently, the poor course of bladder cancer in patients with long-term SCI. The latter led the authors to the conclusion that SCI itself is important in inducing an aggressive form of this disease, as previously published [6].

Interestingly, in that study [6] as well as in the literature (see Reviews [2] and [3]), SCI duration of more than 10 years is an important issue for elevated bladder cancer risk. This is also in line with the youngest bladder cancer case ever published in a spina bifida patient, who was aged 13 years [13]. This is equivalent with a 43-year-old SCI patient with bladder cancer who was paralyzed at the age of

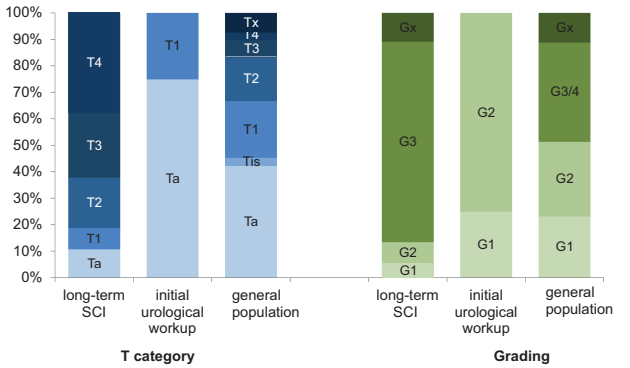

Fig. 1 T category and grading in three different groups of bladder cancer patients. Left column:long-term spinal cord injury patients. Middle column: spinal cord injury patiens at initial urological workup. Right column: general population in Germany (RKI [Robert Koch Institute] data 1999–2016).

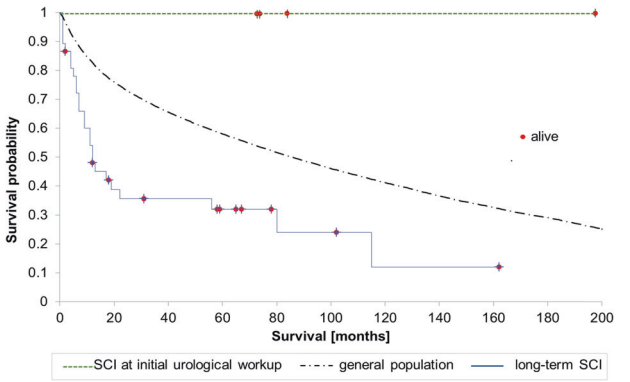

Fig. 2 Kaplan–Meier curves of three different groups of bladder cancer patients. Upper curve: spinal cord injury patients at initial urological workup. Middle curve: general population in Germany (RKI [Robert Koch Institute] data 1999–2016). Lower curve: long-term spinal cord injury patients.

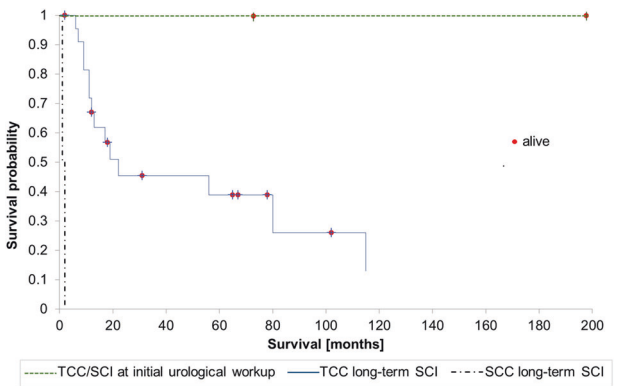

Fig. 3 Kaplan–Meier curves of three different groups of cystectomized patients. Upper curve: spinal cord injury patients with transitional cell carcinoma at initial urological workup. Middle curve: long-term spinal cord injury patients with transitional cell carcinoma. Lower curve: long-term spinal cord injury patients with squamous cell carcinoma.

30. In a recently published large single center study, based on 44 spina bifida patients aged 20 years or older, the range of ten bladder cancer patients was 27–43 years [14].

But what about the prognosis of bladder cancer incidentally observed at initial urological workup after acquired SCI? These cases were excluded from our previous study [6] as well as from many other studies [5, 15–20] because they could not have been induced by SCI.

This question focuses on the impact of SCI on bladder cancer that was already present at the onset of paralysis. Our results show striking differences compared with bladder cancer diagnosed in long-term SCI patients. The reported data indicate that an incidental bladder cancer observed at initial urological workup is obviously not influenced by bladder management of SCI patients at least within the first 5 years. It is highly interesting from clinical and basic research point of view observing the course of these cases after SCI duration of 10 years or more. Thus, the reanalysis and publication of all available published and unpublished cases which were observed within the first 10 years after SCI would be the next step to particularly back the role of genetically based differences as first described by Manach et al. [7].

Apart from its retrospective study design the number of patients observed is limited. Nevertheless, the results of this study support the hypothesis that long-term changes in the urothelium due to a combined effect of neurogenic dysfunction and clinically manifest urinary tract infection or clinically inapparent asymptomatic bacteriuria often accompanied with SCI may at least in part explain the aggressive behavior of bladder cancer after long-term acquired paralysis [6, 20]. The latter is in line with the findings in people with congenital SCI (spina bifida) [13, 14].

Conclusions

In incidental bladder cancer observed at the initial urological workup after acquired SCI, the duration of SCI, at least in the first 5 years, does not noticeably contribute to a poor prognosis, i.e., progression to muscle invasive bladder cancer (≥T2) or a higher grading (G3).

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgements We thank Dr. Kraywinkel, Robert Koch Institute, Berlin, Germany, for providing the bladder cancer data in the general population in Germany.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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