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REVIEW

Incidence of urological cancers in neurological patients: a review of the literature from the EAU Young Academic Urologist Functional Group

Fabiana CANCRINI [1] *, Nadir OSMAN [2], Steeve DOIZI [3], Cyrille GUILLOT-TANTAY [4], Tanja HÜSCH [5], Ester ILLIANO [6], Manuela TUTOLO [7], Antonio TIENZA [8], M. Gokhan CULHA [9], Luís VALE [10, 11], Nicholas RAISON [12], François HERVE [13], Pietro GRANDE [14], Morgan ROUPRET [15], Véronique PHÉ [3]

[1]Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University, Rome, Italy; [2]Department of Urology, Royal Hallamshire Hospital, Sheffield, UK; [3]Department of Urology, Tenon Hospital, Sorbonne University, Paris, France; [4]Department of Urology, Foch Hospital, Suresnes, France; [5]Department of Urology and Pediatric Urology, Medical Center, Johannes Gutenberg University of Mainz, Mainz, Germany; [6]Andrology and Urogynecology Clinic, Santa Maria Hospital, University of Perugia, Terni, Italy; [7]Unit of Urology, Division of Oncology, Urological Research Institute, IRCCS San Raffaele Hospital, Milan, Italy; [8]Department of Urology, Son Espases University Hospital, Health Research Institute of the Balearic Islands (IdISBa), Palma, Spain; [9]Department of Urology, Okmeydani Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye; [10]Department of Urology, CHS-João, Porto, Portugal; [11]Department of Biomedicine, Faculty of Medicine, University of Porto, Porto, Portugal; [12]Deptartement of Urology ST7, NIHR Guy's Hospital, King's College London, London, UK; [13]Department of Urology, Saint Luc University Hospital, Bruxelles, Belgium; [14]Department of Urology, Bicetre Hospital, Saclay University, Paris, France; [15]Department of Urology, Pitie-Salpêtrière Hospitals, Sorbonne University, Paris, France

*Corresponding author: Fabiana Cancrini, Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University, Via di Grottarossa 1035, 00189 Rome, Italy. E-mail: fabiana.cancrini@gmail.com

ABSTRACT

INTRODUCTION: Urological cancers can be challenging in the diagnosis and treatment of patients with neurological diseases. As a result, there are still uncertainties regarding the incidence and risk factors favouring the development of urological cancers in these patients. The aim of this study was to review the available evidence regarding the incidence for the development of urological cancers in neurological patients to provide a basis for future recommendations and research.
EVIDENCE ACQUISITION: A narrative review of the literature in Medline and Scopus up to June 2019 was performed.
EVIDENCE SYNTHESIS: After screening 1729 records, 30 retrospective studies were retained. For bladder cancer (BC), 21 articles were identified, including a total of 673,663 patients. Among these patients, 4744 had a diagnosis of BC (1265 females, 3214 males, gender not reported in 265). In this group, 2514 were diagnosed with BC associated with a neurological disease. For prostate cancer (PC), 14 articles were identified, including a total of 831,889 men. Among these patients, 67,543 had a diagnosis of PC and 1457 had PC and a neurological disease. Two articles reported kidney cancer (KC), one reported testicular cancer (TC) and none described penile cancer or urothelial carcinomas of the upper urinary tract in neurological patients.
CONCLUSIONS: The incidence of urological cancers, especially BC and PC, in patients with neurological diseases appears comparable to the general population. However due to the paucity of studies, specific recommendations for the management are lacking in neurologically disabled patients. In this report we investigated the frequency of urinary tract cancers in patients with neurological diseases. We conclude that urological cancers, especially bladder and prostate cancer, in patients with neurological diseases occur with similar frequency as in the general population.

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KEY WORDS: Urinary bladder neoplasms; Multiple sclerosis; Parkinson disease; Prostatic neoplasms; Spinal cord injuries; Urinary bladder, neurogenic.

Introduction

Urological cancers are one of the most common type of malignancy. Prostate cancer is the second most common cancer in men, with an incidence of 29.3/100,000 men, and comprises 7.1% of all cancer diagnoses.[1] Bladder cancer is four times more common in men than women, with an incidence of 9.6/100,000 among men and 2.4/100,000 among women worldwide.[2]

Neurological diseases are also very common and have increased in incidence over the past few decades. Multiple sclerosis (MS) is the leading cause of non-traumatic neurological disease worldwide. The incidence of MS in the US adult population was 450.1/100,000 women and 159.7/100,000 men in 2010.[3] Spina bifida (SB) has an incidence of 4.7/10,000 live births worldwide[4] and the incidence of Parkinson's disease (PD) is estimated to have increased between 1976 and 2005, particularly in men ≥70-years-old.[5] Every year, spinal cord injury (SCI) occurs in approximately 17,000 individuals in the USA, 80% of which are men.[6] Advancements in technology and routine check-ups have improved the life-expectancy of these patients which now approaches that of the general population,[6] exposing them to age-related problems, particularly the development of cancer.

Most of these neurological disorders lead to the development of neurogenic bladder dysfunction. Better understanding of urological cancers in neurological patients is of major interest to urologists, not just because lower urinary tract symptoms may be caused by cancer lesions which might be overlooked in these patients, delaying diagnosis, but also because management strategies should consider both neurological and urological disorders. The involvement of multidisciplinary teams will give patients the best treatment options, which may differ from those used in non-neurological patients.

The objective of this narrative review was to explore the incidence of urological cancers in neurological patients in order to identify possible differences between neurological and general populations. This is an important area that seeks to clarify the multidisciplinary management of patients with a combination of a neurological and urological disorder. In light of the progress made on the long-term survival of patients with neurological disorders, it may be important to define specific screening and long-term follow-up strategies for urological cancers in this subgroup of patients.

Evidence acquisition

Data sources and searches

A narrative review of the literature was performed using Medline, Scopus and Web of Science databases for relevant articles published from 1981 up to June 2019. Both medical subject headings and free text protocols were searched. The search was conducted by combining the following terms: 'Bladder, Cancer'; 'Neoplasm, 'Prostate', Kidney'; 'Renal Clear Cell Carcinoma'; 'Upper-Tract Transitional Cell Carcinoma'; 'Testicular' Cancer; 'Multiple Sclerosis'; 'Spina Bifida'; 'Spinal Cord Injuries'; 'Alzheimer's Disease'; 'Parkinson's Disease'. We also searched the reference lists of all included manuscripts and relevant review articles for other possible relevant studies. No date (time) restriction was applied, only articles published in English, French or Italian were considered for final analysis.

Study selection

Study selection was performed according to the PICO method for qualitative studies. We decide to proceed with a narrative review since randomized study were not available in this field.

All original studies that reported the incidence of urological cancers in neuro-urological patients were included. Case reports, case studies, commentaries, reviews, studies not published as full-text and those not discriminating between non-neuro-urological and neuro-urological patients were excluded. Each article's title and abstract were reviewed for their appropriateness and their relevance with regards to the relationship between urological cancers and neurological disease by two authors and a third ones resolved eventual discrepancies.

Data extraction, risk of bias assessment and data synthesis

The variables assessed included year of publication, type of study, type of cancer and incidence.

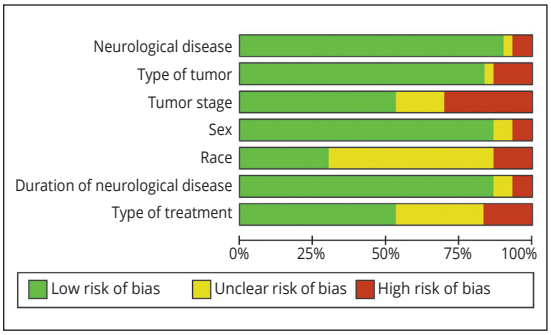

Figure 1.—Risk of bias assessment.

Relevant data regarding population characteristics and clinical presentation were also retrieved: population size, age, type of neurological disorder, gender. Finally, the level of evidence of each study was determined according to the Oxford Centre for Evidence-Based Medicine (2011). Data from eligible reports were extracted in duplicate and discrepancies were resolved by a third reviewer.

Risk of bias in non-comparative studies cannot be assessed with the Cochrane Risk of Bias Assessment tool used for randomized controlled trials.[7] Therefore, in non-comparative studies we addressed the external validity by assessing whether specified confounding factors were reported. A list of the seven most important potential confounders was compiled. For each study, we asked whether each confounder was considered and whether, if necessary, the confounder was controlled for in the analysis. The potential confounding factors were: underlying neurological disease (*e.g.* SCI, MS, etc.), type of tumour, tumour stage, gender, ethnicity, duration of neurological disease since onset and type of treatment (Figure 1, 2).[8-37]

Evidence synthesis

Bladder cancer

Among the 21 BC articles selected,[8-27, 37] a total of 673,663 patients were included. Of these patients, 331,018 (49.13%) had a neurological disease: SB (N.=9, 0.003%), MS (N.=7845, 2.3%), SCI (N.=206 519, 62.4%), PD (N.=116 642, 35%).

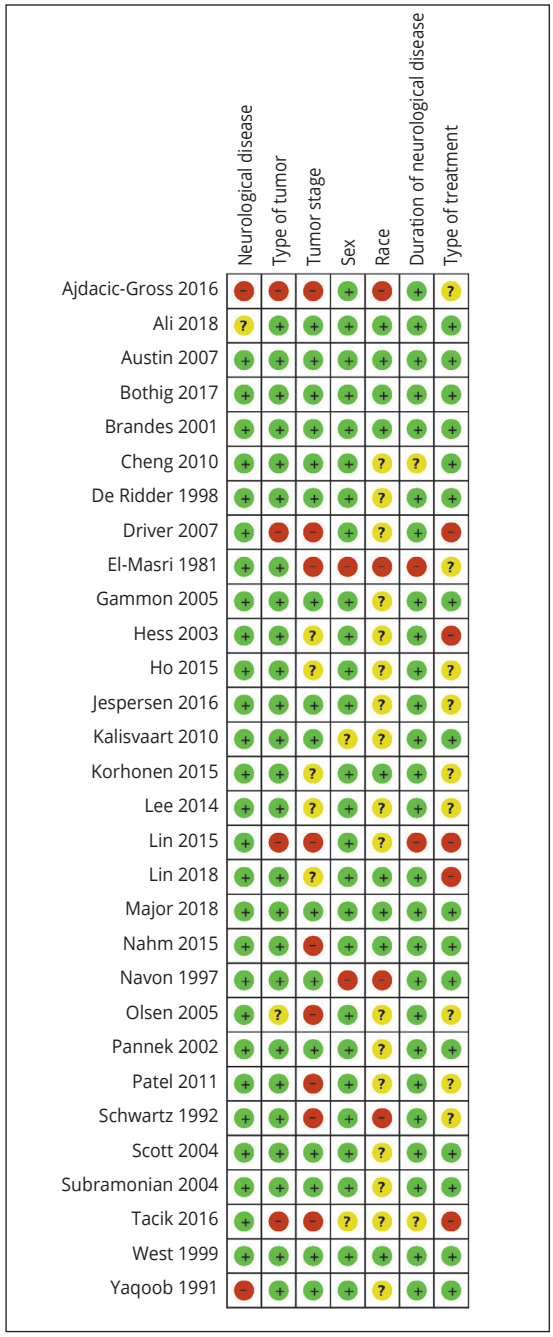

Figure 2.—Risk of bias sorted by article.[8-37]

From 4744 patients with BC, 2514 (52%) had also a neurological disease: SB (N.=9, 0.35%), MS (N.=30, 1.2%), SCI (N.=2305, 92%), PD (N.=167, 6.6%). Gender distribution of patients with BC was 1265 (26.7%) female, 3214

TABLE I.—*Epidemiology and incidence of bladder cancer in the included studies.*

Article	Type of tumor	Neuro-logical disease	Type of study	Sample size	Cases BCa	Incidence case	Incidence control	HR/ OR/ SIR	Female	Male	Gender NS	Median age
Ali 2018[8]	BC	NP	Retrospective	27	27	2-4%	2-4%		3	24	-	67.5
El-Masri 1981[9]	BC	SCI	Retrospective	6744	25	*0.3%	3%		NA	NA	25	<40
De Ridder 1998[10]	BC	MS	Retrospective	2351	7	0.29%	NA		2	5	-	58
Subramonian 2004[11]	BC	SCI	Retrospective	1324	4	*0.3%	NA		1	3	-	58
Hess 2003[12]	BC	SCI	Retrospective	16	16	NA	NA		0	16	-	61
Kalisvaart 2010[13]	BC	SCI	Retrospective	1319	32	*2.4%	NA		NA	NA	32	NA
Nahm 2015[14]	BC	SCI	Retrospective	45.486	99	*0.2%	NA	6.7	21	78	-	73
Yaqoob 1991[15]	BC	SCI	Retrospective	14	4	NA	NA		NA	NA	4	NA
Ho 2015[16]	BC	SCI	Retrospective	10.896	SCI 1816 Control 1816	0.88%	0.11%	5.74	SCI 544 Not-SCI 544	SCI 1272 Not-SCI 1272	-	47
Bothig 2017[17]	BC	SCI	Retrospective	6599	24	*0.36%	NA	6.7	3	21	-	57.67
Cheng 2010[18]	BC	SCI	Retrospective	2569	9	*0.35%	NA		NA	NA	9	56
Austin 2007[19]	BC	SB	Retrospective	8	8	NA	NA	NA	7	1	-	41
West 1999[20]	BC	SCI	Retrospective	33565	130	0.39%	NA		1	129	-	57.3
Navon 1997[21]	BC	SCI	Retrospective	14	14	NA	0.54		NA	NA	14	58.4
Pannek 2002[37]	BC	SCI	Retrospective	43561	37	0.11%	NA		8	29	-	53.3
Driver 2007[22]	BC	PD	Retrospective	974 (PD 487)	PD 3 Control 5	*0.6%	*1%	0.68	0	8	-	59.7
Lin 2015[23]	BC	PD	Retrospective	186.069 (PD 62.023)	NA	NA	NA	1.59	NA	NA	NA	NA
Olsen 2005[24]	BC	PD	Retrospective	14088	50	*0.35%	NA	0.52	NA	NA	50	72.8
Ajdacic-Gross 2016[25]	BC	PD MS	Retrospective	PD 39.066 MS 5.489	PD 92 MS 18	*PD 0.2% *MS 0.3%	NA	PKD 0.92 MS 2.19	NA	NA	110	NA
Tacik 2016[26]	BC	PD	Retrospective	1449 (PD 971)	PD 15 Control 6	1.5%	1.3%	0.88	NA	NA	21	67
Lee 2014[27]	BC	SCI	Retrospective	272.005 (SCI 54.401)	SCI 84 Control 403	*0.1%	0.18%	0.91	131 SCI 27 Control 194	356 SCI 57 Control 299	-	52.2
Total				673.663 Neurol. Pt 331.018 SB 9 MS 7845 SCI 206.519 PD 116.642	4744 Neurol. Pt 2514 SB 9 MS 30 SCI 2305 PD 167				1265	3214	265	58

AZD: Alzheimer disease; BC: bladder cancer; MS: multiple sclerosis; PD: Parkinson's disease; SB: spina bifida; SCI: spinal cord injuries. *Calculated.

(67.7%) male and 265 (5.5%) not reported (M:F ratio 2.5). Median age of the patients with BC was 58 years (Table I).[8-27, 37]

Prostate cancer

Fourteen articles[22-35] with a total of 831,889 male patients were identified. Neurological diseases affected 208,268 (25%) patients: Alzheimer's disease (AZD) (N.=128, 0.06%), MS (N.=5489, 2.6%), SCI (N.=55 401, 26.6%), PD (N.=47,250, 70.7%). Of the 67,530 patients diagnosed with PC, 1457 (2.15%) had a neurological disease: AZD (N.=43, 3.0%), MS (N.=17, 1.2%), SCI (N.=139, 9.6%), PD (N.=1258, 86.2%). Median age at diagnosis of PC was 71 years (Table II).[22-35]

TABLE II.—*Epidemiology and incidence of prostate cancer in the included studies.*

Article	Type of tumor	Neuro-logical disease	Type of study	Sample size	Cases PC	Incidence case	Incidence control	HR/OR/SIR	Median age
Lin 2018[28]	PC	AZD	Retrospective	8404 (AZD 128)	2101 AZD 43	2.10%	1.30%	1.52	74
Major 2018[29]	PC	PD	Retrospective	17.666	120 23/120 Entacarp. 97/120 Levodopa	*0.13% (E)	*0.54% (L)	1.08	71
Korhonen 2015[30]	PC	PD	Retrospective	11.396	359 154/359 Entacarp. 205/359 Levodopa	*1.3% (E)	*1.7% (L)	0.98	72.6
Schwartz 1992[31]	PC	MS	Retrospective	NA	NA	NA	NA	NA	NA
Jespersen 2016[32]	PC	PD	Retrospective	27.2574 (PD 1901)	PCa 45.429 PDK 245	*12%	*16%	0.73	72
Patel 2011[33]	PC	SCI	Retrospective	694 (SCI 350)	SCI 7 Control 18	2%	5%	NA	72
Scott 2004[34]	PC	SCI	Retrospective	2597 (SCI 636)	SCI 11 Control 919	1.70%	4.40%	NA	>50
Gammon 2005[35]	PC	SCI	Retrospective	PCa 16.878	SCI 14	NA	NA	NA	57
Driver 2007[22]	PC	PD	Retrospective	974 (PD 487)	PD 24 Control 34	*5%	*6.9%	0.74	59.7
Lin 2015[23]	PC	PD	Retrospective	186069 (PD 62.023)	NA	NA	NA	1.8	N.A
Olsen 2005[24]	PC	PD	Retrospective	14088	90	*0.6%	NA	0.74	72.8
Ajdacic-Gross 2016[25]	PC	PD MS	Retrospective	PD 39.066 MS 5.489	PD 430 MS 17	*PD 1.1% *MS 0.3%	NA	PD 1.41 MS 1.28	NA
Tacik 2016[26]	PC	PD	Retrospective	853 (PD 623)	PD 80 Control 24	12.8%	11.1%	1.1	67
Lee 2014[27]	PC	SCI	Retrospective	272.005 (SCI 54.401)	SCI 107 Control 671	*0.19%	*0.24%	0.73	52.2
Total				831.889 Neurol. Pt 208.268 AZD 128 MS 5489 SCI 55.401 PD 147.250	67543 Neurol. Pt 1457 AZD 43 MS 17 SCI 139 PD 1258				71

AZD: Alzheimer disease; PC: prostate cancer; MS: multiple sclerosis; PD: Parkinson's disease; SB: spina bifida; SCI: spinal cord injuries *Calculated.

Kidney cancer

Few data exist on KC in neurological patients. Based on the articles we found, the incidence of KC does not appear to differ between neurological patients and the general population (Table III).[26, 36]

Testicular and other urological cancers

Testicular cancer (TC) in PD patients was investigate by Tacik *et al.*;[26] the authors examined the incidence of various types of cancer in PD patients compared to healthy controls from the Mayo Clinic in Jacksonville, USA. They found

TABLE III.—*Epidemiology and incidence of renal and testis cancer in the included studies.*

Article	Type of tumor	Neuro-logical disease	Type of study	Sample size	Cases	Incidence case	Incidence control	HR/OR/ SIR	Median age
Brandes 2001[36]	KC	SCI	Retrospective	27	27	NA	NA	NA	59
Tacik 2016[26]	KC TC	PD	Retrospective	1.449	KC+ PD 10/971 KC + Contr. 2/478 TC + PD 2/623 TC+ Contr. 1/230	KC 1% TC 0.3%	KC 0.4% TC 0.5%	KC 1.54 TC NA	67

AZD: Alzheimer disease; KC: kidney cancer; MS: multiple sclerosis; PD: Parkinson's disease; SB: spina bifida; SCI: spinal cord injuries; TC: testis cancer.

two cases of TC among 623 patients with PD *vs*. one case of TC in 230 control patients. Since the incidence was below 0.3% the OR was not calculated (Table III).[26]

We were not able to find any prospective or retrospective studies on the incidence of penile cancer or urothelial carcinomas of the upper urinary tract in neurological patients.

Discussion

In this narrative literature review we evaluated the incidence and of different urological cancers in patients with neurological disorders.

Trends for BC primarily reflect smoking patterns, in addition to occupational or environmental exposure. Furthermore, smoking is very common in neurological patients,[38] probably because of their social and economic status and the psychological aspect of this habit.[39] The majority of patients with a diagnosis of BC included in this review were male. The most represented neurological disease in our review, was SCI (62%). The first reports of an association between BC and SCI appeared in 1961, but these data have been refuted in more recent epidemiological studies.[40] Nevertheless, BC tends to be diagnosed at a more advanced pathological stage and a younger age in SCI patients than in the general population. Several specific risk factors have been identified in SCI patients including indwelling catheters (ICs), UTIs and bladder calculi.[41] Most investigations have explored the role of ICs as a possible independent risk factor for BC development in SCI patients and recent data support this theory, particularly when ICs are used for ≥10 years.[16]

In SCI patients the presenting symptoms of BC may be atypical and early recognition is often challenging. A single episode of hematuria, investigated by cystoscopy, may miss lesions which resemble inflammation, but rapidly evolve into BC. Symptoms of an overactive bladder may induce the physician to look for BC.

Rare histologically sub-types of BC may be also missed during cystoscopy when performed by urologists having no experience with neurological patients. Currently there are no screening tools available for histological sub-types of BC, cytology is not useful, due to the presence of inflammatory artefacts, and cystoscopy can be challenging and is usually performed too late. Due to the lack of specific recommendations for BC treatment in this patient subgroup, it may be more appropriate to refer to a centre experienced in both uro-oncology and neuro-urology, especially in the case of muscle-invasive disease. Cystectomy and urinary diversion may have a great impact on a patient's level of disability and quality of life (QoL), multidisciplinary decision making by dedicated staff may improve the outcomes of surgery and the same may apply to the application of chemotherapy.

Male neurological patients, due to increased medical support and life-expectancy, especially in highly developed countries, are faced with the same disease as the general male population.

In our review, the most represented neurological disease in patients with PC was PD (71%). The incidence of PC in PD patients was around 0.8%, which is lower than that in non-PD patients. A study by Magnon *et al.*[42] tested the hypothesis that prostate tumours are infiltrated by autonomic neo-nerves that affect cancer development and dissemination. They found that the autonomic nervous system exerts a dual function in PC: sympathetic neo-nerves promote early stages of tumour genesis while parasympathetic nerve fibres promote cancer dissemination. These finding may explain the lowest incidence of PC in PD patients receiving medical treatments.

The second biggest population in the PC group was SCI patients, with a 0.25% incidence of PC. The 2018 review of Barbonetti *et al.*[43] on "Risk of prostate cancer in men with spinal cord injury" confirms the lower incidence of PC in SCI patients. Accordingly, the large between-study heterogeneity of serum prostate specific antigen (PSA) levels makes this marker a poor reliable screening tool for PC following SCI. Additional reasons for avoiding screening SCI patients for PSA include the perception that chronic inflammation and catheterization frequently yield falsely elevated PSA levels in these patients. The interruption of neural pathways to the prostate has been suggested to be a possible mechanism underlying the lower risk of PC in individuals with SCI.[44] The low cancer detection rate and higher incidence of higher grade and higher stage pros-

tate malignancies in SCI patients raise the suspicion that this population has not experienced the stage PC migration observed in the general population participating in PC screening programs.

On the basis of QoL comparisons between patients with SCI and PC *vs*. SCI alone, we need to consider the consequences of PC treatment. Radiotherapy or focal treatments seem to be better tolerated than surgery, especially in terms of the reduced risk of subsequent urinary incontinence[45]. Radical prostatectomy could be more challenging due to comorbidities and reduced patient mobility (*e.g.* tetraplegia), although possible bladder sequalae after radiotherapy should not be ignored.

Gammon *et al.*[35] hypothesized that the technical aspects of surgery would be compromised in neurological patients and reported higher intraoperative bleeding and a higher rate of postoperative complications in SCI patients treated by radical prostatectomy. Despite this, these data may not reflect reality as they come from a retrospective open prostatectomy series performed in the late 1990s and surgical techniques have evolved considerably over the last 20 years. Nevertheless, the major concern regarding surgery in these patients remains urinary continence, which is not just a psychological problem but could become a medical problem due to the increased risk of bedsores in incontinent neurological patients. Management of postoperative urinary incontinence is therefore of utmost importance.[46] Although incontinence may seem a better option compared to retention, patients with an underactive bladder still need ISC as they will suffer incontinence associated with chronic urinary retention. The artificial urinary sphincter in this group of patients is at higher risk of erosion due to the trauma induced by ISC,[47] therefore containment with uro-condoms or a suprapubic catheter may be preferable.

Due to the lack of data it is difficult to define the risk of KC in neurological patients although the few available data found no difference compared to the general population.

With regard to TC, it appears that adults with SCI are at greater risk of developing epididymal-orchitis than able-bodied individuals.[48] These authors found that 38.5% of SCI patients had suffered at least one episode of epididymal-orchitis. The diagnosis of testicular tumours in this group of patients may therefore be delayed.

Implications for practice

The incidence of neurological disorders is increasing in developed countries due to improvements in medical care and assistance and the increase in average age of the population. Considering these factors, neurological patients that used to die from complications of neurological diseases are now experiencing the same cancer risk as the general population. The occurrence of urological cancers in neuro-urological patients appears to be similar to that in the general population. However, some groups of patients such as SCI patients have a higher incidence of aggressive BC and PD patients have a lower incidence of PC.

Follow-up of these patients should focus on both the specific risk and general risk, for example SCI patients should be followed for BC more than other groups, while all neurological patients should be monitored for urinary function with blood tests and ultrasound. This should help with the early diagnosis of KC in order to minimize the risk of progression and complications. Surgery for BC and PC should be discussed by multidisciplinary neuro-urology and oncology boards, due to its impact on a patient's QoL. The latest EAU guidelines on neuro-urology[49] only suggest follow-up for these patients, due to the increased incidence of muscle invasive BC in neuro-urological patients.[40] The exact frequency of cystoscopy with or without cytology remains unclear, as is the frequency and type of follow-up for other urological cancers. The advent of new technologies, as robotic surgery, still needs to be investigated in this particular population, focusing on accessibility, safety data, gender gap, costs and learning curve.[50]

Further studies are needed to assess the incidence, risk factors and prognosis of urological malignancies in neurological patients.

Limitations of the study

Some limitations of the study need to be addressed. In this review we focussed specifically on the incidence of different cancers in neuro-

logical patients without considering the possible confounders such as the impact of different medical treatments for neurological diseases on oncogenesis, and without specifying the effective presence of neurogenic bladder diagnosis. Furthermore, a subgroup analysis of the impact of every neurological disease on every type of cancer, and on cancer stratification, was not possible due to the lack of available studies. An additional limitation was the retrospective nature of most studies included.

Conclusions

Although the risk of urological cancer in neuro-urological patients seems to reflect that in the general population, there is a lack of high-quality evidence to substantiate this. Further, prospective, studies are needed to verify our conclusion, in order to define early detection strategies and follow-up of this population, perhaps also by focusing on less representative neurological disease, and specifying the presence of neurogenic bladder. Management strategies should consider both neurological and urological disorders.

Take-home messages

The incidence of urological cancers, especially BC and PC, in patients with neurological diseases seems not to differ from that in the general population. Still due to the paucity of studies, recommendations for the management are lacking in these neurologically disabled patients. The inclusion of neurological patients in oncological clinical trials would be reasonable in the future, since this population is increasing and experiencing the same types of cancer as non-neurological patients. We need to understand whether new therapies have the same efficacy and tolerance in neurologically disabled patients.

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