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ORIGINAL ARTICLE

Erectile Dysfunction

Erectile dysfunction in nonmuscle-invasive bladder cancer patients before and after transurethral resection (TUR) of bladder tumor in China

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The aim of this study was to investigate the incidence of erectile dysfunction (ED) in nonmuscle-invasive bladder cancer (NMIBC) patients before and after transurethral resection (TUR) in China. Clinical data from 165 male patients with NMIBC who received adjuvant intravesical chemotherapy after TUR in Neijiang First People's Hospital (Neijiang, China) between January 2010 and June 2019 were retrospectively reviewed. The sexual function of these patients was evaluated before and 1.5 years after initial TUR by the International Index of Erectile Function-5 (IIEF-5). An age-specific subanalysis was performed among the patients: <45 years old (Group 1, $n = 19$) and ≥ 45 years old (Group 2, $n = 146$). Before and 1.5 years after TUR, the incidence rates of ED in Group 1 were 15.8% and 52.6%, and those in Group 2 were 54.1% and 61.0%, respectively. The difference between groups was statistically significant at the preoperative stage (15.8% vs 54.1%, $P = 0.002$) but not at the postoperative stage (52.6% vs 61.0%, $P = 0.562$). Compared with the preoperative stage, the incidence of ED at the postoperative stage was increased significantly in Group 1 (15.8% vs 52.6%, $P = 0.017$) but not in Group 2 (54.1% vs 61.0%, $P = 0.345$). In conclusion, the incidence of ED increased in male NMIBC patients under the age of 45 years after TUR in China. These patients should be offered professional counseling during the follow-up period.

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Keywords: erectile dysfunction; male sexual dysfunction; nonmuscle-invasive bladder cancer; transurethral resection

INTRODUCTION

Bladder cancer is one of the most common types of neoplastic disease in the urinary system in China.¹ Its incidence has been increasing, and the disease has a high rate of recurrence, particularly among males.² With the popularization of physical examination, an increasing number of early-stage bladder cancer patients can be detected.³ Transurethral resection (TUR) of bladder tumors plus intravesical therapy is the standard treatment for nonmuscle-invasive bladder cancer (NMIBC).

In addition to the tumor therapy itself, quality of life (QoL) should also be addressed during the entire treatment and rehabilitation process. Sexuality, an essential component of QoL, is an important evaluation index for QoL.⁴ It has been reported that any malignant pelvic tumor or required treatment, such as radical resection and/or radiotherapy, can eventually result in sexual dysfunction.⁴ Most of the present data on changes in sexual function, however, were obtained from muscle-invasive bladder cancer (MIBC) patients.⁵ Irreversible sexual dysfunction caused by radical treatment was observed in the majority of these MIBC patients.⁶ Scarce data available on NMIBC patients have come to a similar conclusion that tumor treatment may also have a detrimental impact on the sexual function of patients with bladder cancer.^{7–11}

To date, no information has been available on the change in sexual function of NMIBC patients in China, a relatively traditional nation

with conservative sexual attitudes. Thus, the present study aimed to investigate whether TUR and adjuvant intravesical chemotherapy will influence sexual function in male patients in China. We studied changes in sexual function by comparing the incidence of erectile dysfunction (ED) at various intervals among such patients. ED, which was once known as male impotence, refers to a man's inability to have or maintain an erection; this phenomenon leads to high pressure on both himself and mutual relationships, thereby decreasing the individual's self-confidence.¹²

PATIENTS AND METHODS

The inclusion criteria were as follows: (1) married male patients who underwent TUR in Neijiang First People's Hospital (Neijiang, China) from January 2010 to June 2019; (2) patients diagnosed with NMIBC; (3) patients who underwent perfusion chemotherapy regularly after the operation; and (4) patients who were willing to participate in this study. The exclusion criteria were as follows: (1) patients with incomplete personal information; (2) patients suffering from other types of malignant tumors; (3) patients treated with radiation and/or chemotherapy and/or hormonotherapy prior to his visit; (4) patients with preoperative psychological disorders; or (5) patients who suffered recurrence within 1.5 years after TUR.

Based on the abovementioned criteria, 165 male patients were enrolled in this study. A total of 29.1% (48/165) of patients were

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diagnosed with high-risk¹³ (CIS/T1/pTa G3) NMIBC after initial TUR. Among these 48 patients, 43 received TUR for the second time within 4–6 weeks after the first time, and the remaining 5 patients underwent initial TUR only.

The 165 NMIBC patients were divided into two groups based on their age, including Group 1 (19 patients who were <45 years of age) and Group 2 (146 patients who were ≥45 years of age). For each patient, the following clinical factors were collected: age, level of education, body mass index (BMI), number of lesions, tumor size, tumor grade, hypertension, diabetes, chemotherapeutic agents, second TUR, preoperative Zung Self-Rating Anxiety Scale (SAS) score,¹⁴ and 1.5-year SAS score after initial TUR. Patients were regarded as drinkers or smokers if they drank or smoked in the year before TUR. Patients were considered to be hypertensive patients if they needed medications to control hypertension.

Zung's SAS is a norm-referenced scale that enjoys widespread use of a screener for anxiety disorders.¹⁴ Participants are instructed to give their answers based on their experiences over the last week. The Zung's SAS includes 20 questions scored on a scale ranging from 1 ("none or a little of the time") to 4 ("most or all of the time"), resulting in a total score ranging from 20–80.¹⁴ In this study, we used Zung's SAS to assess the anxiety of these patients and classified them into the following groups: normal (≤49), light anxiety (50–59), moderate anxiety (60–69), and severe anxiety (≥70).¹⁵

The sexual function of these patients was evaluated by the International Index of Erectile Function-5 (IIEF-5) questionnaire developed by Rosen *et al.*¹⁶ If the score was <21, ED was diagnosed. The SAS and IIEF-5 questionnaires were administered before and 1.5 years after initial TUR. After gaining understanding of the contents of the scales, the patients were required to fill in all scales independently.

All patients in our hospital were asked to undergo long-term follow-up with rigid cystoscopy, and the follow-up duration was determined based on the European Association of Urology (EAU) guideline.¹³

This research was approved by the ethics board of Neijiang First People's Hospital (Neijiang, China; approval number: NJ-KT-2020-043), and written informed consent was obtained from all patients. The patient's data in this study were anonymized before being processed.

Statistical analyses

All statistical analyses in this study were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Student's *t*-test was used to compare means of continuous data. The Chi-square test was used to compare categorical data between groups. In all tests, $P < 0.05$ was used as the cutoff for statistical significance.

RESULTS

The demographic characteristics of the two groups are listed in **Table 1**. The mean age in Group 1 was significantly lower than that in Group 2 (mean ± standard deviation [s.d.]: 36.8 ± 6.5 years vs 67.7 ± 8.0 years, $P < 0.001$). The incidence of hypertension and diabetes was significantly higher in Group 2 than that in Group 1. The education level of the patients in Group 1 was higher than that of those in Group 2. Compared to the preoperative SAS scores, the SAS scores at 1.5 years postoperatively were significantly higher in Group 1 (mean ± s.d.: 54.1 ± 5.1 vs 34.1 ± 4.5, $P < 0.001$) but not in Group 2 (mean ± s.d.: 45.0 ± 5.2 vs 43.9 ± 5.9, $P = 0.075$).

The incidence rates of ED in both groups in the two different periods are recorded in **Table 2**. Before and 1.5 years after TUR,

Table 1: Patient demographics of the two groups undergoing transurethral resection

Characteristic	Group 1 (n=19)	Group 2 (n=146)	P
Age (year), mean±s.d.	36.8±6.5	67.7±8.0	<0.001
Smoking (n), yes/no	8/11	91/55	0.091
Drinking (n), yes/no	13/6	105/41	0.751
Education, n (%)			<0.001
Less than high school	1 (5.3)	105 (71.9)	
High school graduate	4 (21.1)	32 (21.9)	
College or higher	14 (73.6)	9 (6.2)	
BMI (kg m ⁻²), mean±s.d.	22.8±3.2	23.5±2.5	0.257
Diabetes mellitus (n), yes/no	1/18	47/99	0.015
Preoperative hypertension (n), yes/no	3/16	61/85	0.029
SAS (preoperation), mean±s.d.	34.1±4.5	43.9±5.9	<0.001
SAS (postoperation), mean±s.d.	54.1±5.1	45.0±5.2	<0.001
Tumor size (cm), n ^a			0.428
<3	17	115	
≥3	2	31	
Number of lesions (n)			0.491
Single	16	124	
2–7	3	22	
Tumor grade, n (%)			0.976
G1	5 (26.3)	37 (25.3)	
G2	11 (57.9)	83 (56.8)	
G3	3 (15.8)	26 (17.8)	
Chemotherapeutic agents (n)			0.779
Pirarubicin	8	69	
Mitomycin C	6	35	
Gemcitabine	5	42	
Second TUR (n), yes/no	6/13	37/109	0.761
Treatment situation (preoperative), n			NS
Sildenafil	1	6	
Psychosexual	1	20	
No treatment	1	53	
Treatment situation (postoperative), n			NS
Sildenafil	1	7	
Psychosexual	3	24	
No treatment	6	56	

^aThe diameter of the largest lesion. Group 1: NMIBC patients (<45 years old); Group 2: NMIBC patients (≥45 years old). SAS: Self-Rating Anxiety Scale; TUR: transurethral resection; BMI: body mass index; NS: not significant; NMIBC: nonmuscle-invasive bladder cancer; s.d.: standard deviation

Table 2: The incidence of erectile dysfunction at different time periods

Time period	Group 1 (n=19)	Group 2 (n=146)	P
Preoperation, n (%)	3 (15.8)	79 (54.1)	0.002
Postoperation, n (%)	10 (52.6)	87 (61.0)	0.562
P	0.017	0.345	

The group information is the same as that in **Table 1**

the incidence rates of ED in Group 1 were 15.8% and 52.6%, and those in Group 2 were 54.1% and 61.0%, respectively. The difference between groups (Group 1 vs Group 2) was statistically significant at the preoperative stage ($P = 0.002$) rather than that at the postoperative stage ($P = 0.562$). Compared with the preoperative stage, the incidence of ED at the postoperative stage was increased significantly in Group 1 ($P = 0.017$) but not in Group 2 ($P = 0.345$).

The grade of severity of ED in the two study groups at different time periods is listed in **Table 3**. Before TUR, the severity of ED in the two groups was mainly mild or moderate degree, rather than severe degree. Even in Group 2, severe ED patients accounted for <10% among all the ED patients. After TUR, the proportion who suffered from severe ED showed no significant change. Of 10 patients with ED in Group 1, only 1 had severe ED. In Group 2, the degree of ED was severe in 11.5% of patients after TUR, by contrast, 8.9% of patients at the preoperative stage.

DISCUSSION

It is well known that sexual dysfunction increases with age. In this study, the incidence of ED was obviously higher among aging male patients than that among young male patients before TUR. The reason for changes in the sexual behavior of aging males may include depression, anxiety, low hormone levels, a lack of sexual reciprocity between lovers, and repetitive and monotonous sexual relationships.^{17,18} Mack and Frick⁹ followed 85 patients (median age: 59 [range: 26–85] years, and 75% of the patients were men) who received superficial bladder cancer therapy with Bacillus Calmette–Guérin (BCG) and filled out questionnaires at several intervals; the results revealed an impact on sexual activity at diagnosis and initial treatment but improvement during maintenance therapy. Krajewski *et al.*¹⁰ studied 252 male NMIBC patients and found that TUR may adversely affect sexual function and lead to anxiety and depression.

The results in this study, surprisingly, do not correspond with previous reports.^{7–11} The sexual function of these aging males suffered no adverse effects from the complete treatment process, including TUR, postoperative instillation of chemotherapy, and rigid cystoscopy. The possible reasons for this phenomenon are as follows. First, transurethral electric resection and electrocoagulation were performed repeatedly on the bladder for the duration of the procedure. In the traditional view, the nervi erigentes run in the groove between the rectum and prostate in a neurovascular bundle. This bundle is located 1.5–3 mm posterolateral to the prostatic capsule, extends distally to the apex of the prostate, and then enters the deep perineal pouch, which is posterolateral to the membranous urethra.¹⁹ Recently, on account of periprostatic nerves dispersing on the ventrolateral and dorsal surfaces of the prostate rather than confining in a single dorsolateral “bundle,” many anatomic studies have updated the understanding of cavernous nerves and the classically described neurovascular bundle (NVB).^{20–22} Regardless of anatomy views on the nervi erigentes, the process of TUR will not affect the nervi erigentes. Second, rigid cystoscopy, which is currently the most common method of monitoring for bladder cancer recurrence and progression in China, is well accepted by most patients. It has been proven to bring about temporary impairment of sexual function and transient decrease of libido among sexually active patients, but libido and satisfaction from sexual intercourse will recover

to baseline 1 month later.²³ Third, side effects such as pain, dysuria, and urinary frequency from commonly used chemotherapy drugs such as pirarubicin (THP), mitomycin C (MMC), and gemcitabine are minimal. It has not been reported that the drugs mentioned above can lead to sexual dysfunction. Nevertheless, more research is needed on the effect of perfusion chemotherapy and surveillance methods on sexual function. As far as we know, BCG treatment may cause erectile difficulties.⁸ However, none of these patients in our hospital received adjuvant immunotherapy due to the inaccessibility of BCG in our institute until 2019.

All of the patients in this study had experienced TUR, instillation of chemotherapy, and rigid cystoscopy; however, the decline of sexual function occurred among young male patients only. In general, younger individuals are healthier than older individuals, and the former group is less likely to have diseases that may lead to sexual dysfunction in men, such as hypertension, diabetes, and hyperlipemia. We concluded that psychological and emotional burden are main causes of sexual dysfunction among younger patients with NMIBC, on the basis of their higher postoperative SAS score. It has been reported that mental factors are of vital importance in making one easily subject to sexual concern, in causing sexual intercourse obstacles, and in maintaining sexual dysfunction in the long run.²⁴ There are several possible reasons why these younger patients suffer from considerable psychological and emotional burden. First, the better knowledge of cancer, the more serious symptoms of anxiety.^{25–28} Of patients with a college degree or higher in this study, 60.9% (14/23) were young men. As the Internet is now used widely in China, most young men like online searching for health and medical information, especially when they suffer from the illness themselves, while few elderly people will do that. Almost all young patients have a full understanding of the illness through the Internet, including local recurrence, progression to muscle-invasive bladder cancer, distant metastasis, radical cystectomy, and ileal conduit urinary diversion. Young patients are especially fearful of deteriorative self-management conditions and reduced QoL if they receive radical cystectomy and urinary diversion. Most older people with lower academic qualifications and less income in China cannot distinguish between cancer and benign tumors. In general, patients with malignant tumors are told a white lie by their children or immediate relatives in China.²⁹ However, young patients are not liable to be deceived in such a society with an advanced information network. Older people rarely use their cell phones to access the Internet but instead use them only for making or receiving calls, particularly in rural regions. Many older patients believe that bladder tumors are benign diseases and are cured by minimally invasive surgery and intravesical drug treatment. As a result of younger people worrying about the recurrence and deterioration of bladder cancer too much, they suffer more severe anxiety. Second, financial hardship among cancer survivors is significant in China, especially in younger patients.³⁰ Most young and middle-aged men have great family responsibilities and economic pressure during their thirties and forties. Unlike developed western countries, in China, taking care of elderly parents, especially those without a pension who live in the countryside, is a part of traditional Chinese culture. It is clear that young and middle-aged men experience more stress than elderly people in China because they not only have to support their parents financially but also have to rear and educate their own children. Once they know that they have a malignant disease, they will face more enormous psychological pressure than elderly patients. Enormous psychological and emotional pressure will negatively impact their relationship with their partner, including loss of intimacy. Third, sexual dysfunction patients with cancer have faced double

Table 3: The grade of severity of erectile dysfunction at different time periods

ED severity	Group 1 (n=19)		Group 2 (n=146)	
	Preoperation	Postoperation	Preoperation	Postoperation
Mild, n (%)	1 (33.3)	3 (30.0)	16 (20.3)	19 (21.8)
Mild-to-moderate, n (%)	1 (33.3)	4 (40.0)	34 (43.0)	32 (36.8)
Moderate, n (%)	1 (33.3)	2 (20.0)	22 (27.8)	26 (29.9)
Severe, n (%)	0 (0)	1 (10.0)	7 (8.9)	10 (11.5)

The group information is the same as that in **Table 1**. ED: erectile dysfunction

discrimination in China for a long time because of public ignorance regarding cancer and sex.^{31,32} Unfortunately, there is still a large unmet need for psychosocial rehabilitation of Chinese cancer survivors.³¹ To avoid other people's discrimination, many cancer survivors choose to conceal their illness.³¹ Likewise, many patients suffering from sexual dysfunction will not go to ask for help from doctors actively,³² as confirmed herein. Few patients sought medication or psychotherapy whether before or after TUR, and thus, the deteriorative symptoms of sexual dysfunction will bring about heavy burden on the patients.

One of several limitations of this study is the small sample size, especially in Group 1. We have observed that majority of patients were drinkers and almost half were smokers in this study, and their drinking or smoking behaviors may affect the results of the young group, fostering greater anxiety or ED. However, the intra-group disparity could not be examined further due to the small sample size. Second, this is a preliminary and retrospective study, and the main purpose is to study changes in the incidence of ED among NMIBC patients before and after TUR, so we did not apply multivariate statistical analysis. Third, we did not analyze the difference in the constituent ratio of the grade of severity of ED because the number of ED patients in both groups was limited. Finally, there were no records on physical activity or exercise levels in this study. Zhou *et al.*³³ found that exercise can improve depressive symptoms, anxiety, and QoL, all of which may impact sexual health.

The incidence of ED among male NMIBC patients under the age of 45 years after TUR has increased in China. Clinicians should pay more attention to changes in the sexual function of these patients after TUR. Such a young group of bladder cancer patients dealing with cancer treatment and ED should be evaluated for psychological impacts based on their age, and they should also receive lifestyle counseling (e.g., smoking cessation) to reduce the risk of recurrence of cancer as well as the progression/increased severity of ED based on these same lifestyle factors.

AUTHOR CONTRIBUTIONS

PG designed the study, collected and analyzed the data, and wrote the article. YW, YFX, and TBL contributed to the collection and analyses of data. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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