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ORIGINAL ARTICLE

An increased body mass index is associated with a worse prognosis in patients administered BCG immunotherapy for T1 bladder cancer

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Abstract

Purpose The body mass index (BMI) may be associated with an increased incidence and aggressiveness of urological cancers. In this study, we aimed to evaluate the impact of the BMI on survival in patients with T1G3 non-muscle-invasive bladder cancer (NMIBC).

Methods A total of 1155 T1G3 NMIBC patients from 13 academic institutions were retrospectively reviewed and patients administered adjuvant intravesical Bacillus Calmette–Guérin (BCG) immunotherapy with maintenance were included. Multivariable Cox regression analysis was performed to identify factors predictive of recurrence and progression.

Results After re-TURBT, 288 patients (27.53%) showed residual high-grade NMIBC, while 867 (82.89%) were negative. During follow-up, 678 (64.82%) suffered recurrence, and 303 (30%) progression, 150 (14.34%) died of all causes, and 77 (7.36%) died of bladder cancer. At multivariate analysis, tumor size (hazard ratio [HR]:1.3; $p=0.001$), and multifocality (HR:1.24; $p=0.004$) were significantly associated with recurrence (c-index for the model:55.98). Overweight (HR: 4; $p<0.001$) and obesity (HR:5.33 $p<0.001$) were significantly associated with an increased risk of recurrence. Addition of the BMI to a model that included standard clinicopathological factors increased the C-index by 9.9. For progression, we found that tumor size (HR:1.63; $p<0.001$), multifocality (HR:1.31; $p=0.01$) and concomitant CIS (HR: 2.07; $p<0.001$) were significant prognostic factors at multivariate analysis (C-index 63.8). Overweight (HR: 2.52; $p<0.001$) and obesity (HR: 2.521 $p<0.001$) were significantly associated with an increased risk of progression. Addition of the BMI to a model that included standard clinicopathological factors increased the C-index by 1.9.

Conclusions The BMI could have a relevant role in the clinical management of T1G3 NMIBC, if associated with bladder cancer recurrence and progression. In particular, this anthropometric factor should be taken into account at initial diagnosis and in therapeutic strategy decision making.

Keywords Bladder cancer · Body mass index · Obesity · Prognosis

Introduction

Obesity is a growing global health burden. A recently published meta-analysis showed that the number of obese subjects has significantly increased in the last three decades [1]. Unfortunately, obesity is associated with a higher incidence and aggressiveness of several type of cancers, such as breast, prostate, ovarian, gastric, renal and colon cancers [2]. Data on the relationship between obesity and bladder cancer are

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conflicting. Some authors reported that obesity is associated with a worse clinical outcome of bladder cancer patients, whereas other studies concluded that the body mass index (BMI) is not linked to worse oncological outcomes of these patients [3–6]. At the initial diagnosis, most patients present non-muscle-invasive bladder cancer (NMIBC), generally treated with transurethral resection of the bladder tumor (TURBT), followed in some cases by intravesical therapy [7]. However, about 60% of these patients experience recurrence and about 10% progress to muscle-invasive disease at 5 years; the set of T1 high-grade (HG) NMIBCs shows the highest rate of progression [7].

In this regard, a recent meta-analysis of 14 prospective cohort studies involving 12,642 cases showed a nonlinear positive relationship between the BMI and bladder cancer (SRR = 1.03, 95% CI 1.01–1.06, *P*-nonlinearity = 0.031), suggesting that each 5 kg/m^2 increase of the BMI corresponded to a 3.1% increase of bladder cancer risk, especially when the BMI exceeded 30 kg/m^2.

However, knowledge of the role of the BMI in patients with high-risk NMIBC is limited by retrospective data [8] and no study design standardization (i.e., lack of data on repeat transurethral resection of the bladder and the intravesical therapy protocol).

In this study, we aimed to evaluate the impact of the BMI on survival in patients with high-risk non-muscle-invasive bladder cancer.

Patients and methods

A total of 1155 primary T1G3 NMIBC patients administered TURBT from 13 academic institutions between January 1st, 2002 and December 31st, 2012 were retrospectively analyzed. Inclusion criteria included Bacillus Calmette–Guérin (BCG) treatment with maintenance; 109 patients treated with intravesical chemotherapy were excluded. Demographic, clinical and pathological data were collected and entered in a computerized database. Histology was performed by experienced uro-pathologists at each institution. Tumors were histologically classified according to the TNM system of Union for International Cancer Control (UICC) and to the 1973 World Health Organization (WHO) grading system. The re-TURBT Protocol included tumor scar and base resection, together with the bladder neck (for CIS) and red bladder patches. Re-TURBT was performed within 6 weeks after the first TURBT [9]. Each patient underwent adjuvant intravesical BCG immunotherapy according to the European Association of Urology (EAU) recommendations, consisting of a 6-week induction course of intravesical BCG followed by the standard maintenance scheme, namely intravesical BCG—standard dose—once a week for 3 weeks, administered at 3, 6, 12, 18, 24, 30 and 36 months from the start of therapy. In total, 303 (29%) of patients completed the treatment protocol as planned [10]. The upper urinary tract was evaluated using radiological imaging in all subjects yearly or when clinically indicated to exclude the presence of concomitant carcinoma. The BMI was defined as the weight in kilograms divided by the square height in meters (kg/m^2) using pre-TURBT data, and patients were assigned according to the International Classification of adults to the underweight, overweight and obesity group according to the BMI [11].

Follow-up

Patients were followed up every 3 months according to EAU guidelines with cystoscopy and urinary cytology [10]. Endpoints were time to recurrence, progression, overall and cancer-specific survival. Recurrence was defined as the appearance of any tumor, and progression as muscle-invasive disease during follow-up. Patients with muscle-invasive disease on re-TUR and those who failed BCG underwent radical cystectomy [12].

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR) and differences between groups were assessed with the Kruskal–Wallis test or Mann–Whitney *U* test as appropriate. Categorical variables were tested with the Chi square test or Fisher exact test.

Multivariable Cox regression analysis was performed to identify predictive factors of recurrence and progression, using the variables collected.

For statistical analysis, we assigned patients to the underweight (BMI < 18.5), normal weight (BMI 18.5–24.99), overweight (BMI 25–29.99) and obese (BMI ≥ 30) categories [11]. Kaplan–Meier curves were applied to calculate the association between BMI and recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS). Log-rank test was used to verify statistical significance between curves.

All statistical analyses were completed using Stata software, version 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.). For all statistical comparisons, a value of $p < 0.05$ was considered statistically significant.

Results

Association of the BMI with clinical and pathological features

Median age was 71.0 years [Interquartile Range (IQR) 65.0–78.0] and median BMI was 27.0 (IQR 24.0–29.0). As to the BMI distribution, 22 patients (2.1%) had a BMI < 18.5, 326 (31.2%) a BMI > 18.5 − < 24.99, 474 (45.3%) a BMI > 25 − < 30 and 224 patients (21.4%) a BMI ≥ 30. Gender distribution was 82.6% (864) males and 17.4% (182) females. Of the whole cohort, 221 patients (22.13%) had previously received chemotherapy instillation, 53 (5.07%) Epirubicin and 168 (14.54%) Mitomycin. After re-TURBT, 288 (27.53%) showed residual high-grade NMIBC, while 867 (82.89%) were negative. All patients received BCG immunotherapy; median duration of the regimen was 12.0 months (IQR 6.0–36.0).

Table 1 lists the baseline characteristics of the study cohort according to the BMI. A larger proportion of patients with a BMI ≥ 25 kg/m^2 were current smokers (51.3%, p < 0.001) compared to normal BMI or underweight patients. Tumor characteristics did not differ between BMI groups.

Association of BMI with recurrence and progression

Within a median time of 26 months (IQR 9–47), 678 (64.82%) patients suffered recurrence, and within a median time of 43 months (IQR 36–58), 303 (30%) patients underwent progression. Kaplan–Meier survival analysis showed that overweight and obese patients had a significantly reduced recurrence-free survival (RFS) as compared to normal weight or underweight patients ($p < 0.001$, Fig. 1a). Five-year RFS was 69.4% (CI 63.5–74.5) in patients with

Table 1 Association of clinical and pathologic features with BMI in 1046 patients treated with BCG after primary T1G3 NMIBC

	BMI 18.5–24.99	BMI < 18.5	BMI 25–29.99	BMI ≥ 30	*p*
Total, *n* (%)	326 (31.2)	22 (2.1)	474 (45.3)	224 (21.4)	
Age (years)					
Mean (SD)	70.1 (9.5)	73.6 (8.4)	69.8 (9.5)	69.4 (20.8)	0.46
Gender, *n* (%)					
Male	266 (81.6)	18 (81.8)	394 (83.1)	186 (83)	0.94
Female	60 (18.4)	4 (18.2)	80 (16.9)	38 (17)	
Smoking status					
Never	85 (26.1)	3 (13.6)	124 (26.1)	85 (38)	**< 0.001**
Current	136 (41.7)	6 (27.3)	243 (51.3)	100 (44.6)	
Former	105 (32.2)	13 (59.1)	107 (22.6)	39 (17.4)	
Multifocality, *n* (%)					
Single	189 (58)	11 (50)	267 (56.3)	118 (52.7)	0.6
Multiple	137 (42)	11 (50)	207 (43.7)	106 (47.3)	
Size, *n* (%)					
< 3 cm	120 (36.8)	6 (27.3)	164 (36.4)	81 (36.2)	0.77
≥ 3 cm	206 (63.2)	16 (72.7)	310 (63.6)	143 (63.8)	
Concomitant CIS, *n* (%)					
No	280 (85.9)	21 (95.5)	407 (85.9)	188 (83.9)	0.51
Yes	46 (14.1)	1 (4.5)	67 (14.1)	36 (16.1)	
Survival outcomes					
Recurrence, *n* (%)					
No	231 (70.9)	20 (90.9)	98 (20.7)	19 (8.5)	**< 0.001**
Yes	95 (29.1)	2 (9.1)	376 (79.3)	205 (91.5)	
Progression, *n* (%)					
No	271 (83.1)	20 (90.9)	302 (63.7)	150 (67)	**< 0.001**
Yes	55 (16.9)	2 (9.1)	172 (36.3)	74 (33)	
Death	42 (12.9)	4 (18.2)	76 (16)	28 (12.5)	0.46
Death due to BC	20 (6.1)	2 (9.1)	36 (7.6)	19 (8.5)	0.77

Bold values identify statistically significant variables

BCG Bacillus Calmette–Guérin, *NMIBC* non-muscle-invasive bladder cancer, *CIS* carcinoma in situ, *BC* bladder cancer, *BMI* Body mass index

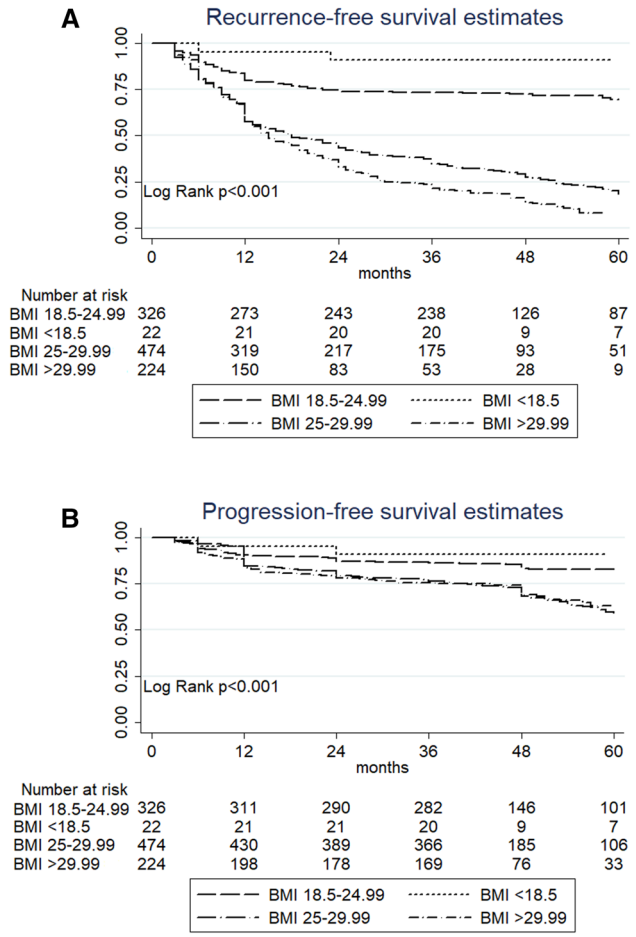

Fig. 1 Comparison of recurrence-free survival **a** and progression-free survival **b** according to BMI status

a normal BMI, 90.9% (CI 68.3–97.6) in patients with a BMI < 18.5, vs. 18.5% (CI 14.6–22.7) in overweight patients and 7.3% (CI 4.1–11.9) in obese patients. In the multivariable model, we found that tumor size [hazard ratio (HR): 1.3; $p = 0.001$] and multifocality (HR: 1.24; $p = 0.004$) were significantly associated with recurrence (c-index 55.98). Overweight (HR: 4; $p < 0.001$) and obesity (HR:5.33 $p < 0.001$) were significantly associated with an increased risk of recurrence. Addition of the BMI to a model that included standard clinicopathological factors increased the C-index by 9.9 (Table 2a).

In terms of progression, Kaplan–Meier survival analysis showed that overweight and obese patients had a significantly shorter progression-free survival (PFS) than normal weight or underweight patients ($p < 0.001$, Fig. 1b). Five-year PFS was 82.9% (CI 77.9–86.8) in patients with a normal BMI, 90.9% (CI 68.3–97.6) in patients with a BMI < 18.5, vs. 59.3% (CI 53.4–64.6) in overweight patients and 63.1% (CI 54.2–70.6) in obese patients. At multivariate analysis, tumor size (HR: 1.63; $p < 0.001$), multifocality (HR: 1.31; $p = 0.01$) and concomitant carcinoma in situ (CIS) (HR: 2.07; $p < 0.001$) were significantly associated with progression (c-index 63.8). Overweight (HR: 2.52; < 0.001) and obesity (HR: 2.521 $p < 0.001$) were significantly associated with an increased risk of progression. Addition of the BMI to a model that included standard clinicopathological factors increased the C-index by 1.9 (Table 2b).

Association of the BMI with overall and cancer-specific survival

Within a median follow-up of 48 months (IQR: 40–68), 150 (14.34%) died due to overall causes, while 77 (7.36%) died of BC. At univariable and multivariable Cox regression analysis, the BMI was not a predictive factor for overall survival (OS) or for cancer-specific survival (CSS) (data not shown). Kaplan–Meier survival analysis did not show a significance difference in survival among patients from different BMI subgroups. Five-year OS was 88.8% (CI 83.8–92.3) in patients with a normal BMI, 77.1% (CI 42.3–92.4) in patients with a BMI < 18.5, 84.9% (CI 80.1–88.6) in overweight patients and 81.6% (CI 73–87.8) in obese patients. Five-year CSS was 96.3% (CI 92.8–98.1) in patients with a normal BMI, 88.8% (CI 43.3–98.3) in patients with a BMI < 18.5, 92.5% (CI 88.7–95) in overweight patients and 88.1% (CI 80.4–92.9) in obese patients (Fig. 2a, b).

Discussion

In the current study, we evaluated the impact of the BMI on the oncological prognosis in patients affected by high-grade NMIBC. In particular, we showed that overweight (BMI 25–29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were associated with a greater risk of progression. Instead, a higher risk of recurrence was demonstrated only for obese patients. Previous studies showed that a higher BMI was predictive of worse outcomes in subjects diagnosed with clinical T1 high-grade NMIBC [8] and in patients who underwent radical cystectomy [3]. The association of obesity with a poor clinical outcome in T1G3 NMIBC could be explained on the basis of several factors. In particular, it is well known that obesity is characterized by insulin resistance and low-grade systemic inflammation, which may affect the oncological outcomes of NMIBC patients as a result of insulin, IGF-1, cytokines and growth factors' effects [13]. In this regard, obese subjects showed increased levels of insulin and IGF-1 [14]. Several epidemiological studies indicated that IGF-1 played an important role in the incidence and progression of different types of cancer such as breast, prostate, lung, liver and colorectal cancers [15–18].

Furthermore, obesity is associated with high levels of inflammatory cytokines, such as leptin, IL-6 and TNF-α

Table 2 Univariable and multivariable Cox regression analyses predicting recurrence (A) and progression (B) in 1046 patients with primary T1G3 NMIBC treated with Bacillus Calmette–Guérin

A	Recurrence-free survival					
Variables	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age cont.	0.99	0.98–1	0.16	0.99	0.98–1	0.15
Gender (male vs. female)	1.24	1.03–1.49	**0.02**	1.08	0.9–1.31	0.37
Size (< 3 vs. ≥ 3) cm	1.28	1.09–1.51	**0.002**	1.3	1.1–1.53	**0.001**
Multifocality (single vs. multiple)	1.3	1.12–1.51	**0.001**	1.24	1.07–1.45	**0.004**
Concomitant CIS (no vs. yes)	1.17	0.95–1.44	0.13	1.13	0.91–1.39	0.23
Harrell's C index	**55.98**					
BMI	**Ref.**					
< 18.5 kg/m^2	0.27	0.06–1.12	0.07	0.27	0.06–1.11	0.07
25–29.99 kg/m^2	4.02	3.21–5.05	**< 0.001**	4	3.18–5.01	**< 0.001**
≥ 30 kg/m^2	5.29	4.13–6.77	**< 0.001**	5.33	4.16–6.83	**< 0.001**
Harrell's C index	**65.88**					
B	Progression-free survival					
Variables	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age cont.	0.99	0.98–1	0.27	0.99	0.98–1	0.45
Gender (male vs. female)	1.35	1.03–1.77	**0.02**	1.22	0.92–1.61	0.15
Size (< 3 vs. ≥ 3) cm	1.78	1.37–2.3	**< 0.001**	1.63	1.26–2.11	**< 0.001**
Multifocality (single vs. multiple)	1.46	1.16–1.83	**0.001**	1.31	1.04–1.64	**0.01**
Concomitant CIS (no vs. yes)	2.19	1.69–2.85	**< 0.001**	2.07	1.59–2.7	**< 0.001**
Harrell's C Index	**63.8**					
BMI	**Ref.**					
< 18.5 kg/m^2	0.56	0.13–2.33	0.43	0.64	0.15–2.66	0.54
25–29.99 kg/m^2	2.50	1.84–3.39	**< 0.001**	2.52	1.85–3.42	**< 0.001**
≥ 30 kg/m^2	2.51	1.77–3.58	**< 0.001**	2.51	1.76–3.57	**< 0.001**
Harrell's C index	**65.7**					

Ref.: BMI 18.5–24.99 was used as a reference value

Bold values identify statistically significant variables

NMIBC non-muscle-invasive bladder cancer, *CI* confidence interval, *HR* hazard ratio, *CIS* carcinoma in situ, *BMI* Body mass index

produced by adipocytes and immune cells infiltrating adipose tissue. Concurrently, lower amounts of adiponectin, an anti-inflammatory adipokine with anticancer properties, were released by adipocytes [19]. Such a systemic milieu produces a cancer-promoting microenvironment [20].

Indeed, several studies have already demonstrated a detrimental impact of obesity on oncological outcomes in bladder cancer.

In particular, Lin et al. showed that the recurrence rate of bladder cancer was significantly higher in obese (HR = 1.76, 95% CI 1.36–2.28) compared to normal weight patients. Stratification analysis showed that females had a higher risk of recurrence than males (HR = 1.17, 95% CI 1.05–1.31). Dose–response relationship analysis revealed a linear association between the BMI and risk of recurrence. Each 1 kg/m2 increase in BMI was related to a 1.3% increased risk of bladder cancer recurrence (HR = 1.01, 95% CI = 1.01–1.02).

By contrast, there is a growing body of literature showing a negative influence of obesity on genitourinary malignancies [21]. Nevertheless, the data are not conclusive. For instance, Calle et al. carried out a large prospective study on 900,000 USA adults, investigating the role of obesity in the mortality risk of many types of cancer. Their findings showed that the risk of mortality of both prostate cancer and kidney cancer was significantly increased with increasing BMI values, whereas they did not find a significant association with bladder cancer [22].

On the contrary, in a prospective study of 18,000 middle-aged men, the authors showed an elevated risk of bladder

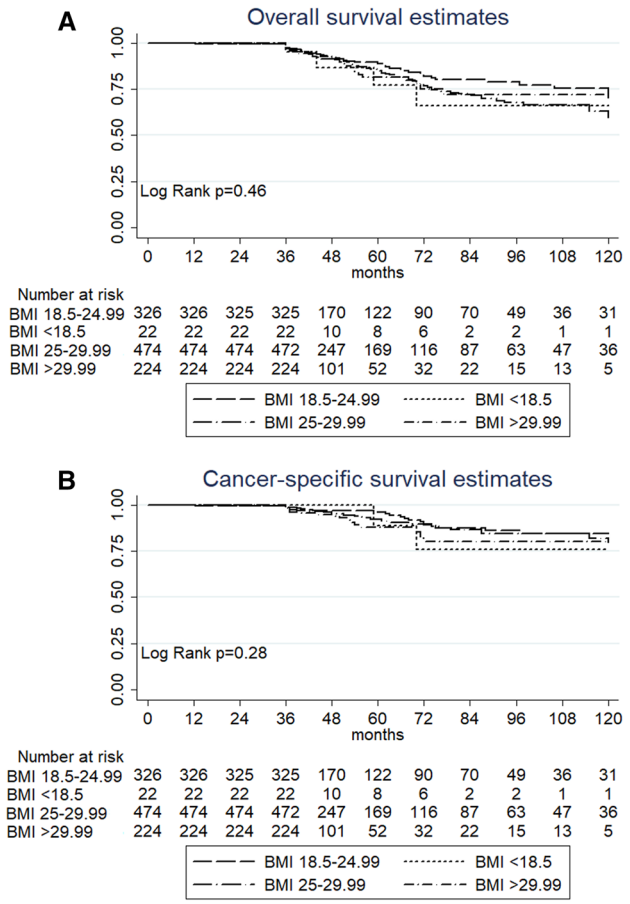

Fig. 2 Comparison of overall survival **a** and cancer-specific survival **b** according to BMI status

cancer-related mortality in men who were either overweight (HR 1.68, 95% CI 1.06–2.65) or obese (HR 1.19, 95% CI 0.27–5.18) [23].

With regard to the relationship between obesity and NMIBC, in a retrospective cohort study of 892 patients with primary superficial high-grade BCa, Kluth et al. showed that obesity was associated with an increased risk of disease recurrence (HR 2.66, 95% CI 2.12–3.32), disease progression (HR 1.49, 95% CI 1.00–2.21), cancer-specific mortality (HR 3.15, 95% CI 1.74–5.67) and any cause of mortality (HR 1.42, 95% CI 1.06–1.92) [8]. Similarly, in a USA population-based study of 726 patients with superficial BCa and a 6-year median follow up, Wyszynski et al. reported that high BMI values at diagnosis were associated with a modestly increased risk of recurrence (HR 1.33, 95% CI 0.94–1.89) [24]. The same data also suggested that among current smokers, the risk of recurrence was increased more than twofold in overweight as compared with the normal weight patients (HR 2.67, 95% CI 1.14–6.28).

Collectively, the results obtained in our study in agreement with others suggest that urologists should adopt a prudent policy for T1G3 NMIBC obese patients. Subjects with BMI values higher than 25 kg/m^2 should be invited to undergo a weight loss program in order to improve their cancer-specific outcomes. Since the incidence of obesity is on the rise, increasing numbers of obese subjects may be expected to develop bladder cancer, so an elevated BMI should be considered as a relevant factor when clinicians are choosing the best therapeutic strategy.

Our study suffers from some limitations. Firstly, the study design is multicentric and retrospective, so it includes selection bias. There may be different treatment patterns across centers, the pathological evaluation was not centralized and various different surgeons were involved. Moreover, some metabolic phenotype details such as glycemic control and dyslipidemia were not available. This is a relevant issue, since type two diabetes, which is often diagnosed in obese subjects, has been shown to be an independent factor worsening the oncological outcome of bladder cancer patients [25].

Further studies are warranted to evaluate whether a BMI evolution during follow-up significantly affects clinical outcomes.

Conclusion

The BMI seems to be associated with bladder cancer recurrence and progression. Taking into account this anthropometric factor at the initial diagnosis and when planning the therapeutic strategy could be relevant in the clinical management of T1G3 NMIBC. Future studies are needed to better define the impact of the BMI in clinical decision making for these patients.

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Author contributions MF, MDV, GIR, ARAF, VM, GL: protocol/project development. All authors: data collection or management. All authors: data analysis. MF,GIR, MDV, FC, GL: manuscript writing/editing

Compliance with ethical standards

conflict of interest The authors declare that they have no conflict of interest, nothing to declare.

Research involving human participants and/or animals This is a retrospective study. Institutional review board approval was granted by means of a general waiver for studies with retrospective data analysis in each center. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent to take part was given by all participants.

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