SCANDINAVIAN JOURNAL OF UROLOGY
2020, VOL. 54, NO. 1, 40–45
https://doi.org/10.1080/21681805.2019.1708968

ARTICLE

The value of tumour weight as a predictive factor for recurrence and progression in non-muscle invasive bladder cancer

Guillermo Fernández-Conejo[a], Enrique de la Peña[a], Virginia Hernández[a], Ana Guijarro[a], Alejandro Castro[a], Elia Pérez-Fernández[b] and Carlos Llorente[a]

[a]Department of Urology, Hospital Universitario Fundación Alcorcón, Madrid, Spain; [b]Unit of Research, Hospital Universitario Fundación Alcorcón, Madrid, Spain

ABSTRACT

Objective: To further assess the influence of the weight after TURBT as a predictive factor for recurrence and progression in NMIBC.

Materials and methods: A cohort of patients with a first episode of NMIBC between 1999 and 2016 was analysed retrospectively. We studied the correlation between the tumour's size and weight, the time-dependent ROC curves for the optimal weight value for the prediction of recurrence and progression and their association with the risk of recurrence and progression at one and five years.

Results: We analysed 470 patients who met inclusion criteria. Median (IQR) follow-up time was four-years (2.2–6.7), 227 (48.3%) patients had a recurrence and 46 (9.8%) progressed. Median (IQR) weight after resection was 2 g (0.8–6) and its correlation with size was 0.56. The optimal value for the prediction of recurrence was 4 g. The RFS at one and five years with a weight <4 g was 77.7% and 53.5%, respectively, compared to 57.8% and 34.7% with higher weight ($p < .001$). PFS at one and five years was 98% and 92.7% for a weight <4 g compared to 91.4% and 83.1% for tumours >4 g, respectively ($p = .02$). On multivariate analysis, a higher weight was associated with an increased risk of recurrence: HR [95%:CI] = 1.52[1.05–1.86], and progression: HR[95%:CI] = 1.87[1.01–3.47] ($p < .05$).

Conclusion: The weight of the specimen obtained after TURBT is a predictive factor of both recurrence and progression in NMIBC that may be more accurate than tumour size and easily and objectively measured. An increase of 52% and 87% in the risk of recurrence and progression, respectively, was found in tumours weighing more than 4 g.

Abbreviations: TUR: transurethral resection; TURBT: transurethral resection for bladder tumour; NMIBC: non-muscle invasive bladder cancer; BC: bladder cancer; RFS: recurrence-free survival; PFS: progression-free survival; SD: standard deviation; ROC: receiver operating characteristic; MMC: Mitomycin C; CIS: carcinoma *in situ*; BCG: Bacillus Calmette-Guérin; EORTC: *European Organisation for Research and Treatment of Cancer*; CUETO: Club Urológico Español de Tratamiento Oncológico; HR: Hazard Ratio; CI: Confidence Interval

ARTICLE HISTORY
Received 18 September 2019
Revised 27 November 2019
Accepted 20 December 2019

KEYWORDS
Weights and measures; urinary bladder neoplasms; recurrence; disease progression

Introduction

The predictive tools for recurrence and progression in non-muscle invasive bladder cancer (NMIBC) can help the clinician to optimise treatment. Currently, there are two risk tables with a widespread application: the EORTC (European Organisation for Research and Treatment of Cancer) and the CUETO (Club Urológico Español de Tratamiento Oncológico) [1,2]. These risk tables include various risk factors that can be objectively labelled such as T-stage, grade and number of tumours which can be reliably reproduced.

Additionally, the size of the tumour is another feature included in the aforementioned predictive tables. However, its subjectivity should be taken into account because the endoscopic assessment of tumour size is not easily measured precisely and thus is not reproducible, being highly operator-dependent [3].

In addition, there are also several limitations in establishing tumour size, especially in cases of multiple tumours in exophytic lesions with a small implantation base, or in the opposite scenario where a flat lesion with a large implantation size can be found.

Hypothetically, the weight of the tumour of the sample obtained after transurethral resection (TUR) might more accurately represent the real tumour volume rather than tumour size does.

In 2012, tumour weight was first described as a new prognostic factor for recurrence in NMIBC by our group. It was found that tumours weighing >6 g have a 1.7-fold higher likelihood of recurrence than those tumours that weighed less [4]. After that, Kwon et al. reported that the weight of the tumour was also an independent factor of progression for NMIBC [5].

The aim of this study is to further assess the influence of the weight of the specimen after TURBT as a predictive factor for recurrence and progression in NMIBC with a more mature cohort and longer follow-up.

CONTACT Guillermo Fernández-Conejo gfernandezc@fhalcorcon.es Calle Budapest, no. 1. 28922 Alcorcón, Madrid, Spain

Table 1. Clinical and pathological characteristics of the patients.

Variables	Total $n = 470$
Age (SD)	69.1 (11.8)
Male gender, *n* (%)	396 (84.3)
Multiple tumour, *n* (%)	146 (31.2)
Size $\geq$ 3 cm, *n* (%)	184 (39.1)
Weight (g), (median, IQR)	2 (0.8–6)
Stage, *n* (%)	
Ta	254 (51.4)
T1	217 (43.9)
Grade, WHO (1973), *n* (%)	
G1	165 (35.1)
G2	188 (40)
G3	115 (24.5)
High-grade, WHO (2004), *n* (%)	301 (64.3)
Postoperative single dose MMC, *n* (%)	285 (61)
Adjuvant treatment, *n* (%)	
MMC	52 (11.1)
BCG	96 (20.4)
No treatment	322 (68.5)
Maintenance of adjuvant treatment, *n* (%)	64 (81)

Material and methods

A cohort of patients prospectively recorded in our institutional database of bladder cancer (BC) was retrospectively analysed. All consecutive patients diagnosed with NMIBC with completed TURBT from July 1999 to December 2016 were included in the study. Only patients who had both weight and size of the tumour registered were selected for the current study.

Demographic variables were collected, as well as any known prognostic factors involved in the natural history of NMIBC. The specimen weight after resection was also included for analysis. Patients classified as high-risk NMIBC with T1 stage and high grade were included, but those with carcinoma *in situ* (CIS) were excluded. Patients submitted to re-TUR were included in the study when NMIBC was present at the second TUR specimen and the weight of both specimens was added. Patients with incomplete TURBT were excluded from the analysis. Histopathology results were classified according to the 2009 TNM system [6] and WHO (1973 and 2004) grading systems [7,8].

Complete TURBT was always attempted and a biopsy of the deep muscle at the tumour base was obtained to the point where healthy muscle or peri-vesical fat were seen. This sample was usually submitted separately to the laboratory. Operations were performed by eight urologists with more than 10 years experience or by residents supervised by these same urologists. Tumour size was defined as the largest dimension; this measure was assessed endoscopically by the surgeon with a resection loop of 0.5 cm as a reference. One single immediate, postoperative intravesical instillation of chemotherapy with mitomycin C (MMC) was administered following the European guidelines' recommendations at each time-period. MMC was not administered in the following situations: (1) gross active haematuria; (2) resection of the ureteric orifice; or (3) when the operating urologist had a well-founded suspicion of bladder perforation.

The TURBT specimen was placed in formaldehyde for its fixation before being sent to the pathology laboratory. Laboratory technicians measured, weighed and processed the specimens following the same protocol and using the same precision scales (GF-200R, A & D Co. Ltd, Tokyo, Japan), with a lower detection value of 0.001 g. In those cases where more than one sample was obtained at the time of TURBT, only those specimens with reported tumour were included in the analysis. Tumour weight was included in the pathology report along with the standard evaluation.

Intermediate-risk patients, with high probability of recurrence, were offered a si-week course of MMC, and high-risk patients were offered BCG induction plus maintenance if a response at three months was obtained. Follow-up was carried out every three months for the first year with cystoscopy and cytology, every 4four months during the second year and every six months thereafter.

The outcomes of the study were recurrence-free survival (RFS) and progression-free survival (PFS). Recurrence was defined as the diagnosis of a new NMIBC during the follow-up. Progression was defined as an upstaging to muscle-invasive BC at any time during follow-up or the development of metastatic disease.

Measurable variables are expressed as mean (standard deviation [SD]) if they are normally distributed, or median (interquartile range [IQR]) otherwise. Correlation between the weight and tumour's size was performed using Spearman's correlation coefficient. Recurrence- and progression-free survival (RFS and PFS) curves were estimated using the Kaplan–Meier method, and differences were evaluated using the log-rank test.

For the estimation of the optimum weight cut-off point, time-dependent receiver-operating characteristic (ROC) curves for recurrence and progression at one year were calculated. We selected the best cut-off point as that which maximises specificity and sensitivity both for recurrence and progression. R 3.4.2 (http://www.r-project.org) and R package 'timeROC' was used to estimate time-dependent ROC curve (timeROC) and Area Under timeROC curve (AUC) [9].

Multivariate Cox proportional hazard regression was used to assess the association of the threshold value of weight value obtained previously as an independent risk factor for recurrence and progression. All variables significantly associated with the outcome in the univariate analysis were considered in the multivariate model as well as corresponding interaction terms. A manual backward modelling strategy was used to eliminate variables from the maximum model to obtain the most parsimonious model to assess the effect of the independent variables on outcome. All tests were two-tailed and a *p*-alue $<.05$ was considered to indicate statistical significance. Statistical analyses were performed using the SPSS 17.0 statistical package for Windows (SPSS Inc, Chicago, IL, USA).

Results

In total, 470 patients with a first diagnosis of NMIBC between July 1999 and December 2016 who met the inclusion criteria as previously mentioned were analysed. Median time of follow-up was four years (IQR: 2.2–6.7). Fifty-eight (12.3%) patients died, and 18 (3.8%) died due to BC. There were 227 (48.3%) patients who had a recurrence and 46 (9.8%) who

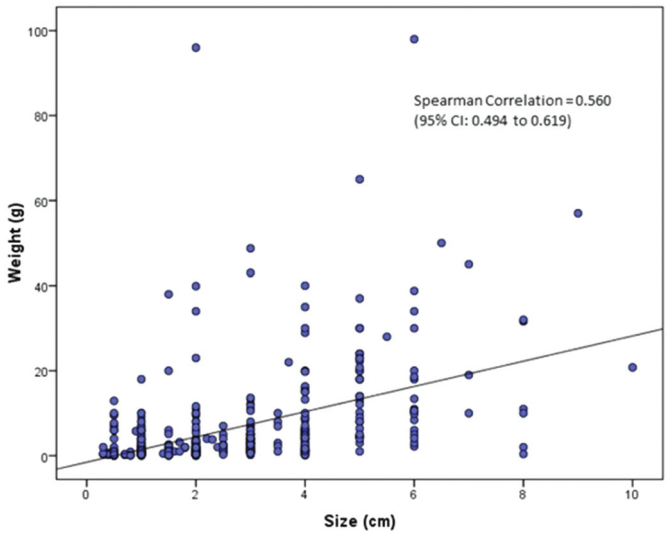

Figure 1. Calculated correlation of weight and size of the tumour.

progressed. The baseline characteristics of the patients are presented in Table 1.

The median weight after resection was 2 g (IQR: 0.8–6). A direct correlation of 0.56 (95% CI: 0.49–0.62) between size and weight was found (Figure 1).

The time-dependent ROC curves for recurrence and progression at one year for tumour weight were obtained. An optimal weight cut-off point was set at 4 g for both recurrence (AUC= 0.634) and progression (AUC = 0.665), with a sensitivity and specificity of 49% and 73% and 69% and 68%, respectively (Figure 2). The number of patients with a resected tumour weight of <4 g and >4 g was 313 (66.6%) and 157 (33.4%), respectively.

We found that the RFS at one and five years in patients with tumours that weighed <4 g was 77.7% and 53.5% compared to 57.8% and 34.7%, respectively, in tumours with a higher weight ($p < .001$, Figure 3). Likewise, the PFS at one and five years for both groups was 98%, and 92.7% for tumours that weighed <4 g compared to 91.4% and 83.1%, respectively, for tumours that weighed >4 g ($p = .02$, Figure 4).

Sample weights above 4 g led to an increased risk of recurrence with a hazard ratio (HR) of 1.71 (95% CI: 1.31–2.24) in the univariate analysis ($p < .001$). Other associated prognostic factors were multiplicity and a tumour size higher than 3 cm as risk factors and postoperative single dose of MMC as protective factor (Table 2). In the multivariate analysis, where all the previous variables were included, it was found that a weight >4 g was a risk factor for recurrence with a HR of 1.52 (95% CI: 1.14–2.01) after adjustment ($p = .005$). It was also noticed that adjuvant treatments with MMC and BCG became significant protective factors for recurrence after the multivariate analysis was accomplished ($p < .005$) (Table 3).

Likewise, a tumour weight higher than 4 g, together with other prognostic factors was also associated with a higher risk of progression in the univariate analysis with a HR of 2.35 (95% CI: 1.31–4.21, $p = .005$) (Table 4). These statistically significant findings were still present after the multivariate

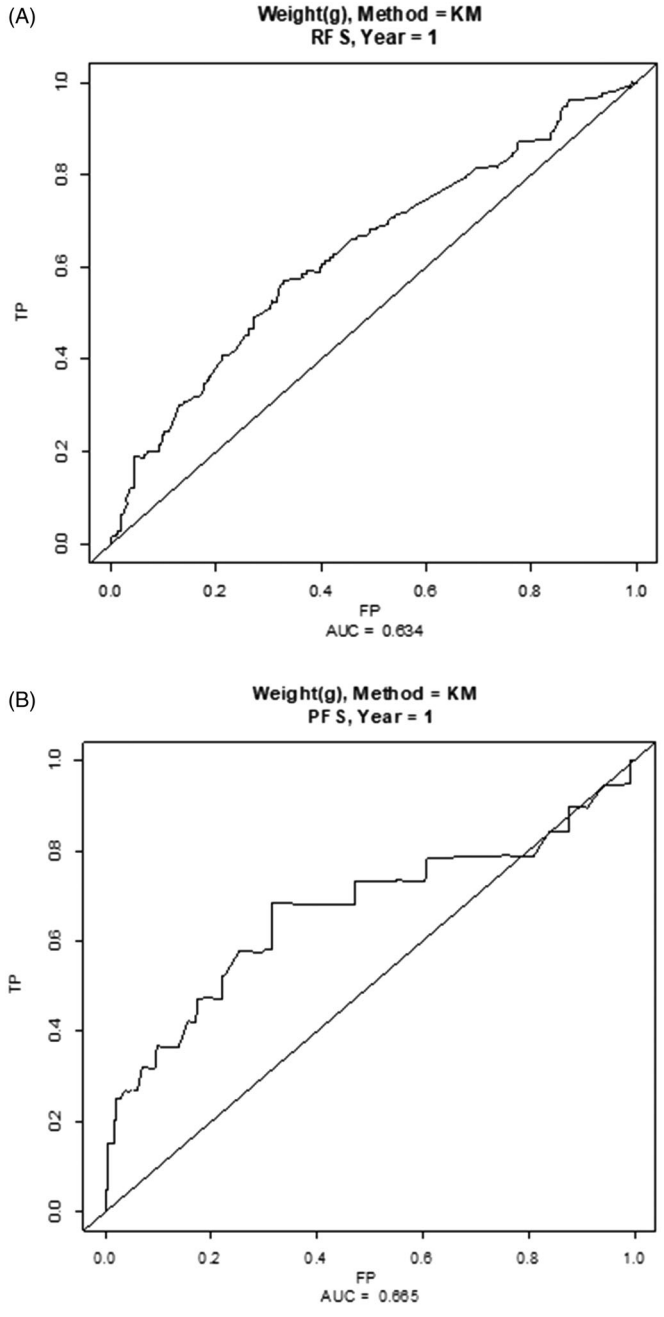

Figure 2. Time-dependent ROC curves for RFS (A) and PFS (B) at 1 year depending on tumour weight.

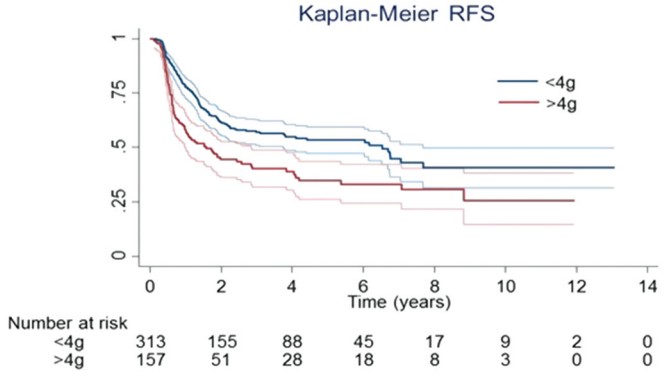

Figure 3. RFS Kaplan-Meier curves comparing both groups and their CI.

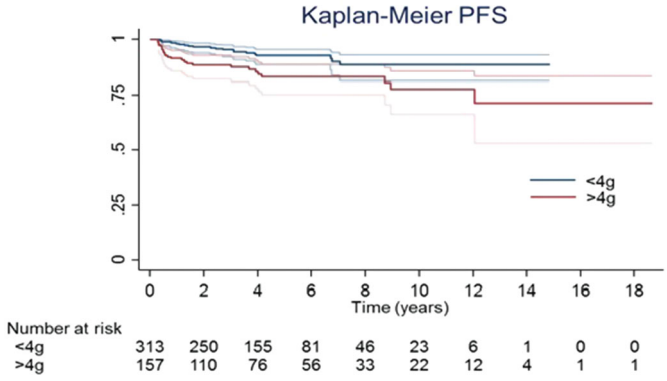

Figure 4. PFS Kaplan-Meier curves comparing both groups and their CI.

Table 2. HR estimation by univariate COX regression model for recurrence.

	Univariate COX regression model	
Variable	HR (CI 95%)	*p* Value
Weight > 4 g	1.71 (1.31–2.24)	<.001
Gender (male)	1.08 (0.75–1.55)	.678
Multiplicity	1.84 (1.41–2.42)	<.001
Size >3 cm	1.72 (1.33–2.24)	<.001
Stage		
Ta	1 (ref.)	
T1	1.22 (0.94–1.59)	.139
High-grade	1.11 (0.84–1.51)	.464
Postoperative MMC	0.63 (0.49–0.82)	.001
Adjuvant treatment		
No treatment	1 (ref.)	
MMC	0.67 (0.42–1.06)	.087
BCG	0.76 (0.54–1.06)	.108

Table 3. HR estimated by multivariate COX regression model for recurrence.

	Multivariate COX regression model	
Variable	HR (CI 95%)	*p* Value
Weight > 4 g	1.52 (1.14–2.01)	.005
Gender (male)	1.02 (0.71–1.48)	.904
Multiplicity	2.08 (1.57–2.76)	<.001
Stage		
Ta	1 (ref.)	
T1	1.18 (0.86–1.62)	.309
High-grade	1.27 (0.92–1.75)	.145
Postoperative MMC	0.67 (0.51–0.88)	.005
Adjuvant treatment		
No treatment	1 (ref.)	
MMC	0.47 (0.29–0.77)	.003
BCG	0.49 (0.32–0.73)	.001

analysis was performed, with a 1.87-fold (95% CI: 1.01–3.47) increased risk of progression if a weight higher than 4 g was reported. We also noticed that both multiplicity and high grade were prognostic factors for progression, and especially the latter one that would multiply the risk of progression by six (Table 5).

Discussion

The assessment of prognostic factors in NMIBC and their nomograms may be useful for patient counselling and to predict the probability of recurrence and progression during follow-up. They are also effective tools for selecting patients for adjuvant therapies that have demonstrated a benefit in terms of recurrence [10,11] and progression [12].

Table 4. HR estimated by univariate COX regression model for progression.

	Univariate COX regression model	
Variable	HR (CI 95%)	*p* Value
Weight > 4 g	2.35 (1.31–4.21)	.004
Gender (male)	1.1 (0.49–2.45)	.823
Multiplicity	2.25 (1.25–4.03)	.007
Size > 3 cm	1.98 (1.11–3.55)	.021
Stage		
Ta	1 (ref.)	
T1	3.44 (1.81–6.55)	<.001
High-grade	8.08 (2.87–22.76)	<.001
Postoperative MMC	0.78 (0.43–1.41)	.409
Adjuvant treatment		
No treatment	1 (ref.)	
MMC	1.7 (0.7–4.16)	.244
BCG	2.27 (1.17–4.25)	.015

Table 5. HR estimated by multivariate COX regression model for progression.

	Multivariate COX regression model	
Variable	HR (CI 95%)	*p* Value
Weight > 4 g	1.87 (1.01–3.47)	.047
Multiplicity	1.91 (1.05–3.48)	.035
Stage		
Ta	1 (ref.)	
T1	1.49 (0.71–3.11)	.287
High-grade	6.43 (2.13–19.38)	.001
Adjuvant treatment		
No treatment	1 (ref.)	
MMC	0.84 (0.34–2.1)	.706
BCG	0.99 (0.48–2.06)	.982

The importance of tumour size as a prognostic factor is widely accepted [2,13]. However, there are several studies that have questioned the role of this variable in the prognosis of the disease [5].

In our opinion, two issues with this variable might explain these discrepancies. First, the measurement of tumour size is completely subjective, with important inter-observers differences reported in the literature [14]. Secondly, tumour size does not determine the overall tumour volume, especially in those cases with multifocal disease or in tumours with discrepancies between the tumour base and the tumour burden sizes. Hence, if one takes into account the largest tumour size and their number, it might lead to situations where patients with very different tumour burden are placed in the same risk category of recurrence and progression. For example, one patient with four tumours of 4, 1, 1 and 2 cm would have the same tumour burden as another one with four tumours of 4, 4, 3 and 3 cm since both patients have their largest tumour implant of 4 cm. Presumably, this would not happen with the tumour weight. Therefore, the weight of the resected specimen could more accurately represent the real burden of the neoplasm as it takes into account another important variable: the density of the tumour. In our research (Figure 1), the most common outliers are papillary tumours with large size and low weight, which reflect low tumour density. In contrast, we can also find small tumours with high weight due to their solid composition. Hence, weight can explain the recurrence and progression in these cases with smaller size.

Since the first publication in which we described the tumour weight as potentially relevant for prognosis in

NMIBC [4], few publications have attempted to confirm these results [5].

In the present study, with a larger sample size and longer follow-up time, a weight of 4 g was found as the optimal cut-off point for the prediction of both one-year recurrence and progression. In our previous publication, this cut-off was set at 6 g. but the ROC curve was only produced for the prediction of recurrence and it was not time-dependent. Sensitivity and specificity have changed slightly, with a decrease in sensitivity (60–49%) and an increase in specificity (62–73%). However, in the present study the risk of progression was also taken into account when the optimal cut-off point was selected, improving its prognostic performance for both endpoints. Kwon et al. [5] set the optimal cut-off point for the prediction of both recurrence and progression at 2 g with a sensitivity and specificity of 70.5% and 57%, respectively.

There are currently no tools available that provide an optimal assessment of the risk of recurrence. The CUETO and EORTC tables [15], both using several prognostic factors (including tumour size >3 cm), cannot reach a C-index higher than 0.6 for the prediction recurrence despite being the most widely applied tool for that purpose [16]. Although the aim of our study is not the development of a prognostic model, the predictive ability by including the variables of our multivariate analysis would raise the C-index for recurrence and progression to 0.66 and 0.79, respectively, showing that both prediction tables would increase their prognostic performance if weight instead of size were included.

In the present study, the increased likelihood of recurrence in those patients with a high specimen weight was lower than in our previous report but with a narrower confidence interval and stronger statistical significance. The new threshold value of 4 g compared to the previous one, after adjusting for other prognostic factors, changes from a HR of 1.7–1.5 [4]. This can be explained by the larger population of the current study (470 versus 144), so we are now able to calculate with greater accuracy the value of weight with very similar RFS rates at three years, as compared with our first study: 51.7% and 55.3%, respectively.

Moreover, Kwon et al. did not find a statistically significant association between weight and recurrence, but they did find an association between weight and the risk of progression. The risk of progression was four times higher in those patients with a specimen weight over 2 g. In addition, they only found high grade, not size nor stage, to be associated with the risk of progression [5].

In terms of progression, the multivariate analysis in our study also showed that weight influences the PFS: a weight of the specimen higher than 4 g. would turn into a two-fold increase of the risk of progression. High-grade disease remains the most important prognostic factor for progression in our present study. On the other hand, the results obtained by Kwon et al. should be interpreted with caution because of the low number of cases with progression (7.4%) associated with a low cut-off point, which can lead to overestimating the increased risk of progression due to its lower specificity.

One of the limitations of our study is the fact that some healthy tissue might be included with the tumour, overestimating the real weight of the sample. Also, the thermal and electrical injuries in the tissue during resection are inevitable and a small part of the tissue might be fulgurated. However, this canapply to all cases and should not lead to a significant bias. The long period of time would be another limitation due to changes in the surgical and sample processing techniques, although these changes may be minor ones. Finally, the lack of randomisation and the retrospective design of the study make it necessary to confirm these results in future prospective studies.

In conclusion, this study confirms, with an increased number of patients and longer follow-up, that the weight of the specimen after resection in NMIBC is a prognostic factor for recurrence and also for progression. The weight of the tumour may be measured more accurately than the tumour size, with less variability and it can also more accurately estimate the overall tumour burden in cases of multifocal disease. An increase of 52% and 87%, respectively, in the risk of recurrence and progression were found for tumours heavier than 4 g. More studies are warranted to confirm the value of including this variable in current risk calculators and its accuracy compared to the size of the tumour.

Disclosure statement

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments ethical standards.

For this type of study formal consent is not required (a retrospective study).

This article does not contain any studies with animals performed by any of the author.

Authors contribution

G. Fernández-Conejo: Conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

E. de la Peña: Conception and design, manuscript writing, final approval of manuscript.

V. Hernández: data analysis and interpretation manuscript writing, final approval of manuscript.

A. Guijarro: collection and assembly of data, manuscript writing, final approval of manuscript.

A. Castro: collection and assembly of data, manuscript writing, final approval of manuscript.

E. Pérez-Fernández: Data analysis and interpretation, manuscript writing, final approval of manuscript.

C. Llorente: Conception and design, manuscript writing, final approval of manuscript.

ORCID

Guillermo Fernández-Conejo http://orcid.org/0000-0002-7317-9107

References

[1] Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting non-muscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol. 2009;182(5):2195–2203.

[2] Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49(3):466–475.

[3] Racioppi M, Cappa E, D'Agostino D, et al. Size of bladder cancers: correlation among different types of measurement. Urol Int. 2013;90(2):191–194.

[4] De La Pena E, Hernandez V, Blazquez C, et al. Weight of the resected specimen after transurethral resection as a new predictive variable for recurrence of non-muscle-invasive bladder tumour. BJU Int. 2013;111(4 Pt B):E196–E201.

[5] Kwon DH, Song PH, Kim HT. Multivariate analysis of the prognostic significance of resection weight after transurethral resection of bladder tumor for non-muscle-invasive bladder cancer. Korean J Urol. 2012;53(7):457–462.

[6] Sobin Lh GM, Wittekind C. TNM classification of malignant tumors. UICC international union against cancer. 7th ed. Hoboken (NJ): Wiley-Blackwell; 2009.

[7] Montironi R, Mazzucchelli R, Scarpelli M, et al. Morphological diagnosis of urothelial neoplasms. J Clin Pathol. 2007;61(1):3–10.

[8] Sauter G, Amin M. Tumours of the urinary system: non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, et al., editors. WHO classification of tumours of the urinary system and male genital organs. Lyon: IARCC Press; 2004.

[9] Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics. 2000;56(2):337–344.

[10] Jarvinen R, Kaasinen E, Sankila A, et al. Long-term efficacy of maintenance bacillus Calmette-Guerin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. Eur Urol. 2009;56(2):260–265.

[11] Huncharek M, McGarry R, Kupelnick B. Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res. 2001;21(1B):765–769.

[12] Malmstrom PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol. 2009;56(2):247–256.

[13] Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, et al. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J Urol. 2000;163(1):73–78.

[14] Hatano T, Oda M, Ogawa Y, et al. Exact documentation of location and size of bladder tumor with a three-dimensional mapping device. Int J Urol. 1996;3(1 Suppl):S46–S47.

[15] EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2019. ISBN 978-94-92671-04-2. http://uroweb.org/guidelines/compilations-of-all-guidelines/

[16] Ravvaz K, Walz ME, Weissert JA, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in a United States population. J Urol. 2017;198(4):824–831.