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Review

Oncological impact of cystoscopic findings in non-muscle-invasive bladder cancer: a meta-analysis

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Objective

To assess the association between cystoscopic findings and oncological outcomes in patients with non-muscle-invasive bladder cancer (NMIBC) given that the oncological impact of quantity and quality assessment of tumours with cystoscopy has not been well verified.

Methods

Multiple databases were queried in May 2022 for studies investigating the association of oncological outcomes, such as recurrence-free (RFS), progression-free (PFS), and cancer-specific survival (CSS), with cystoscopic findings, including multiplicity, size, and gross appearance of tumours in patients with NMIBC.

Results

Overall, 73 studies comprising 28 139 patients were eligible for the meta-analysis. Tumour multiplicity was associated with worse RFS (pooled hazard ratio [HR] 1.61, 95% confidence interval [CI] 1.48–1.74) and PFS (pooled HR 1.44, 95% CI 1.18–1.76) in NMIBC patients (including both Ta and T1). Tumour size (≥3 cm) was associated with worse RFS (pooled HR 1.97, 95% CI 1.69–2.30) and PFS (pooled HR 1.81, 95% CI 1.52–2.15) in NMIBC patients. In patients with T1 bladder cancer (BCa), tumour multiplicity and size (≥3 cm) were also associated with worse RFS, PFS and CSS. By contrast, among patients treated with bacillus Calmette-Guérin (BCG), tumour multiplicity was not associated with worse RFS, and tumour size (≥3 cm) was not associated with worse PFS. Sessile tumours were associated with worse RFS (pooled HR 2.14, 95% CI 1.52–3.01) and PFS (pooled HR 2.17, 95% CI 1.42–3.32) compared to pedunculated tumours. Compared to papillary tumours, solid tumours were associated with worse RFS (pooled HR 1.84, 95% CI 1.25–2.72) and PFS (pooled HR 3.06, 95% CI 2.31–4.07) in NMIBC patients, and CSS in T1 BCa patients (pooled HR 2.32, 95% CI 1.63–3.30).

Conclusions

Cystoscopic findings, including tumour multiplicity, size, and gross appearance, strongly predict oncological outcomes in NMIBC patients. Cystoscopic visual features can help in the decision-making process regarding the timeliness and extent of tumour resection as well as future management such as intravesical therapy.

Keywords

non-muscle-invasive bladder cancer, cystoscopy, multiplicity, size, gross appearance, recurrence, progression, #BladderCancer, #blcsm, #uroonc

Introduction

Cystoscopy is an essential procedure for the diagnosis and follow-up of bladder cancer (BCa) patients [1]. Cystoscopic findings, such as tumour size and number, have been recognized as accurate prognosticators of tumour recurrence and progression in patients with non-muscle-invasive bladder cancer (NMIBC) [1]. Indeed, these two factors are included in the guideline-endorsed risk classification/models based on large cohorts to guide clinical decision making. However, the clinical value and cut-off values vary across the different prognostic models [2–5] and the additive value of each variable alone is not yet established through systematic comparison [6].

In addition, the European Association of Urology (EAU) guideline endorses describing the macroscopic features of bladder tumours, such as site, size, number, appearance and mucosal abnormalities during cystoscopy [1]. However, apart from the size and number of tumours, the association between the gross appearance of tumours and oncological outcomes has not yet been assessed. Therefore, we aimed to thoroughly review the available literature in order to assemble all the evidence regarding the prognostic value of cystoscopic findings, including tumour multiplicity, size, and gross appearance in NMIBC patients.

Methods

The protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42022313955).

Search Strategy

This systematic review and meta-analysis was carried out based on the guidelines of the Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology Statement (Fig. S1) [7]. In May 2022, we performed a literature search in the PUBMED®, Web of Science™, and Scopus® databases to identify studies investigating the prognostic value of macroscopic tumour features, including tumour multiplicity, size, and gross appearance in NMIBC patients. The keywords used in our search strategy were as follows: (bladder OR urothelial) AND (tumour OR cancer OR carcinoma) AND (TURBT OR transurethral) AND (recurrence OR progression OR survival OR prognosis OR prognostic OR predictive) AND (size OR diameter OR number OR multiple OR multiplicity OR multifocality OR papillary OR sessile OR pedunculated OR appearance). The detailed search strategy is shown in Appendix S1. The primary outcomes of interest were recurrence-free survival (RFS), progression-free survival (PFS) and cancer-specific survival (CSS). Two investigators conducted initial screening based on the titles and abstracts to identify eligible studies. Potentially relevant studies were subjected to a full-text review. Additionally, manual searches of the reference lists of relevant articles were also performed to identify additional studies. Disagreements were resolved by consensus with co-authors.

Inclusion and Exclusion Criteria

Studies were included if they investigated patients diagnosed with NMIBC who had been treated with transurethral resection of bladder tumour (TURBT) with or without intravesical instillation therapy (Patients), with adverse tumour features identified by cystoscopy (Interventions), compared to those without adverse tumour features identified by cystoscopy (Comparisons), to assess the independent prognostic value of these cystoscopically identified adverse tumour features with regard to RFS, PFS and CSS (Outcome), utilizing multivariable Cox regression analysis in non-randomized observational, randomized, or cohort studies (Study design). Studies lacking original patient data, reviews, letters, editorial comments, replies from authors, case reports, and articles not written in English were excluded. The references of all included papers were scanned for additional studies of interest. We excluded the original studies for four major prognostic models (the European Organization for Research and Treatment of Cancer [EORTC] published in 2006 and 2016, Spanish Urological Club for Oncological Treatment [CUETO] and EAU [2–5]) in order to minimize heterogeneity and to compare each hazard ratio (HR) of our analyses with their reported outcomes.

Data Extraction

Data were extracted independently by two authors. The first author's name, the publication year, recruitment periods, the number of patients, the inclusion criteria, pathological stage and grade, bladder instillation therapy, repeat resection, age, sex, concomitant carcinoma *in situ* (CIS), tumour diameter, multifocality, gross appearance, follow-up periods, and

significant variables included in the multivariable analysis were extracted. Subsequently, the HRs and 95% CIs of pretreatment cystoscopically identified adverse tumour features associated with RFS, PFS and CSS were retrieved. All HRs were derived from multivariable analyses using Cox regression models. In cases of suspected duplicate cohorts from the same author or institution, the higher-quality or the most recent data were used in the analyses. All discrepancies were resolved by consensus with co-authors.

Risk of Bias Assessment

We assessed the study quality and risk of bias using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, referring to the Cochrane Handbook for Systematic Reviews of Interventions. Each bias domain and overall risk of bias were judged as 'low', 'moderate', 'serious' or 'critical' risk of bias. The main confounders were identified as the critical prognostic factors of RFS. The presence of confounders was determined by consensus and review of the literature. The ROBINS-I assessment of each study was performed independently by two authors (Table S1).

Statistical Analyses

Forest plots were used to analyse and summarize the multivariable HRs and to describe the association between cystoscopic findings and oncological outcomes. Heterogeneity among the outcomes of included studies in this meta-analysis was assessed using Cochrane's Q test. When significant heterogeneity (P value of <0.05 in the Cochrane Q test) was observed, we investigated the cause of heterogeneity and a random-effects model was applied [8,9]. A fixed-effects model was used to calculate pooled HRs for non-heterogeneous results [10]. Funnel plots were used to assess publication bias (Fig. S2). The Egger's test was performed to investigate publication bias when more than 10 studies were included in the analysis [11]. All analyses were performed separately depending on the T stage stratified by Ta only, mixed cohort of NMIBC (including both Ta and T1), and T1 only. Subgroup analysis was conducted in studies assessing T1 patients according to inclusion criteria whether all patients received BCG bladder instillation therapy or not. All analyses were conducted using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and the statistical significance level was set at $P < 0.05$.

Results

Study Selection and Characteristics

Our initial search identified 3584 records. After removing duplicates, 2380 records remained for screening of the titles and abstracts (Fig. 1). After screening, a full-text review was performed for 201 articles. According to the inclusion criteria, we finally identified 72 studies comprising 28 139 patients eligible for the meta-analysis [12–83]. The demographics of each included study are shown in Table 1 and Table S2. Of the 72 included studies, five included only Ta NMIBC patients [12–16], and 26 studies included only T1 NMIBC patients [17–42]. The other 41 studies included both Ta and T1 patients [43–83].

Meta-Analysis of the Prognostic Impact of Tumour Multiplicity

All results of the meta-analyses are summarized in Table 2.

Ta Patients Only

Five studies, comprising 1861 patients, provided data on RFS in Ta NMIBC patients regarding tumour multiplicity. As shown in Fig. 2A, tumour multiplicity was significantly associated with worse RFS compared to solitary tumours (pooled HR 1.86, 95% CI 1.34–2.57; $P < 0.001$). The Cochrane's Q test revealed significant heterogeneity ($P = 0.006$).

Patients with NMIBC Including Both Ta and T1

For RFS analysis, 31 studies comprising 15 367 patients were included in the meta-analysis. The forest plot showed that tumour multiplicity was significantly associated with worse RFS (Fig. 2B; pooled HR 1.61, 95% CI 1.48–1.74, $P < 0.001$). The Cochrane's Q test ($P = 0.004$) revealed significant heterogeneity.

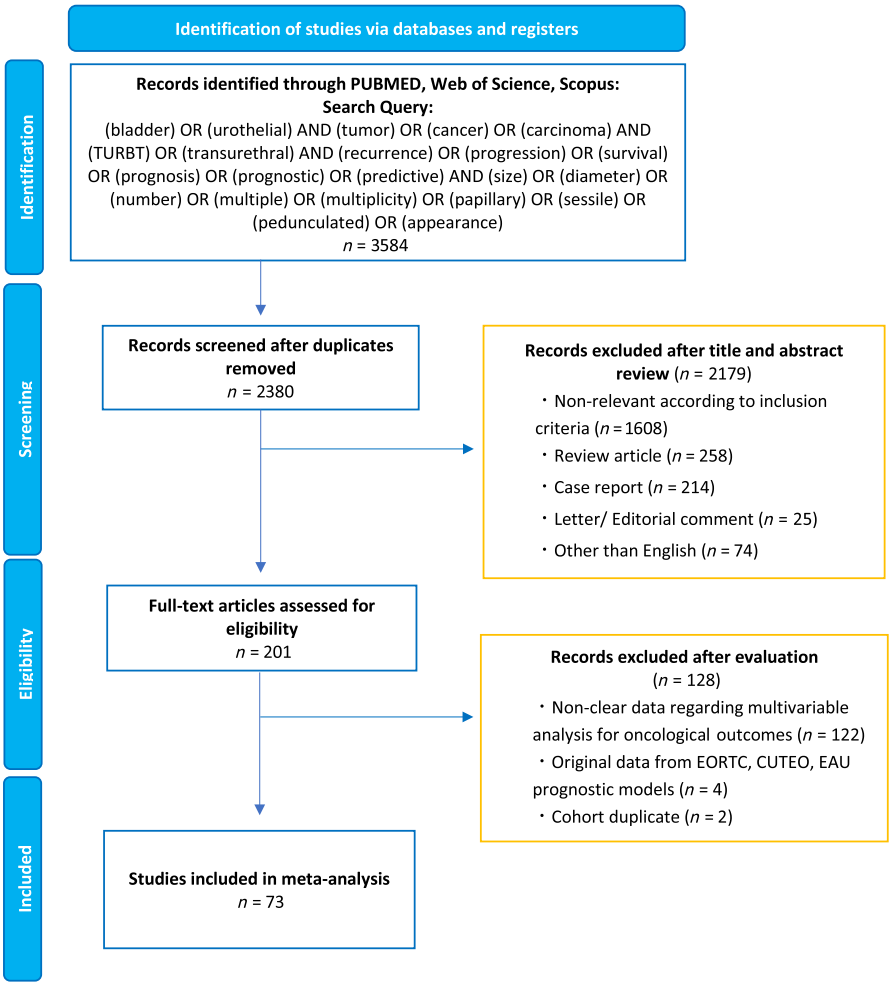
For PFS analysis, 14 studies comprising 6180 patients were included in the meta-analysis. The forest plot showed that tumour multiplicity was significantly associated with worse PFS (Fig. 2B; pooled HR 1.44, 95% CI 1.18–1.76, $P < 0.001$). The Cochrane's Q test ($P = 0.19$) revealed no significant heterogeneity.

T1 Patients Only

For RFS analysis, 11 studies comprising 2956 patients were included in the meta-analysis. The forest plot showed that tumour multiplicity was significantly associated with worse RFS compared to solitary tumours (Fig. 2C; pooled HR 1.37, 95% CI 1.12–1.67, $P = 0.002$). The Cochrane's Q test revealed significant heterogeneity ($P = 0.023$). However, subgroup analysis among T1 NMIBC patients treated with BCG revealed no statistically significant differences in RFS between patients with solitary tumours and those with multiple tumours (pooled HR 1.14, 95% CI 0.85–1.54).

For PFS analysis, 11 studies comprising 3182 patients were included in the meta-analysis. The forest plot showed that tumour multiplicity was significantly associated with worse

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart, detailing the article selection process.



PFS (Fig. 2C; pooled HR 1.39, 95% CI 1.10–1.76, $P = 0.006$). The Cochrane's Q test revealed significant heterogeneity ($P = 0.018$). Subgroup analysis among T1 NMIBC patients treated with BCG showed that tumour multiplicity remained associated with worse PFS despite BCG treatment (pooled HR 1.61, 95% CI 1.16–2.22).

For CSS analysis, five studies comprising 1860 patients were included in the meta-analysis. The forest plot showed that tumour multiplicity was significantly associated with worse CSS (Fig. 2C; pooled HR 1.53, 95% CI 1.21–1.92, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.33$).

Meta-Analysis of the Prognostic Impact of Tumour Size

Ta Patients Only

Two studies, comprising 1083 patients, provided data on RFS in Ta NMIBC patients who did or did not harbour tumours larger than 3 cm. The forest plot revealed that patients with tumours ≥3 cm had significantly worse RFS (Fig. 3A; pooled HR 2.31, 95% CI 1.79–3.01, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.8$).

Patients with NMIBC Including Both Ta and T1

For RFS analysis, 25 studies comprising 13 423 patients were included in the meta-analysis. The forest plot showed that patients with tumours ≥3 cm had significantly worse RFS (Fig. 3B; pooled HR 1.97, 95% CI 1.69–2.30, $P < 0.001$). The Cochrane's Q test revealed significant heterogeneity ($P < 0.001$).

For PFS analysis, 11 studies comprising 6634 patients were included in the meta-analysis. The forest plot showed that patients with tumours ≥3 cm had significantly worse PFS (Fig. 3B; pooled HR 1.81, 95% CI 1.52–2.15, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.068$).

T1 Patients Only

For the analysis of RFS, 12 studies comprising 2289 patients were included in the meta-analysis. As shown in Fig. 3C, patients with tumours ≥3 cm had significantly worse RFS (pooled HR 1.50, 95% CI 1.31–1.72, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.7$). Subgroup analysis among T1 NMIBC patients treated with BCG showed that tumour size ≥3 cm remained associated with worse RFS (pooled HR 1.35, 95% CI 1.06–1.73).

For PFS analysis, 13 studies comprising 3406 patients were included in the meta-analysis. The forest plot showed that patients with tumours ≥3 cm had significantly worse PFS (Fig. 3C; pooled HR 1.57, 95% CI 1.16–2.14, $P = 0.004$). The Cochrane's Q test revealed significant heterogeneity ($P = 0.018$). Subgroup analysis among T1 NMIBC patients treated with BCG showed no statistical differences in PFS between patients with ≥3 cm tumours and those with <3 cm tumours (pooled HR 1.15, 95% CI 0.57–2.29).

For CSS analysis, seven studies comprising 5166 patients were included in the meta-analysis. The forest plot revealed that patients with tumours ≥3 cm had significantly worse CSS (Fig. 3C; pooled HR 1.43, 95% CI 1.23–1.66, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.075$).

Meta-Analysis of the Prognostic Impact of Tumour Gross Appearance

Papillary vs Solid Tumours

For RFS analysis, eight studies comprising 1301 patients provided data on RFS in patients with solid vs papillary tumours. As shown in Fig. 4A, solid tumours were associated with significantly worse RFS compared to papillary tumours (pooled HR 1.84, 95% CI 1.25–2.72, $P = 0.002$). The Cochrane's Q test revealed significant heterogeneity ($P = 0.045$).

For PFS analysis, nine studies comprising 1557 patients were included in the meta-analysis. As shown in Fig. 4A, solid tumours were associated with significantly worse PFS compared to papillary tumours (pooled HR 3.06, 95% CI 2.31–4.07, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.4$).

For CSS analysis, four studies comprising 2444 patients with T1 NMIBC were included in the meta-analysis. The forest plot showed that solid tumours were also associated with worse CSS compared to papillary tumours (Fig. 4A; pooled HR 2.23, 95% CI 1.63–3.30, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.8$).

Pedunculated vs Sessile Tumours

For RFS analysis, three studies comprising 563 patients provided data on RFS in NMIBC patients with pedunculated or sessile tumours. The forest plot showed that sessile tumours were associated with significantly worse RFS compared to pedunculated tumours (Fig. 4B; pooled HR 2.14, 95% CI 1.52–3.01, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.052$).

For PFS analysis, three studies comprising 529 patients provided data on PFS in NMIBC patients with pedunculated or sessile tumours. The forest plot showed that sessile tumours were also associated with significantly worse PFS compared to pedunculated tumours (Fig. 4B; pooled HR 2.17, 95% CI 1.42–3.32, $P < 0.001$). The Cochrane's Q test revealed no significant heterogeneity ($P = 0.23$).

Risk of Bias and Publication Bias Assessment

The risk of bias judgements for each domain in each included study are summarized in Table S1. Among studies included, 10 studies had a low risk of bias, whereas the others (86%) had a moderate or serious risk of bias using the ROBINS-I tool [11].

Funnel plots of each analysis are depicted in Fig. S2. The Egger's test revealed no statistical evidence of publication bias for analyses as follows: association of RFS and PFS with tumour multiplicity in NMIBC patients ($P = 0.94$ and $P = 0.63$, respectively); association of RFS and PFS with tumour multiplicity in T1 BCa patients ($P = 0.73$ and $P = 0.12$, respectively); association of RFS and PFS with tumour size in NMIBC patients ($P = 0.07$ and $P = 0.23$, respectively); and association of RFS and PFS with tumour size in T1 BCa patients ($P = 0.14$ and $P = 0.74$, respectively).

Discussion

Using the cumulative data from 28 139 NMIBC patients, we confirmed the prognostic importance of cystoscopic findings, such as tumour multiplicity, size and gross tumour appearance. In addition, our analyses showed that tumour multiplicity and size were associated with worse RFS, PFS and CSS in T1 BCa patients; however, this association weakened in subgroup analyses of patients treated with BCG. Furthermore, we found that solid tumours as well as sessile tumours were associated with worse RFS and PFS in patients with NMIBC; solid tumours were also associated with worse CSS in patients with T1 BCa.

Several prognostic models have been developed to risk stratify patients diagnosed with NMIBC and guide healthcare providers towards the optimal treatment in NMIBC management [1]. Five major prognostic models/classifications have been established and are referenced in the EAU

Table 1 Demographics of included studies.

Author	Year	Recruitment	No. of patients	T stage	Grade (WHO 1973 or 2004)	Age, years or *n* (%)
Ta patients only						
Cai	2007	1993–1996	143	Ta	G1/2/3 = 41/74/28	Median 67.8
Bosset	2015	1995–2008	481	Ta	LG	Mean 65 ± 12
Akitake	2018	2010–2015	245	Ta	LG (G1:91/G2:154)	Median 69
Shindo	2021	2007–2018	390	Ta	HG (G2:162/G3:228)	Median 74.3
Kohada	2021	2006–2018	602	Ta	G1/2 = 154/448	Median:72
T1 patients only						
Hara	2003	1995–1997	97	T1	HG (G3)	Median 66
Andius	2007	1987–1988	121	T1	G1/2/3 = 5/48/68	Median 74
Cho	2009	2001–2007	118	T1	G1/2/3 = 3/60/55	Median 67
Park	2009	1989–2005	194 (144)	T1	HG (G3)	Median 63
Alkhateeb	2010	1990–2008	191	T1	G1/2/3 = 2/56/133	Mean 69
Okajima	2010	1999–2001	1919	T1	G1/2/3 = 168/1026/715	>70: 1001 (52)
Bertz	2011	1989–2006	309	T1	HG (G2/3 = 89/220)	Median 71.7
Segal	2011	1995–2005	278	T1	HG (G3)	Median 72.8
Ajili	2013	2008–2010	45	T1	LG/HG = 27/18	Mean: 74
Alvarez-Mugica	2013	1989–1996	108	T1	HG	Median: 65.6
Kluth	2013	1996–2007	916	T1	HG	Median: 68
Olsson	2013	1992–2001	211	T1	HG (G2/3 = 36/175)	Median: 74
Ruan	2013	2007–2010	126	T1	LG/HG = 71/55	Mean:64.5
Angulo	2014	1981–2006	210	T1	HG (G3)	Mean: 70.6
Pellucchi	2014	2004–2011	291	T1	HG (G2/3 = 124/142)	Median: 68
Orsola	2015	2005-	200	T1	HG	Median: 71
Shen	2016	2005–2011	418	T1	LG/HG = 204/207	Mean: 65.1
Breyer	2017	1989–2009	231	T1	LG/HG = 4/227	Median: 72
Busetto	2017	2006–2013	101	T1	HG (G3)	>76: 34 (34)
Fujii	2017	2001–2015	148	T1	HG	Median: 72
Li G	2017	2004–2015	1676	T1	LG/HG = 685/991	Mean: 66
Hurle	2018	1998–2010	185	T1	HG	Median: 72
Eldin	2020	2016–2018	57	T1	LG/HG = 23/34	Mean:63.6
Asimakopoulos	2021	2009–2017	204	T1	G1/2/3 = 28/1/175	Mean: 72
Yanagisawa	2021	2013–2018	123	T1	HG	Median: 72
Busquets	2022	2014–2016	187	T1	HG	Mean: 75.3
Both Ta and T1 patients						
Kondo	1999	1989–1997	45	Ta/T1 = 35/10	G1/2/3 = 7/30/8	Mean: 59
Ali-El-Dein	2003	1991–2000	377	Ta/T1 = 38/339	G1/2/3 = 54/241/82	Mean: 55.4
Kwon	2006	1996–2004	128	Ta/T1 = 56/69	G1/2/3 = 20/45/63	Mean: 64
Nonomura	2006	1995–2001	71	Ta/T1 = 52/19	G1/2 = 36/35	Median: 64
Sakai	2006	1988–2004	154	Ta/T1 = 107/47	G1/2/3 = 44/101/9	>70: 61 (40)
Joo	2007	1998–2002	147	Ta/T1 = 90/57	LG/HG = 101/38	Mean: 64.2
Kikuchi	2009	1999–2001	3237	Ta/T1 = 1651/1586	G1/2/3 = 782/1850/605	Median: 69.9
Behnsawy	2010	2000–2007	161	Ta/T1 = 107/54	G1/2/3 = 49/89/23	>70: 82 (51)
Cai	2010	2002–2003	77	Ta/T1 = 48/29	G1/2/3 = 35/28/14	Mean: 71
Ha	2010	1995–2007	103	Ta/T1 = 23/80	LG/HG = 87/16	Median: 66
Hernandez	2011	1998–2008	417	Ta/T1 = 227/164	G1/2/3 = 220/142/40	Mean: 68.8
Jancke	2011	1992–2001	472	Ta/T1 = 357/115	G1/2/3 = 98/264/110	Mean: 72
Chen	2012	1999–2009	348	Ta/T1 = 220/128	G1/2/3 = 125/176/47	Median: 68
Jeong	2012	NA	55	Ta/T1 = 12/43	G1/2/3 = 13/34/8	Median: 64
Kwon	2012	1990–2010	406	Ta/T1 = 274/132	LG/HG = 165/241	Mean: 64.4
Ajili	2013	2000–2007	112	Ta/T1 = 68/44	LG/HG = 92/20	Mean: 63.9
Ali-El-Dein	2013	1984–2009	1019	Ta/T1/Tis = 71/916/32	G1/2/3 = 132/649/238	Median: 44
Ayari	2013	1990–1992	93	Ta/T1 = 69/24	G1/2/3 = 27/58/8	>70: 39 (42)
Nishiyama	2013	1995–2010	153	Ta/T1 = 74/79	G1/2/3 = 2/89/62	Mean: 68.5
Rink	2013	1987–2007	2043	Ta/T1 = 1608/435	G1/2/3 = 482/691/870	Median: 67
Zachos	2013	2001–2011	144	Ta/T1 = 112/32	HG	Mean: 69.8
Ding	2014	2002–2010	332	Ta/T1 = 204/128	G1/2/3 = 114/168/50	Median: 67
Klatte	2014	1996–2007	931	Ta/T1/Tis = 556/360/15	G1/2/3 = 184/349/398	Median: 67
Lin	2014	2004–2007	178	Ta/T1 = 65/113	G1/2–3 = 61/117	>65: 112 (63)
Ofude	2015	2001–2012	469	Ta/T1 = 388/81	G1/2/3 = 103/271/94	Median: 71
Abufaraj	2017	NA	827	Ta/T1/Tis = 463/346/18	G1/2/3 = 195/267/365	Median: 67
Cui	2017	2008–2013	329	Ta/T1 = 247/82	G1/2/3 = 55/189/85	Median: 63

Sex (M/F)	Recurrent tumour, *n* (%)	Concomitant CIS, *n* (%)	Size≥3 cm, *n* (%)	Multiplicity, *n* (%)	Gross appearance, *n* (%)
116/27	All recurrent	8 (5.6)	39 (27)	87 (61)	NA
388/93	NA	NA	72 (15)	133 (27)	NA
200/45	All newly diagnosed	NA	45 (18)	92 (38)	NA
309/81	All newly diagnosed	56 (14)	69 (18)	188 (48)	Papillary:378 (97), Pedunculated: 259 (66)
477/125	402 (67)	None	17 (2.8)	289 (48)	NA
76/21	NA	17 (18)	69 (18)	55 (57)	NA
86/35	All newly diagnosed	39 (32)	NA	38 (31)	Papillary: 56 (46)
101/17	Recurrent: 21 (18)	5 (4.2)	48 (41)	>4: 61 (52)	NA
121/23	All newly diagnosed	17 (12)	52 (36)	88 (61)	Papillary: 85 (59)
148/43	Recurrent: 96 (50)	56 (29)	83 (43)	84 (44)	NA
1524/395	NA	NA	336 (18)	913 (48)	Papillary: 1577 (82), Pedunculated: 1072 (54)
237/72	NA	106 (34)	181 (59)	106 (34)	NA
227/51	Recurrent: 147 (53)	43 (15)	NA	117 (43)	Papillary: 154 (66)
41/4	Recurrent: 19 (42)	2 (4.4)	29 (65)	20 (44)	NA
100/8	All newly diagnosed	32 (30)	29 (65)	46 (43)	NA
726/190	All newly diagnosed	53 (5.8)	237 (26)	370 (40)	NA
175/36	All newly diagnosed	NA	109 (52)	65 (31)	NA
103/23	NA	None	≥1.8: 46 (37)	51 (41)	NA
187/23	NA	None	NA	87 (41)	Papillary: 159 (76)
237/29	All newly diagnosed	None	71 (27)	90 (34)	NA
179/21	All newly diagnosed	57 (29)	86 (43)	91 (46)	Papillary: 166 (83)
348/70	276 (66)	NA	91 (22)	235 (56)	NA
181/50	All newly diagnosed	56 (24)	129 (56)	42 (18)	Solid: 24 (10)
78/23	All newly diagnosed	20 (20)	11 (11)	77 (76)	NA
125/23	19 (13)	61 (41)	35 (24)	85 (58)	Papillary: 121 (82)
1376/300	All newly diagnosed	NA	587 (35)	730 (44)	NA
143/42	39 (21)	37 (20)	85 (46)	60 (32)	NA
50/7	All newly diagnosed	8 (14)	37 (65)	23 (40)	Papillary: 43 (75)
180/24	All newly diagnosed	5 (2.5)	43 (21)	98 (48)	Solid: 2 (1)
92/31	28 (21)	20 (16)	NA	76 (62)	Sessile: 59 (48)
152/16	NA	28 (17)	55 (33)	76 (45)	Papillary: 142 (85)
36/9	All newly diagnosed	1 (2)	>2 cm: 14 (31)	14 (31)	Papillary: 44 (98), Sessile: 9 (20)
*418/115	155 (41)	20 (5.3)	130 (35)	243 (65)	Papillary: 346 (92)
112/16	All newly diagnosed	27 (21)	68 (53)	NA	Papillary: 105 (82), Sessile: 13 (10)
50/21	16 (23)	NA	NA	38 (54)	Papillary: 61 (86)
131/23	All newly diagnosed	None	40 (26)	55 (36)	Papillary and pedunculated: 143 (93)
118/29	All newly diagnosed	None	43 (29)	37 (25) (cut-off:3)	NA
2600/637	All newly diagnosed	None	374 (12)	1312 (41)	Papillary: 2938 (91), Pedunculated: 2251 (70)
137/24	All newly diagnosed	39 (24)	52 (32)	84 (52)	Papillary: 137 (85)
NA	NA	NA	17 (22)	39 (51)	NA
87/16	All newly diagnosed	None	47 (46)	40 (39)	NA
348/69	All newly diagnosed	14 (3.4)	150 (40)	117 (29)	NA
362/110	All newly diagnosed	None	150 (32)	110 (23)	NA
287/61	56 (16)	21 (6.0)	115 (33)	130 (37)	NA
45/10	All newly diagnosed	None	27 (49)	27 (49)	NA
339/67	All newly diagnosed	NA	192 (47)	303 (75) (cut-off:3)	NA
101/11	All newly diagnosed	34 (32)	53 (47)	55 (49)	NA
877/142	187 (18)	115 (11)	539 (53)	475 (47)	Papillary: 901 (88)
72/21	All newly diagnosed	NA	49 (53)	35 (38)	NA
122/31	All newly diagnosed	None	>1: 89 (58)	79 (52)	Papillary and pedunculated: 118 (77)
1608/435	All newly diagnosed	None	514 (25)	619 (30)	NA
180/26	NA	47 (23)	113 (79)	81 (56)	NA
273/59	NA	23 (6.9)	111 (33)	127 (38)	NA
723/208	All newly diagnosed	47 (5.0)	283 (30)	300 (32)	NA
124/54	All newly diagnosed	NA	79 (44)	76 (43)	NA
385/84	267 (57)	26 (5.5)	43 (9.2)	289 (62)	NA
644/183	156 (19)	44 (5.3)	154 (19)	287 (35)	NA
262/67	All newly diagnosed	None	113 (34)	123 (37)	NA

Table 1 (continued)

Author	Year	Recruitment	No. of patients	T stage	Grade (WHO 1973 or 2004)	Age, years or *n* (%)
Kilinc	2017	2002–2010	348	Ta/T1 = 144/204	G1/2/3 = 29/156/163	Median: 63.6
Li H	2017	2007–2015	484	Ta/T1 = 404/80	G1/2/3 = 91/316/77	Median: 64
Xu	2017	2006–2011	869	Ta/T1 = 50/819	LG/HG = 548/321	Mean: 64.9
Alberto	2019	1995–2015	255	Ta/T1 = 219/36	G1/2/3 = 45/153/56	Median: 69
Lu	2019	2012–2016	477	Ta/T1 = 359/118	G1/2/3 = 318/106/53	Median: 64
Yasui	2019	2008–2015	53	Ta/T1 = 42/11	LG/HG = 39/14	Median: 74.1
Fernandez-Conejo	2020	1999–2016	470	Ta/T1 = 254/217	G1/2/3 = 165/188/115	Mean: 69
Fujita	2020	1993–2019	428	Ta/T1 = 13/415	G1/2/3 = 48/255/125	Median: 72
Li X	2020	2012–2015	206	Ta or Tis/T1 = 153/53	LG/HG = 150/56	Median: 62
Semeniuk-Wojtas	2020	2010–2015	101	Ta/T1/Tis = 39/13/7	G1/2/3 = 50/45/5	NA
Stec	2020	2010–2015	134	Ta/T1/Tis = 51/25/9	G1/2/3 = 55/64/14	NA
Ham	2021	2012–2017	356	Ta/T1/Tis = 48/308/14	LG/HG = 175/183	Median: 62/69
Ho	2021	2018–2019	220	Ta/T1 = 166/54	LG/HG = 127/66	Median: 73
Kim	2021	2000–2007	151	Ta/T1/Tis = 87/59/5	G1/G2-3 = 19/131	Mean: 63.6

*HG, high-grade; LG, low-grade; NA, not applicable. *Including both test and validation cohort.*

Table 2 Summary of results.

Endpoints	T stage	Subgroup	HR	95% CI	No. of study	No. of patients
Multiplicity (multiple vs. solitary)						
RFS	Ta		1.86	1.34–2.57	5	1861
	Ta/T1		1.61	1.48–1.74	31	15 367
	T1	All	1.37	1.12–1.67	11	2956
		Patients treated with BCG only	1.14	0.85–1.54	3	444
PFS	Ta/T1		1.44	1.18–1.76	14	6180
	T1	All	1.39	1.10–1.76	11	3182
		Patients treated with BCG only	1.61	1.16–2.22	4	775
CSS	T1		1.53	1.21–1.92	5	1860
Tumour size (>3 cm vs <3 cm)						
RFS	Ta		2.32	1.79–3.01	2	1083
	Ta/T1		1.97	1.69–2.30	25	13 423
	T1	All	1.5	1.31–1.72	12	2289
		Patients treated with BCG only	1.35	1.06–1.73	5	701
PFS	Ta/T1		1.81	1.52–2.15	11	6634
	T1	All	1.57	1.16–2.14	13	3406
		Patients treated with BCG only	1.15	0.56–2.34	4	790
CSS	T1		1.43	1.23–1.66	7	5166
Gross appearance						
Solid vs papillary						
RFS	Ta/T1		1.99	1.50–2.65	6	1044
	T1		1.78	0.45–7.12	2	257
PFS	Ta/T1		3.51	1.70–7.21	3	671
	T1		2.99	2.20–4.07	6	886
CSS	T1		2.32	1.63–3.30	4	2444
Sessile vs pedunculated						
RFS	Ta/T1		2.14	1.52–3.01	3	563
PFS			2.17	1.42–3.32	3	529

CSS, cancer-specific survival; HR, hazard ratio; no., number; PFS, progression-free survival; RFS, recurrence-free survival.

guidelines [1] (Table 3). For RFS, the EORTC risk table published in 2006, which includes 2561 patients with Ta and T1 (78% received intravesical treatment), showed that tumour multiplicity (HR 1.56, 95% CI 1.42–1.71) and tumour size ≥3 cm (HR 1.54, 95% CI 1.32–1.80) were associated with worse RFS [5]. In agreement with these findings, our analyses among NMIBC patients including both Ta and T1 showed that tumour multiplicity (pooled HR 1.61, 95% CI 1.48–1.74) was associated with worse RFS [5]. In addition, our analysis also confirmed that tumour size ≥3 cm (pooled HR 1.97, 95% CI 1.69–2.30) was associated with worse RFS, with an even higher HR than that reported in the EORTC risk table [5].

As for PFS, the EORTC risk table and the EAU risk tables published in 2021 found that tumour multiplicity and size

Sex (M/F)	Recurrent tumour, *n* (%)	Concomitant CIS, *n* (%)	Size≥3 cm, *n* (%)	Multiplicity, *n* (%)	Gross appearance, *n* (%)
285/63	170 (49)	32 (9.2)	194 (56)	153 (44)	NA
383/101	121 (25)	None	78 (16)	203 (42)	NA
707/162	All newly diagnosed	None	283 (33)	351 (40)	NA
209/46	36 (14)	8 (3.1)	18 (7.1)	18 (7.1)	NA
392/85	All newly diagnosed	None	136 (29)	365 (77)	NA
48/5	11 (21)	2 (3.8)	7 (13)	29 (55)	NA
396/74	All newly diagnosed	None	184 (39)	146 (31)	NA
342/186	All newly diagnosed	22 (5.1)	83 (19)	191 (45)	NA
165/41	All newly diagnosed	NA	62 (30)	94 (46)	NA
87/14	All newly diagnosed	2 (2)	45 (45)	34 (34)	NA
113/21	NA	4 (3)	54 (40)	48 (36)	NA
NA	All newly diagnosed	14 (4)	NA	171 (48)	NA
169/51	All newly diagnosed	None	NA	95 (43)	NA
127/24	All newly diagnosed	NA	NA	88 (58)	NA

≥3 cm are also prognosticators of PFS [2,4]. In our analyses among a large group of studies with NMIBC patients, we confirmed that tumour multiplicity (pooled HR 1.44, 95% CI 1.18–1.76) and size ≥3 cm (pooled HR 1.81, 95% CI 1.52–2.15) were associated with worse PFS, in concordance with the HR values from the EORTC and the EAU risk tables [2,4]. Theoretically, one would expect tumour multiplicity to be more likely to affect RFS as it reflects the field effect carcinogenesis, and tumour size to be more likely to affect PFS as it is likely to reflect the growth and thereby invasiveness. However, taken together, tumour multiplicity and size are both independent, reliable prognosticators of both RFS and PFS in patients with NMIBC.

We found that tumour multiplicity and size remained powerful predictors of RFS, PFS and CSS in T1 BCa patients as well. T1 BCa is a heterogeneous disease associated with high rates of disease progression and, eventually, fatality [84–87]. A previous meta-analysis reported that substaging, lymphovascular invasion, CIS, tumour size, age, and BCG instillation therapy were prognosticators of disease progression in T1 BCa patients [88]. Our analyses regarding the impact of tumour size on RFS, PFS and CSS are in line with previous findings [88]. Moreover, we found a significant association of tumour multiplicity with oncological outcomes, including PFS and CSS, in T1 patients. Although several factors affect oncological outcomes in T1 patients, in a clinical setting, quality assessment of tumours with cystoscopy can play an important role for shared decision making regarding early radical cystectomy versus repeat transurethral resection followed by BCG if feasible based on tumour stage at repeat transurethral resection.

When limiting the analyses to T1 patients treated with BCG, we found that the adverse oncological impact of these tumour characteristics diminished in some analyses. Indeed, we have found that tumour multiplicity was no longer associated with poor RFS, and tumour size ≥3 cm failed to be associated with worse PFS. BCG instillation therapy has been shown to improve RFS and PFS in high-risk NMIBC patients [89,90]. This is in line with the EORTC 2016 risk groups that showed a lack of significant impact of tumour size ≥3 cm on both RFS and PFS. Taken together, tumour size ≥3 cm seems to have a limited impact on RFS and PFS in patients treated with BCG instillation.

For association between tumour multiplicity and oncological outcomes in NMIBC patients treated with BCG, both the CUETO scoring model and the EORTC risk groups demonstrated a worse RFS in patients with multiple tumours, including those treated with BCG [2,3]. However, these two models used different cut-off values for defining tumour multiplicity; with three or more tumours in the former [3] and four or more in the latter [2]. In the retrospective data included in our study, almost all studies set the cut-off value as solitary vs multiple tumours. Therefore, the differential cut-off value between these prognostic models and real-world data obscures the real impact of tumour multiplicity on oncological outcomes in NMIBC patients treated with BCG. Further well-designed studies with large cohorts are needed to clarify the oncological impact of tumour multiplicity and determine the optimal cut-off values for tumour multiplicity in NMIBC patients treated with BCG.

Regarding the gross appearance of bladder tumours, solid tumours, which are also described as non-papillary tumours, and sessile tumours are generally considered to convey a less favourable prognosis, likely reflecting a more aggressive pathological stage [22,23,33,91]. Based on the mechanism of carcinogenesis, BCa has been divided into two groups: low-grade/non-invasive tumours characterized by fibroblast growth factor receptor 3 (FGFR3) mutation and high-grade /

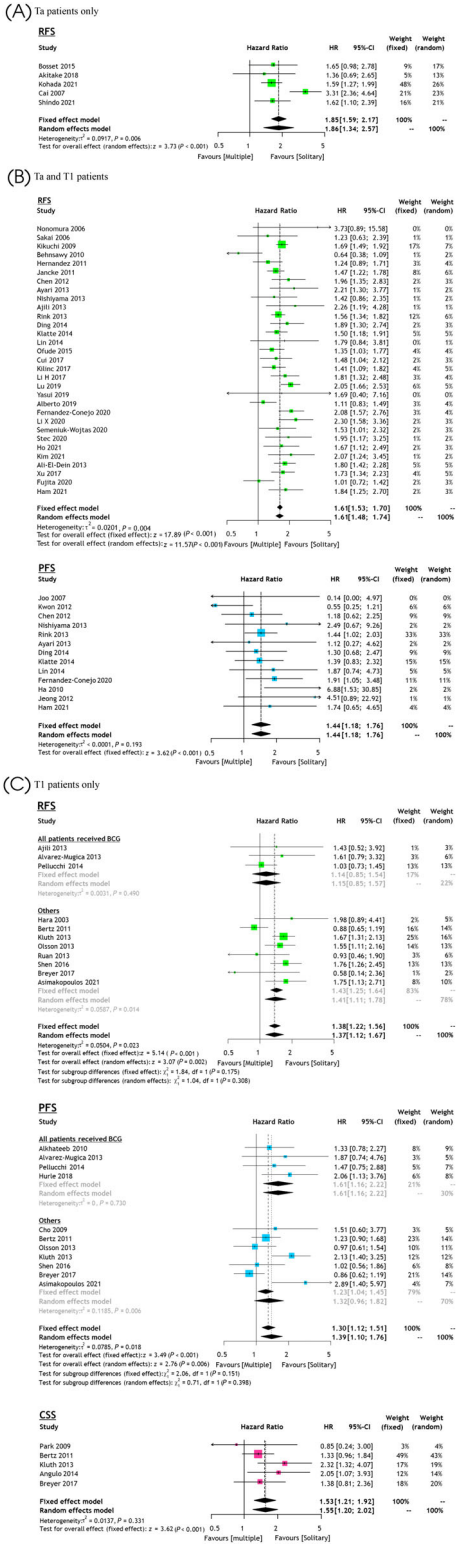


Fig. 2 Forest plots showing association of oncologic outcomes in non-muscle-invasive bladder cancer patients with solitary tumour or multiple tumours: (**A**) Ta patients only, (**B**) Ta and T1 patients, and (**C**) T1 patients only. CSS, cancer-specific survival; HR, hazard ratio; PFS, progression-free survival; RFS, recurrence-free survival.

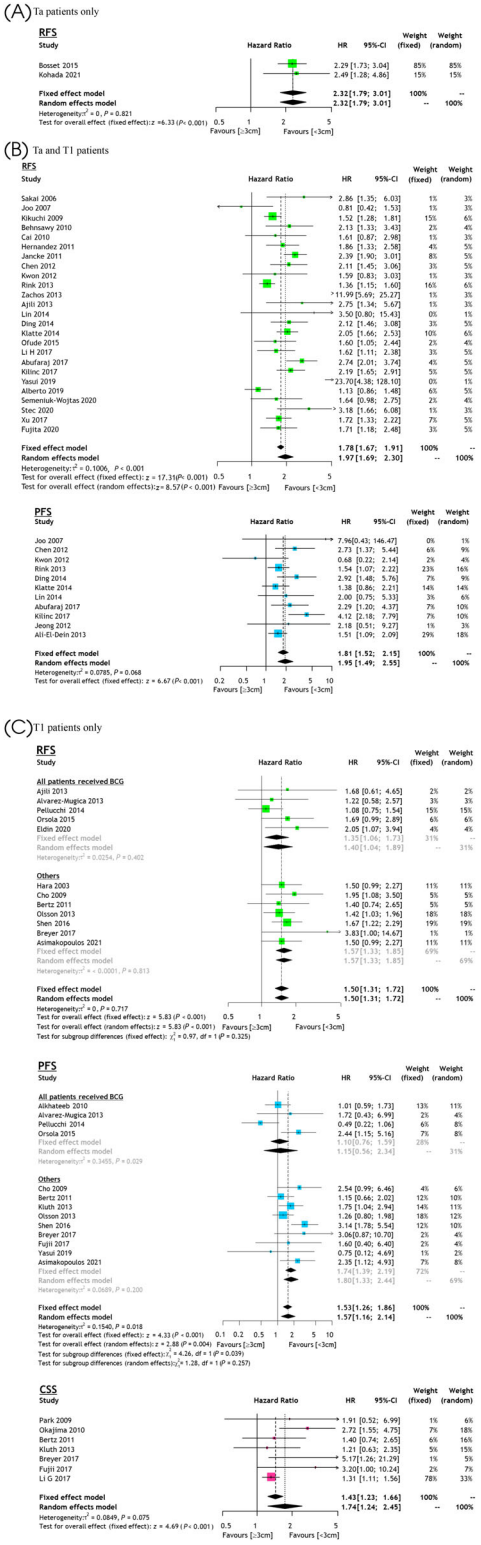


Fig. 3 Forest plots showing association of oncological outcomes in non-muscle-invasive bladder patients with tumour size stratified by 3 cm: (**A**) Ta patients only, (**B**) Ta and T1 patients, and (**C**) T1 patients only. CSS, cancer-specific survival; HR, hazard ratio; RFS, recurrence-free survival; PFS, progression-free survival.

Fig. 4 Forest plots showing association of oncological outcomes in NMIBC patients with gross appearance of tumours: (**A**) solid vs papillary, (**B**) sessile vs pedunculated. CSS, cancer-specific survival; HR, hazard ratio; RFS, recurrence-free survival; PFS, progression-free survival.

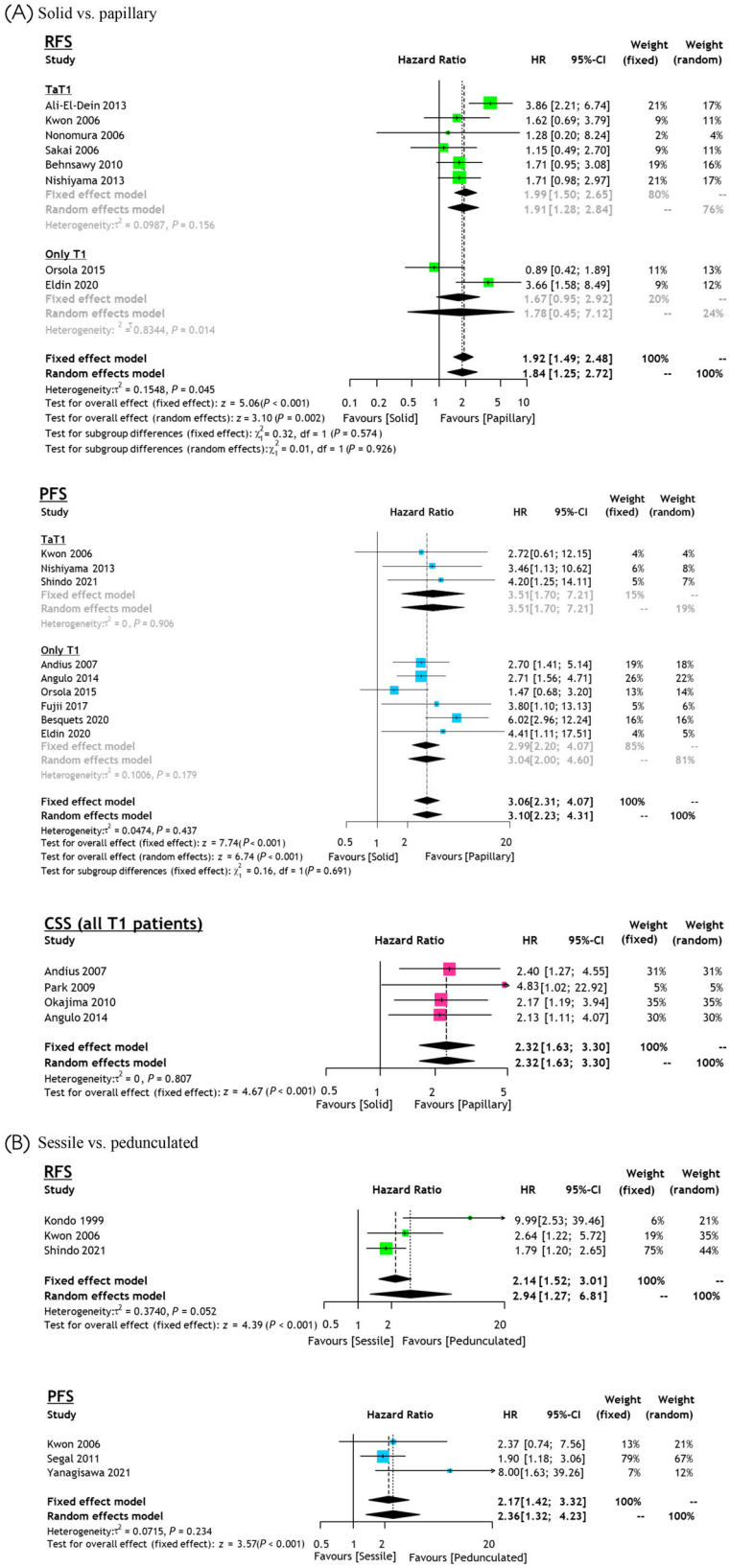


Table 3 Major prognostic models for recurrence and progression in patients with non-muscle-invasive bladder cancer described in the European Association of Urology guidelines.

Name and/or author	Year	Recruitment	Number of patients	Inclusion criteria	Gender, *n*(%)	Age, *n*(%)
Using WHO 1973 classification						
Sylvester et al. EORTC risk tables	2006	1979–1989	2596	Phase III RCTs of post TUR intravesical treatment	M: 2044 (79) F: 515 (20) Unknown: 37 (1.4)	<60 years: 859 (33) 61–70 years: 890 (34) 71–80 years: 690 (27) >80 years: 118 (4.5)
Lammers et al.	2016	1995–2012	724	Intermediate risk defined by EAU guideline	M: 592 (82) F:130 (18) Unknown: 2	Median: 67.5 (range: 33–89) years
Fernandez-Gomez et al. CUETO scoring model	2009	1990–1999	1062	NMIBC treated with BCG	NA	<60 years: 404 (31) 61–70 years: 487 (38) 71–80 years: 367 (28) >80 years: 38 (2.9)
Cambier et al. EORTC risk groups	2016	1992–2005	1812 (Training: 1178, Validation: 634)	Phase III RCTs in Ta–T1 NMIBC	M: 979 (83) F: 199 (17)	<60 years: 333 (28) 61–70 years: 397 (34) 71–80 years: 393 (33) >80 years: 55 (4.7)
Using WHO 2004/2016 and 1973 classification						
Sylvester et al. EAU risk tables	2021	1990–	3401	Primary, TaT1 NMIBC, with or without concomitant CIS; minimum follow-up of 3 months; no cystectomy within 3 months from primary TURBT	M: 2672 (79) F: 729 (21)	Median: 68 (IQR: 60–76) years

CIS, carcinoma in situ; CUTEO, Spanish Urological Club for Oncological Treatment; EAU, European Association of Urology; EORTC, European Organization for Research and Treatment of Cancer; F, female; HR, hazard ratio; IQR, interquartile range; M, male; NA, not applicable; NMIBC, non-muscle-invasive bladder cancer; TUR, transurethral resection; TURBT, transurethral resection of bladder tumour.

invasive tumours characterized by p53 mutation [92]. Theoretically, this differential process of carcinogenesis may affect the gross appearance of these tumours; however, there is still no robust evidence regarding the association between genetic biology and tumour gross appearance [93]. Furthermore, there is also no robust evidence regarding the association between tumour gross appearance and oncological outcomes. Park et al. reported that solid tumours are associated with adverse pathological findings such as lymphovascular invasion and CIS, resulting in unfavourable oncological outcomes in patients with T1 high-grade NMIBC [23]. Solid tumours have also been reported to increase the likelihood of muscle-invasive BCa stage and are, therefore, considered an indicator of the need for early radical cystectomy [94]. Notably, we found that solid tumours and sessile tumours were associated with poor RFS and PFS, and solid tumours were also found to be associated with worse CSS in NMIBC patients, along with higher HR compared to tumour multiplicity or size. Despite the interobserver heterogeneity in evaluating the tumour gross appearance, our analyses support its importance in prognosticating oncological outcomes in NMIBC. These findings might help design

T stage, *n*(%)	Intravesical treatment, *n*(%)	Follow-up, months	Included multivariable variates in models with HR (95% CI)	
			Recurrence	Progression
Ta: 1451 (56) T1: 1108 (43) Unknown: 37 (1.4)	2035 (78)	3.9 years	Prior recurrence rate: HR 1.35 (1.24–1.46) Multiplicity: HR 1.56 (1.42–1.71) (single/2–7/8<) Tumour size (3 cm): HR 1.54 (1.32–1.80) T category: HR 1.21 (1.07–1.37) Grade (G1/2/3): HR 1.17 (1.07–1.28)	Primary or recurrent: HR 1.48 (1.07–2.03) Multiplicity: HR 1.70 (1.29–2.24) Tumour size (3 cm): HR 1.89 (1.40–2.55) T category: HR 2.19 (1.67–2.86) Concomitant CIS: HR 3.41 (2.32–5.01) Grade3: HR 2.67 (1.99–3.59)
Ta G1/2	All Mitomycin C: 218 (30) Epirubicin: 506 (70)	Median: 29.6 (range: 2–239)	Primary or recurrent: HR 1.48 (1.17–1.88) Intravesical treatment history: HR 1.38 (1.05–1.80) Multiplicity: HR 1.56 (1.20–2.01) Epirubicin vs Mitomycin C: HR 1.27 (1.00–1.62)	NA
Ta: 251 (19) T1: 1001 (77) Tis: 44 (3.4)	All BCG	NA	Gender: HR 1.69 (1.24–2.30) Age (<60/60–70/≥71): HR 1.17 (1.02–1.34) Primary vs Recurrent: HR 2.01 (1.61–2.51) No. of tumours (<3/≥3): HR 1.28 (1.10–2.49) Concomitant CIS: HR 1.44 (0.99–2.12) Grade (G1/2/3): HR 1.62 (1.04–2.52)	Age (<60/60–70/≥71): HR 1.29 (1.04–1.61) Primary vs recurrent: HR 1.92 (1.36–2.72) T category: HR 2.35 (1.36–4.08) Grade: HR 2.91 (1.98–4.27)
Ta: 807 (69) T1: 370 (31)	All BCG	7.4 years	Prior recurrence rate no. of tumours (<4/≥4) *tumour size (3 cm) was not significant	T category Grade *tumour size (continuous) and number of tumours (<8, ≥8) were not significant
Ta: 2644 (78) T1: 757 (22)	1829 (54)	3.9 (IQR: 1.9–7.2) years	NA	WHO 2004/2016 classification Age (≤70/>70): HR 1.72 (1.24–2.40) Multiplicity: HR 1.64 (1.17–2.29) Tumour size (3 cm): HR 1.97 (1.41–2.77) T category: HR 2.20 (1.53–3.16) Concomitant CIS: HR 2.76 (1.62–4.70) Grade (LG/HG): HR 2.33 (1.58–3.42)

prospective studies to incorporate solid tumour appearance in the prognostic/predictive models/classification. Furthermore, a more accurate definition or classification of gross cystoscopic appearance reflecting tumour biology is also warranted in order to obtain better generalizability.

Despite confirming the prognostic importance of cystoscopic findings in this study, we found significant heterogeneity in some analyses. We, therefore, conducted several sensitivity analyses to detect the cause of heterogeneity. These analyses suggested that differential patient demographics based on inclusion criteria, such as recurrent tumour and low-grade vs. high-grade tumour in the analysis of Ta patients and proportion of T1 patients in the analysis of NMIBC patients (both Ta and T1 patients), were the possible source of heterogeneity. In addition, in the analysis of T1 patients, despite performing subgroup analyses of all patients treated with BCG or not, we found heterogeneity in some analyses. Based on sensitivity analysis, methodological impact, which or how many variates are included in multivariable analyses, might be a possible cause of heterogeneity. Although we only extracted the data on HR from multivariable Cox regression

analysis, an impact of possible confounders could not be avoided due to the nature of this study which integrated a pile of retrospective data; results should be interpreted with care.

In addition to heterogeneity, our study has several limitations. First, despite no significant publication bias in all analyses, reporting bias could have led to the non-publication of negative results or exclusion of negative results on univariable analysis from multivariable analyses. Second, regarding the gross tumour appearance, the number of included studies is limited owing to the lack of a clear definition and/or interobserver heterogeneity. Third, our analysis did not focus/assess specifically the impact of recently proposed technologies/concepts and procedures such as photodynamic diagnosis and en bloc resection. As en bloc resection and/or chemoablation therapy are being assessed for treatment of NMIBC [95,96], cystoscopic findings at initial diagnosis will be exceptionally important to guide the urologist to determine the optimal personalized management approach for each NMIBC at each specific time.

In conclusion, our analyses confirmed that cystoscopic findings, such as tumour multiplicity and tumour size ≥3 cm, predict oncological outcomes in NMIBC patients. In addition, regarding the gross appearance of tumours, solid/sessile tumours were found to be associated with worse RFS and PFS in patients with NMIBC; solid tumours were also associated with worse CSS in patients with T1 BCa. We also found that the prognostic impact of cystoscopic tumour characteristics can be mitigated in patients receiving intravesical BCG therapy. Our analyses underline the oncological impact of quality and quantity assessment of BCa with cystoscopy at initial diagnosis, helping guide the clinical decision making towards an optimal personalized management of NMIBC. Inclusion of tumour appearance may improve prognostic models. Tumour size and multiplicity require standardization. With increasing interest in chemoablation, active surveillance, and in-office fulguration, cystoscopic findings are increasing in value for clinical decision making.

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Disclosure of Interests

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Abbreviations: BCa, bladder cancer; CIS, carcinoma *in situ*; CSS, cancer-specific survival; CUETO, Spanish Urological Club for Oncological Treatment; EAU, European Association of Urology; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; NMIBC, non-muscle-invasive bladder cancer; PFS, progression-free survival; RFS, recurrence-free survival; TURBT, transurethral resection of bladder tumour.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy for meta-analysis.

Fig. S1. PRISMA checklist 2009.

Fig. S2. Funnel plot of included studies (**A**) association of RFS and tumour multiplicity in Ta patients, (**B**) association of RFS and tumour multiplicity in NMIBC patients, (**C**) association of PFS and tumour multiplicity in NMIBC patients, (**D**) association of RFS and tumour multiplicity in T1 patients, (**E**) association of PFS and tumour multiplicity in T1 patients, (**F**) association of CSS and tumour multiplicity in T1 patients, (**G**) association of RFS and tumour size in Ta patients, (**H**) association of RFS and tumour size in NMIBC patients, (**I**) association of PFS and tumour size in NMIBC patients, (**J**) association of RFS and tumour size in T1 patients, (**K**) association of PFS and tumour size in T1 patients, (**L**) association of CSS and tumour size in T1 patients, (**M**) association of the RFS and solid or papillary tumours in NMIBC patients, (**N**) association of the PFS and solid or papillary tumours in NMIBC patients, (**O**) association of the CSS and solid or papillary tumours in NMIBC patients, (**P**) association of the RFS and sessile or pedunculated tumours in NMIBC patients, (**Q**) association of the PFS and sessile or pedunculated tumours in NMIBC patients.

Table S1. Risk of bias assessment for NRCTs (ROBINS-I).

Table S2. Treatment and oncological outcomes of included studies.