EUROPEAN UROLOGY 75 (2019) 649–658

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Urothelial Cancer

Micropapillary Urothelial Carcinoma of the Bladder: A Systematic Review and Meta-analysis of Disease Characteristics and Treatment Outcomes

Mohammad Abufaraj [a,b,†], *Beat Foerster* [a,c,†], *Eva Schernhammer* [d,e,f], *Marco Moschini* [a,g], *Shoji Kimura* [a,h], *Melanie R. Hassler* [a], *Mark A. Preston* [i], *Pierre I. Karakiewicz* [j], *Mesut Remzi* [a], *Shahrokh F. Shariat* [a,k,l,m,*]

[a] *Department of Urology, Medical University of Vienna, Vienna, Austria;* [b] *Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan;* [c] *Department of Urology, Kantonsspital Winterthur, Winterthur, Switzerland;* [d] *Department of Epidemiology, Harvard T. H Chan School of Public Health, Boston, MA, USA;* [e] *Channing Division of Network Medicine, Department of Medicine, Harvard Medical School, Boston, MA, USA;* [f] *Department of Epidemiology, Center for Public Health, Medical University of Vienna, Vienna, Austria;* [g] *Klinik für Urologie, Luzerner Kantonsspital, Lucerne, Switzerland;* [h] *Department of Urology, Jikei University School of Medicine, Tokyo, Japan;* [i] *Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [j] *Department of Urology, University of Montreal, Montreal, Quebec, Canada;* [k] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria;* [l] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [m] *Department of Urology, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, NY, USA*

Article info

Article history:
Accepted November 28, 2018

Associate Editor:
James Catto

Keywords:
Micropapillary
Urothelial carcinoma
Bladder cancer
Variant histology
Immediate cystectomy
Bladder sparing
Transurethral resection
Prognosis
Bacillus Calmette-Guérin therapy

Abstract

Context: The optimal treatment of urothelial bladder cancer (UBC) with micropapillary (MP) variant histology is not clear.
Objective: To review the current literature on disease characteristics and treatment outcomes of MP UBC.
Evidence acquisition: A systematic search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Cochrane Handbook for Systematic Reviews of Interventions. The primary end points were recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS).
Evidence synthesis: We identified 758 reports comprising a total of 3154 patients, of which 28 and 15 articles were selected for qualitative and quantitative analysis, respectively. In patients with T1 MP UBC, the 5-yr CSS rates for early radical cystectomy (RC) ranged from 81% to 100%, while they were between 60% and 85% for transurethral resection of the bladder and Bacillus Calmette-Guérin (BCG). In studies reporting on neoadjuvant chemotherapy (NAC), the rates of complete pathological response (ypT0) ranged from 11% to 55%. Nevertheless, the use of NAC did not improve RFS (hazard ratio [HR] 1.23, 95% confidence interval [CI] 0.52–2.93, $p = 0.6$), CSS (HR 0.9, 95% CI 0.48–1.7, $p = 0.8$), or OS (HR 1.35, 95% CI 0.98–1.86, $p = 0.1$). Fifty-three percent (95% CI 43–63%) of patients who underwent RC alone had locally advanced disease (≥pT3), and 43% (95% CI 33–52%) were harbouring lymph node metastases. MP component at RC was not significantly associated with worse RFS (HR 1.25, 95% CI 0.88–1.78, $p = 0.2$), CSS (HR 0.96, 95% CI 0.57–1.6, $p = 0.9$), or OS (HR 1.20, 95% CI 0.88–1.62, $p = 0.3$) when adjusted for pathological features.

† Both authors contributed equally to this work.
* Corresponding author. Department of Urology, Medical University of Vienna, Währinger Gürtel 18-20, Vienna A-1090, Austria. Tel. +43 1 40400 2615; Fax. +43 1 40400 2332.
E-mail address: sfshariat@gmail.com (S.F. Shariat).

https://doi.org/10.1016/j.eururo.2018.11.052

Conclusions: While MP UBC is associated with clinicopathological features of advanced disease, it is not associated with worse survival outcomes in patients undergoing RC. NAC results in pathological downstaging in a significant number of patients. Nevertheless, this does not translate into better survival outcomes. The optimal treatment of patients with cT1 remains controversial.

Patient summary: Our results suggest that micropapillary urothelial bladder cancer does not necessarily mandate different treatment algorithms. Nevertheless, each case should be discussed individually considering other clinicopathological factors.

1. Introduction

Since the first description of micropapillary (MP) urothelial bladder cancer (UBC) in 1994 by Amin et al. [1], there have been several reports on this variant histology (VH) [2,3]. The microscopic appearance of MP UBC is conspicuously similar to ovarian papillary serous carcinoma, and defined as small nests and aggregates of tumour cells within lacunae without vascular cores [4,5]. Data on distinct molecular pathways in MP UBC are scarce, but a recent study on gene expression signatures showed that the majority of MP UBCs display expression patterns associated with the luminal subtype found in conventional UBC, whereas expression of basal markers was absent. It is noteworthy that a subset of MP samples of the luminal type has been demonstrated to harbour the so-called p53-like signature, which is a distinct expression signature characterised by an activated wild-type p53-expression signature. This signature has been found to be more resistant to chemotherapy (CHT) in conventional UBC and is also associated with the worst survival outcome among conventional and MP subtypes [6,7].

The currently available clinical data on MP UBC comprise small case series with inconsistent results regarding prognosis and treatment recommendations [5,8]. While, some authors advocate proactive immediate radical cystectomy (RC) in patients with T1 UBC with MP component [9,10], others argue that bladder-conserving strategy such as Bacillus Calmette-Guérin (BCG) therapy can be beneficial with immediate RC not being superior to conservative measures [2,11,12]. Based on expert opinion, the American Urological Association (AUA)/Society of Urologic Oncology joint guidelines recommended offering early RC in T1 patients with VH due to high rates of upstaging [13]. The recent National Comprehensive Cancer Network guidelines states that "there are data suggesting early cystectomy may be preferred because of high risk of progression" [14]. Similarly, a discord persists regarding the benefit of neoadjuvant chemotherapy (NAC) in patients with muscle-invasive UBC (MIBC) harbouring MP component VH [15–17].

The reporting of VHs is expected to rise due to increased awareness of its importance among uropathologists [5]. The paucity and inconsistency of data make robust recommendations difficult. Moreover, it is highly unlikely for a clinical trial addressing these issues to emerge due to a low prevalence of this variant and different treatment options available. Therefore, we sought to systematically review the current literature and meta-analyse the available results. In detail, we aimed to answer the following three questions: (1) Is the presence of MP VH a poor prognostic feature? (2) Do patients with cT1 MP UBC benefit preferentially from early RC or does standard bladder preservation therapy with intravesical BCG confer similar outcomes? (3) Is platinum-based NAC equally effective in patients with MIBC harbouring MP component compared with MIBC patients without MP?

2. Evidence acquisition

2.1. Literature search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18] and the Cochrane Handbook for Systematic Reviews of Interventions [19]. We systematically searched the PubMed, Cochrane Library, American Society of Clinical Oncology, European Society for Medical Oncology, and EMBASE databases (including AUA and European Association of Urology meeting abstracts) in June 2018 to identify studies investigating clinicopathological characteristics and treatment outcomes in MP UBC patients. The search was performed by two authors (M.A., B.F.) using the following string terms: ("bladder cancer" OR "urothelial carcinoma") AND ("micropapillary" OR "variant histology" OR "histologic variants"). Owing to the rarity of this condition, no time or language restrictions were applied and meeting abstracts were considered for inclusion. We also checked the reference lists of relevant publications forward and backward for additional pertinent publications. The international prospective register of systematic reviews (PROSPERO) was searched and checked for relevant registered but not yet published reviews. The protocol of this study was a priori registered in PROSPERO, and the protocol is available online (No. CRD42018085235).

2.2. Inclusion criteria

The population, intervention, comparator, outcome, and study design (PICOS) approach was used to define the eligibility criteria. Studies were selected when patients with MP UBC (P: population) who underwent treatment with curative intent (I: interventions) were compared with patients with alternative curative treatment or different urothelial carcinoma histology (C: comparators) in terms of oncological survival outcomes and disease-specific characteristics (O: outcomes) using randomised controlled or nonrandomised observational approaches. We considered randomised controlled trials (RCTs) and nonrandomised observational cohorts, as well as population-based cohorts (Surveillance, Epidemiology, and End Results, National Cancer Data Base [NCDB]) for inclusion into the systematic review and meta-analysis.

Our predefined comparisons were as follows: (1) transurethral resection of the bladder (TURB) with postoperative intravesical BCG immunotherapy versus early RC; (2) NAC + RC versus RC alone; and (3) MP VH versus pure UBC at RC. The primary end points were recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS). Only studies with multivariable Cox proportional hazard regression models were considered for meta-analysis. Secondary outcomes were the following clinicopathological characteristics at the three comparator's disease phases 1, 2, and 3: gender, clinical, and pathological TNM staging; extent of MP histology, and lymphovascular invasion (LVI). Owing to the rarity of this VH and lack of RCTs, we set a minimum of 20 patients with MP VH for inclusion in the systematic review of observational studies. To avoid small sample bias, only studies with a minimum of 50 patients were considered for pooling proportions of clinicopathological features. We considered any report that documented the presence of MP VH either by pathology or by a chart review including both mixed and pure involvement. Patients with involvement of the urethra or upper urinary tract were excluded.

2.3. *Data collection*

Two authors (M.A. and B.F.) independently screened titles and abstracts of retrieved records. All potentially relevant studies were evaluated as full text or meeting posters if available. In case of multiple reports of the same cohort, the most complete data aggregated with the longest follow-up duration were selected. In case different outcomes were examined, both articles were included to gather comprehensive data. A predefined set of data were independently extracted by two primary authors (M.A. and B.F.) using standard data extraction templates. The extracted data included the following: first author, date, study design, study population, participant demographics, baseline characteristics, intervention and control conditions, outcome measurements (including hazard ratios [HRs], 95% confidence intervals [CIs], and *p* values), times of measurements, and information on the risk of bias (RoB) assessment parameters. Missing information or clarifications were sought by contacting the primary authors. If the authors did not reply, information was declared as not reported. Throughout the whole process, discrepancies were solved by consensus or recourse to the senior author (S.F.S.).

2.4. *RoB assessment*

The RoB was determined using the pragmatic approach for the evaluation of nonrandomised studies by examining the adjustments for confounders according to the Cochrane Handbook for Systematic Reviews of Interventions [19]. The confounding factors were identified as the most important prognostic factors at the time of treatment. The articles were therefore reviewed based on the adjustment for the effects of age, gender, tumour staging and grading, positive surgical margins, and receipt of NAC as well as adjuvant CHT according to the investigated outcomes. The RoB of each study was assessed independently by two authors (M.A. and B.F.). Disagreements were resolved by consensus or consultation with the senior author (S.F.S.). RoB summary and graph figures were generated using the Cochrane Review Manager 5.3 (RevMan 5.3; The Cochrane Centre, Copenhagen, Denmark) [19,20]. The overall RoB level was judged as "low", "intermediate", or "high" risk.

2.5. *Statistical analysis*

We included only multivariable HRs and 95% CIs into meta-analyses due to the retrospective nature of the included studies. Effect summary estimation methods were not used because they are regarded as univariable approaches. Additionally, proportions of clinicopathological features among patients with MP UBC (minimum $n = 50$) were pooled with the Metaprop program of STATA/MP version 14.2 (Stata-Corp., College Station, TX, USA) using Freeman-Tukey double arcsine transformation. Statistical pooling of effect measures was based on the level of heterogeneity among studies. Significant heterogeneity was indicated by a p value of <0.05 in Cochrane Q test and a ratio of >50% in I^2 statistics, which led to the use of random-effect models according to the DerSimonian and Laird method [20]. When no significant heterogeneity was observed, fixed-effect models through the inverse-variance method were used for calculation. We created funnel plots to assess small study effects and publication bias. Results were interpreted carefully due to several possible explanations of funnel plot asymmetry. Statistical analyses were performed using RevMan 5.3 (The Cochrane Centre) and STATA/MP 14.2 (Stata-Corp.). A two-sided p value of <0.05 was considered significant.

3. Evidence synthesis

3.1. *Study population*

We identified 28 studies for qualitative (Supplementary Table 1) and 15 studies for quantitative analyses (Fig. 1). All included studies were nonrandomised and observational. Among a total of 863 459 participants in the selected studies for this systematic review (including populations-based studies), 3154 (0.4%) had MP differentiation. An overview of the available data covered by this systematic review can be found in Supplementary Tables 1–3. The majority of reports came from North America and Europe, with only two publications coming from Australia [21] and North Africa [22].

3.2. *UBC with MP component at diagnosis*

3.2.1. *Clinical characteristics at diagnosis*

Supplementary Table 2 summarises the clinicopathological characteristics of patients with MP UBC at the time of

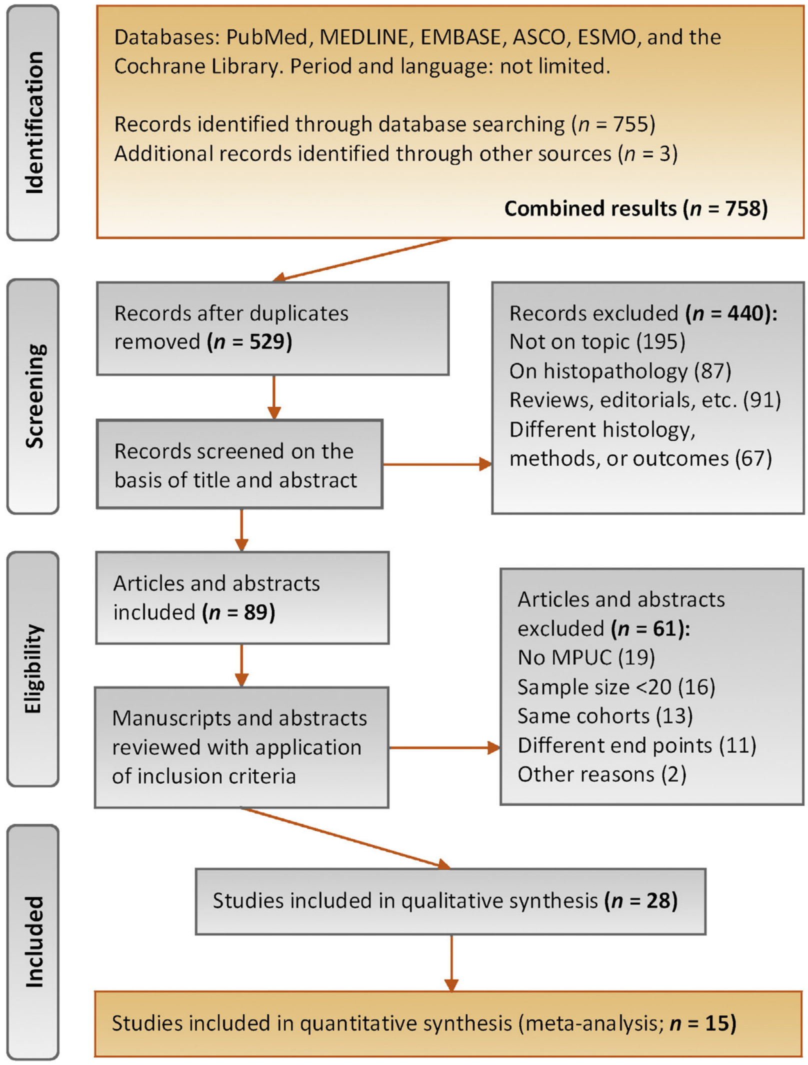

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart. MPUC = micropapillary urothelial carcinoma.

TURB. Overall, there was profound male predominance, with rates ranging from 74% to 97%. The median rate of non–muscle-invasive disease at diagnosis was 41%, highlighting the high prevalence of muscle-invasive MP UBC at diagnosis. Furthermore, the median rates of clinically positive lymph nodes and metastasis were 12.5% and 5%, respectively.

3.2.2. *Early RC versus BCG therapy in clinical T1*

Seven studies reported the outcomes in patients who underwent early RC and eight reported the outcomes of patients who underwent TURB with or without BCG therapy (Table 1) [2,10–12,16,21,23–25]. Even though these studies met our prespecified inclusion criteria, their small sample sizes and significant heterogeneity did not allow for multivariable Cox regression analysis. The best comparable end point was 5-yr CSS. The 5-yr CSS rates for patients treated with early RC ranged from 81% to 100%, while they ranged from 60% to 85% for patients treated with TURB. The two largest series revealed contradictory results. While Willis et al. [10] found a significant difference between the two approaches with 5-yr CSS of 100% for those treated with early RC and 60% for those treated with BCG immunotherapy ($p = 0.006$), Spaliviero et al. [2] did not find any statistically significant difference (81% vs 76%; $p = 0.8$). Upstaging at early RC was reported in five studies, with the rates of upstaging ranging from 23% to 73%. In cohorts of patients who received BCG therapy, the recurrence and progression rates ranged from 41% to 75% and from 18% to 75%, respectively.

3.3. *NAC in patients with muscle-invasive bladder cancer*

3.3.1. *Pathological response rates*

Three studies [16,17,26] reported the clinical features and pathological outcomes of patients who received CHT prior to RC (Table 2). The complete pathological downstaging (ypT0) rates at the time of RC were 55%, 45%, and 11%, respectively. Two studies reported on partial pathological response (≤pT1), which was 55% for both [16,17].

Table 1 – Clinicopathological features and survival outcomes of patients with cT1N0 MPUCB who underwent early RC or TURB[c]

Study (first author, year)	Clinical features, n (%)			Early RC, n (%)					TURB, n (%)							p value
	cT1N0	Males	NAC	N	FU [a] (mo)	Upstage	5-yr CSS	OS [b] (mo)	N	FU [a] (mo)	BCG	Rec	Prog	5-yr CSS	OS [b] (mo)	
Compérat (2010) [21]	33	NR	NR	26	16 [b]	19 (73)	NR	12.2	7	NR	NR	NR	NR	NR	NR	NR
Holyoak (2013) [12]	47 (≤T1)	NR	NR	3	NR	NR	3 (100)	NR	44	NR	NR	NR	NR	36 (81)	NR	NR
Spaliviero (2014) [2]	36	27 (75)	0	15	30	5 (33)	12 (81)	NR	21	36	16 (76)	11 (52)	6 (29)	16 (76)	NR	0.8
Jackson (2015) [23]	24	32 (80)	0	7	31	2 (29)	NR	[d]	17	32	10 (59)	7 (41)	3 (18)	NR	60	NR
Willis (2015) [10]	72	60 (83)	15 (21)	26 [c]	72 [c]	6 (23)	26 (100) [c]	NR [c]	40	56	40 (100)	30 (75)	18 (45)	24 (60)	NR	0.008
Fernández (2017) [16]	38	NR	7 (18)	38	72	NR	34 (90)	NR	–	–	–	–	–	–	–	–
Sui (2016) [11]	NR	NR	NR	33	NR	20 (62)	NR	45	133	NR	NR	NR	NR	NR	[d]	0.058
Tripathi (2017) [24]	96	NR	NR	–	–	–	–	–	96	NR	NR	NR	NR	81 (85)	NR	–
Mendiratta (2018) [25]	29	24 (84)	NR	–	–	–	–	–	12	65	10 (83)	NR	9 (75)	NR	65	–

BCG = Bacillus Calmette-Guérin; CSS = cancer-specific survival; FU = follow-up; MPUCB = micropapillary urothelial carcinoma of the bladder; NAC = neoadjuvant chemotherapy; NR = not reported or reached; OS = overall survival; Prog = progression; RC = radical cystectomy; Rec = recurrence; TURB = transurethral bladder resection.
[a] Median values.
[b] Mean value.
[c] Numbers from a previous study of the same cohort as that of Fernández et al.'s study [16].
[d] Did not reach median survival.

3.3.2. NAC versus RC alone in patients with muscle-invasive bladder cancer

Six studies [11,16,26,27–29] reported on survival outcomes in patients who had CHT prior to RC. Forest plots of HR and 95% CI for RFS, CSS, and OS are illustrated in Fig. 2. No significant heterogeneity in the Cochrane Q or I^2 test was detected for all end points; therefore, a fixed-effect model was used. Four studies reported on the NCDB with a pooled HR of 1.35 (95% CI 0.98–1.86, $p = 0.07$) on OS. We selected the study by Joshi et al. [27] for final analysis because it covered the longest duration with high weight and stable RoB performance. Receiving NAC was not associated with RFS (HR 1.23, 95% CI 0.52–2.93, $p = 0.6$), CSS (HR 0.9, 95% CI 0.48–1.7, $p = 0.8$), or OS (HR 1.06, 95% CI 0.7–1.6, $p = 0.8$) in this pooled analysis. The funnel plot revealed no publication bias (Supplementary Fig. 1). The RoB assessment indicated an intermediate to high level of bias across the studies (Supplementary Fig. 3).

3.4. Radical cystectomy

3.4.1. Patient characteristics

Baseline clinicopathological features of patients with MP UBC who underwent RC are summarised in Supplementary Table 3. Cumulative analysis, which included studies with >50 participants [3,11,16,21,25,40,41], comprised a total of 838 patients and is shown in Table 3. Pooled estimates showed that 84% (95% CI 80–88%) of patients were of male gender and 53% (95% CI 43–63%) of the patients had ≥pT3 disease. Overall, 51% (95% CI 19–83%) of the patients had LVI and 43% (95% CI 33–52%) harboured lymph node metastases in their RC specimens.

3.4.2. Prognostic impact of MP differentiation versus pure urothelial carcinoma

The association of MP histology with survival outcomes was investigated in seven studies [3,11,28–32], which were included in the meta-analysis (Fig. 3). Owing to significant heterogeneity in either Cochrane Q or I^2 tests, a random-effect model was used. Patients harbouring an MP component at RC were not associated with worse RFS (HR 1.25, 95% CI 0.88–1.78, $p = 0.2$), CSS (HR 0.96, 95% CI 0.57–1.6, $p = 0.9$), or OS (1.20, 95% CI 0.88–1.62, $p = 0.3$) compared with those with pure urothelial carcinoma. Inspection of the funnel plots did not demonstrate a publication bias (Supplementary Fig. 2). Assessment of the RoB showed an intermediate to high level of bias across the studies (Supplementary Fig. 4).

4. Discussion

In this systemic review and meta-analysis, we are attempting to provide cumulatively summarised evidence to a controversial area of UBC management. The current literature on MP VH comprises small retrospective studies or population-based registries, reflecting the rarity of this entity and making robust recommendations difficult. Based on this meta-analysis, we confirm that MP UBC is associated with adverse pathological features, but we

Table 2 – Clinicopathological features of patients who underwent NAC and RC for MPUCB

Study (first author, year)	Clinical parameters			Pathological staging, *n* (%)					
	Inclusion cTNM	*N*	Cis NAC, *n* (%)	pT0	pT ≤ 1	pT2	≥pT3	pN+	NOC
Vetterlein (2017) [26]	cT2–4, N0–1, M0	35	NR	4 (11.4)	NR	NR	NR	NR	16 (45.7)
Fernández (2017) [16]	≤cT4, N0, M0	29	22 (76)	16 (55.2)	16 (55.2)	2 (7)	11 (38)	8 (28)	NR
Meeks (2013) [17]	cT2–4, N0–3, M0	29	28 (97)	13 (44.8)	16 (55.2)	3 (10.3)	10 (34.5)	8 (27.6)	NR

Cis = cisplatin based; cTNM = clinical tumour node metastasis; MPUC = micropapillary urothelial carcinoma of the bladder; NAC = neoadjuvant chemotherapy; NOC = non–organ confined; NR = not reported; RC = radical cystectomy.

challenge the common belief that this MP has worse prognosis than pure UBC.

The reported data on T1 MP UBC in TURB specimens were controversial regarding treatment outcomes of BCG immunotherapy versus immediate RC. Furthermore, these data could not be meta-analysed due to a small sample size and notable heterogeneity. The controversial results should be inspected carefully in light of significant case mix and different treatment algorithms between centres. Moreover, the extent and depth of MP component are likely to be important factors that were not consistently reported and might have a key role in affecting the response to intravesical therapies [4,23,33]. For instance, the presence of MP component of >25% was found to be associated with a higher risk of disease progression during BCG therapy [10]. Some authors, however, suggested that BCG may benefit patients with cT1 with a small extent of MP component [2,12,33]. Indeed, an updated report by the MD Anderson Cancer Centre showed that some patients may benefit from BCG therapy, raising an essential point regarding patient selection for bladder-sparing strategy [10]. Additionally, we found that not all patients who underwent conservative treatment received BCG immunotherapy, potentially affecting the validity of the conclusions on the efficacy of BCG from currently available studies.

Detection of MP VH in TURB specimens is subjected to considerable detection bias as the concordance rate between TURB and RC specimens is suboptimal [34]. Importantly, the

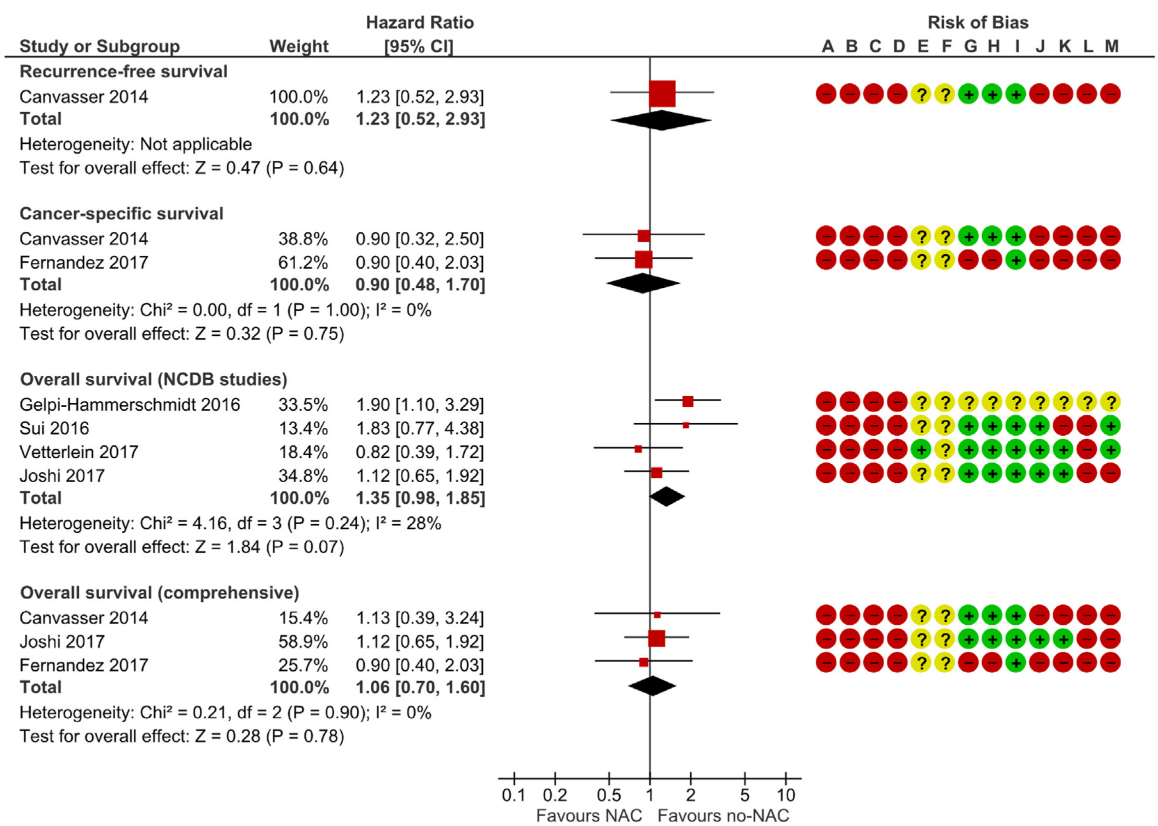

Fig. 2 – Forest plots of studies investigating the association of neoadjuvant chemotherapy with survival outcomes. Weights are from fixed-effect models. (A) Random sequence generation (selection bias); (B) allocation concealment (selection bias); (C) blinding of outcome assessment (detection bias); (D) blinding of outcome assessment (detection bias); (E) incomplete outcome data (attrition bias); (F) selective reporting (reporting bias); and adjustment for the effects of the following confounders: age (G), gender (H), pT stage (I), pathologic grade (J), pN stage (K), positive surgical margins (L), and adjuvant chemotherapy (M). Green circles represent a low risk of bias and confounding, red circles represent a high risk of bias and confounding, and yellow circles represent an unclear risk of bias and confounding. CI = confidence interval; df = degree of freedom; NAC = neoadjuvant chemotherapy; NCDB = National Cancer Data Base.

Table 3 – Clinicopathological features of patients (studies with $n \geq 50$) who underwent RC for MPUC

Study (first author, year)	N	Clinicopathological features, n (%)							
		Males	NAC	pT ≤ 1	pT2	≥pT3	pN+	ConCIS	LVI
Compérat (2010) [21]	57	62 (86)	NR	12 (21)	7 (12)	38 (67)	25 (44)	8 (14)	46 (81)
Wang (2012) [40]	73	62 (85)	3 (4)	10 (14)	15 (21)	48 (66)	37 (51)	NR	53 (73)
Cai (2014) [41]	54	NR	NR	8 (15)	32 (59)	14 (26)	11 (20)	2 (4)	NR
Moschini (2017) [3]	89	79 (89)	2 (2)	NR	NR	48 (54)	36 (40)	24 (27)	11 (12)
Sui (2016) [11]	380	300 (79)	31 (8)	71 (19)	85 (22)	224 (59)	206 (54)	NR	NR
Fernández (2017) [16]	103	64 (86)	0 (0)	31 (42)	8 (11)	34 (47)	32 (45)	40 (54)	31 (42)
Mendiratta (2018) [25]	82	69 (84)	19 (23)	12 (14)	7 (9)	63 (77)	NR	NR	NR
Pooled results, % (95% CI)	838	84 (80–87)	–	20 (14–28)	21 (11–32)	57 (46–67)	43 (33–52)	22 (5–46)	51 (19–83)

CI = confidence interval; ConCIS = concomitant carcinoma in situ; LVI = lymphovascular invasion; MPUC = micropapillary urothelial carcinoma; NAC = neoadjuvant chemotherapy; NR = not reported; RC = radical cystectomy.

quality of TURB is a crucial factor that is subjected to publication under-reporting, affecting the assessment of the predictive value of bladder-conserving strategy [35]. Other important pathological determinants such as LVI and CIS might drive disease outcome and portend worse survival [21,23,33,36]. To assess the predictive and prognostic impact of these factors on disease outcome independently, multivariable models should be constructed. On the contrary, early reports about MP VH advocated immediate RC based on single-institutional experiences [9,37]. The authors argued that immediate RC is an oncologically safe intervention, while TURB with or without BCG is associated with higher recurrence and progression rates, and delays in the time to definitive surgical intervention would increase the risk of non-organ-confined disease. In fact, we observed a high rate of upstaging ranging from one-fourth to three-fourths of patients after immediate RC [10,21]. Indeed, immediate RC is an oncologically safe option, but such a morbid procedure and some encouraging results of transurethral resection with BCG immunotherapy leave the door open for this bladder preserving strategy.

While some authors suggested that immediate RC is an effective therapy in MP UBC patients [9,11,38], others reported that NAC and RC constitute more appropriate strategies than immediate RC [15–17]. Our meta-analysis showed that utilisation of NAC was associated with down-staging in RC specimens for a significant number of patients. Unfortunately, this did not translate into a statistically

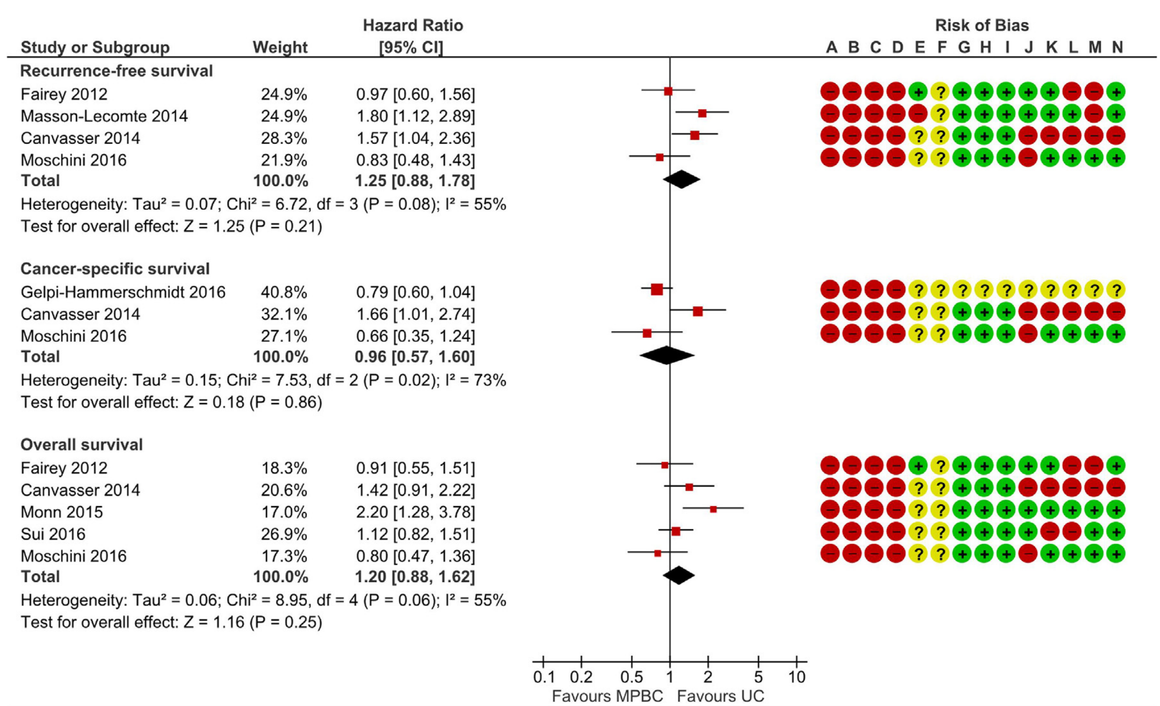

Fig. 3 – Forest plots of studies investigating the association of micropapillary histology at radical cystectomy with survival outcomes. Weights are from random-effect models. (A) Random sequence generation (selection bias); (B) allocation concealment (selection bias); (C) blinding of outcome assessment (detection bias); (D) blinding of outcome assessment (detection bias); (E) incomplete outcome data (attrition bias); (F) selective reporting (reporting bias); and adjustment for the effects of the following confounders: age (G), gender (H), pT stage (I), pathological grade (J), pN stage (K), positive surgical margins (L), neoadjuvant chemotherapy (M), and adjuvant chemotherapy (N). Green circles represent a low risk of bias and confounding, red circles represent a high risk of bias and confounding, and yellow circles represent an unclear risk of bias and confounding.
CI = confidence interval; df = degree of freedom; MPBC = micropapillary bladder cancer; UC = urothelial cancer.

significant improvement in survival outcomes. This apparent controversy could be explained by the aggressive biological behaviour of this VH [26], inclusion of a small number of patients in the studies, and the short follow-up duration [10,11,17]. Up to now, it is difficult to explain the aggressive biological behaviour of MP UBC by molecular findings, as only a handful of studies have specifically addressed differences in gene expression and molecular alterations between conventional and MP UBC. However, whereas conventional UBC can be categorised into basal, luminal, and p53-like subtypes, a recent study using formalin-fixed paraffin-embedded material for gene expression analysis showed that MP UBC is predominantly of the luminal type. In conventional UBC, the luminal type is usually associated with longer survival and a less aggressive disease, but additional downregulation of miR-296 and subsequent upregulation of its targets as well as activation of the RUVBL1 pathway specifically observed in MP UBC might lead to a more aggressive disease course compared with conventional luminal UBC. Furthermore, a subset of MPs showed features of the p53-like subtype, which is associated with resistance to CHT in conventional UBC and which is the most aggressive subtype among all conventional and MP UBCs [6,7]. Thus, molecular differences might also exist between MP UBCs, depending on the presence of the p53-like subtype, which could explain divergent outcomes of NAC treatment. In the absence of strong evidence from well-designed studies, the authors of this review advocate to evaluate each case—regarding NAC—on an individual basis, after thorough discussion at the tumour board.

In this meta-analysis, we found that MP VH did not confer worse survival outcomes after RC when adjusted for the effect of stage, surgical margins, and administration of CHT. Nevertheless, this VH histology was associated with a higher stage, LVI, carcinoma in situ, and propensity of lymph node involvement in comparison with historical RC series that did not report on VH [2,39]. These findings might be explained by the aggressive biological behaviour of tumour cells with propensity towards invasion and metastasis. Despite that our results suggest that MP VH does not necessarily mandate different adjuvant therapies or treatment algorithms compared with pure UBC.

Our study is not devoid of limitations. First, all included studies were retrospective with their own limitations such as selection bias. The effect of MP under-reporting cannot be assessed and other sources of bias have to be reported. Through inclusion of data from multivariable analyses only (mainly adjusted for the effects of major confounders), we could minimise bias and establish an acceptable level of comparability. Second, the small sample size of the included studies may impact the overall quality of data. Future larger studies may overcome this limitation providing more robust evidence. Third, the impact of NAC on the tumour might be affected by the clinical stage. Such data were not available in the literature to stratify the post-CHT response according to each clinical stage. Fourth, a central pathology review to confirm the diagnosis and determine the exact percentage of MP component is of paramount importance to assess this VH appropriately. Unfortunately, this cannot be achieved in a systematic review but should be considered in future collaborative efforts. Uropathologists are encouraged to report the extent and depth of MP in every pathology report, as this seems to play a crucial role in assessing disease behaviour and create comprehensive data for future research. In fact, to improve the quality of recommendations and patient care, well-designed multicentre studies are needed. Additionally, given the unique molecular characteristics, genetic analysis and identification of the distinct genetic signature of MP UBC will improve our understanding of the clinical behaviour of this variant and shed light on the exact role of BCG immunotherapy, NAC, and newer immunotherapeutic agents, paving the way for the era of personalised medicine.

5. Conclusions

We found that MP UBC is associated with adverse clinicopathological features. However, when adjusted for the effect of standard clinicopathological characteristics, MP VH does not confer a worse prognosis as pure UBC in terms of RFS, CSS, and OS probabilities after RC. Moreover, while NAC was not significantly associated with better survival outcomes, it resulted in a significant rate of pathological downstaging. Optimal management of patients with cT1 MP VH remains divergent, and the physician could use these data to discuss management options as part of a shared decision-making process. Patients should be evaluated on an individual basis until further well-designed studies can answer the question regarding the value of treatment intensification in patients with cT1 and MP VH.

Author contributions: Mohammad Abufaraj had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Abufaraj, Foerster, Shariat.
Acquisition of data: Foerster, Abufaraj, Preston, Karakiewicz, Kimura, Hassler, Moschini.
Analysis and interpretation of data: Foerster, Karakiewicz, Abufaraj, Schernhammer, Remzi, Shariat.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Foerster, Abufaraj, Schernhammer.
Obtaining funding: None.
Administrative, technical, or material support: Foerster, Abufaraj, Schernhammer.
Supervision: Shariat.
Other: None.

Financial disclosures: Mohammad Abufaraj certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Mohammad Abufaraj was awarded a European Urological Scholarship Program grant (EUSP/Scholarship S-01-2018). Beat Foerster is supported by the Scholarship Foundation of Swiss Urology.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.11.052.

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