Prognostic Value of Variant Histology in Upper Tract Urothelial Carcinoma Treated with Nephroureterectomy: A Systematic Review and Meta-Analysis

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Purpose: We sought to assess the prognostic value of variant histology in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy.

Materials and Methods: We searched PubMed®, Web of Science™, Cochrane Library and Scopus® databases in May 2019 according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Studies were deemed eligible if they compared overall, cancer specific and recurrence-free survival in patients with upper tract urothelial carcinoma with or without variant histology. Formal meta-analyses were performed for these outcomes.

Results: We identified 32 studies with 16,052 patients, including 26 studies with 12,865 patients that were eligible for the meta-analysis. Variant histology was associated with poor outcomes in terms of cancer specific (pooled HR 2.00, 95% CI 1.57 to 2.56), overall (pooled HR 1.76, 95% CI 1.51 to 2.04) and recurrence-free survival (pooled HR 1.64, 95% CI 1.42 to 1.89). Subgroup analyses revealed that micropapillary (pooled HR 3.02, 95% CI 1.71 to 5.34), and squamous and/or glandular variant histologies (pooled HR 1.48, 95% CI 1.14 to 1.92) were also associated with poor cancer specific survival.

Conclusions: Variant histology in patients with upper tract urothelial carcinoma is associated with an increased risk of cancer specific and overall mortality and disease recurrence. Furthermore, variant histology was independently associated with cancer specific survival in the micropapillary, and squamous and/or glandular variant histology subgroups. It may be useful to incorporate variant histology into prognostic tools that help guide patients and physicians in selecting appropriate treatment strategies for upper tract urothelial carcinoma.

Key Words: histology; urothelium; carcinoma, transitional cell; urologic neoplasms; meta-analysis

Abbreviations and Acronyms

AC = adjuvant chemotherapy
BCa = urothelial carcinoma of the bladder
CSS = cancer specific survival
G = glandular
IRFS = intravesical recurrence-free survival
MP = micropapillary
NOS = Newcastle-Ottawa Scale
OS = overall survival
PC = plasmacytoid
RFS = recurrence-free survival
RNU = radical nephroureterectomy
SA = sarcomatoid
SC = small cell
SQ = squamous
UC = urothelial carcinoma
UTUC = upper tract urothelial carcinoma
VH = variant histology

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Upper tract urothelial carcinoma is a relatively rare malignancy, accounting for only 5% to 10% of all urothelial carcinomas.[1] Radical nephroureterectomy with ipsilateral bladder cuff excision is the standard treatment for patients with high risk nonmetastatic upper tract urothelial carcinoma. Despite definitive therapy, up to 30% of patients experience disease recurrence and cancer related death, particularly those with locally advanced disease.[2–5] To help improve prognostication, clinical and pathological factors have been identified to guide clinical decision making and improve evidence-based patient counseling.[1,6–8] These factors are mainly used to evaluate pathological features such as tumor stage, grade, size, architecture, multiplicity and necrosis, concomitant carcinoma in situ and lymphovascular invasion.

Variant histology is a recently identified important prognostic factor in patients affected by urothelial carcinoma of the bladder with its presence connecting poorer survival outcomes compared to pure urothelial histology.[9–13] UTUC is histologically similar to BCa.[14] The initial research on VH in UTUC suggests that it represents an unfavorable prognostic factor in most studies. However, because of the rarity of the disease and small number of patients, the prognostic and clinical significance of VH has not been established with sufficient evidence in UTUC. We conducted a systematic review and meta-analysis to summarize the existing data regarding this relationship and to determine whether VH can predict oncologic outcomes in patients undergoing RNU for UTUC.

MATERIALS AND METHODS

Search Strategy

The systematic review and meta-analysis were performed according to the PRISMA statement.[15] PubMed, Web of Science, Cochrane Library and Scopus databases were searched on May 20, 2019 to identify reports published until April 2019 regarding the prognostic value of VH in UTUC. The study protocol is registered in the International Prospective Register of Systematic Reviews database (PROSPERO CRD 42019138109).

The keywords used in our search strategy included nephroureterectomy AND cancer OR carcinoma OR UC OR UTUC, AND urothelial OR renal pelvis OR ureter OR upper tract OR upper urinary tract, AND variant OR histology OR difference OR differentiation OR VH OR CVH (concomitant variant histology), AND survival OR outcome OR prognostic OR mortality OR progression OR recurrence. The primary outcome of interest was cancer specific survival and the secondary outcomes were overall and recurrence-free survival. The detailed database search strategy is presented in the supplementary Appendix (https://www.jurology.com).

Initial screening was performed independently by 2 investigators based on the titles and abstracts to identify ineligible reports. Reasons for exclusions were noted. Potentially relevant reports were subjected to a full text review and the relevance of the reports was also confirmed after the data extraction process. Disagreements were resolved via consensus with a third investigator.

Inclusion and Exclusion Criteria

Studies were included if they investigated patients treated for UTUC with variant histology who had undergone nephroureterectomy (intervention) compared to those without variant histology (comparison) to assess the prognostic effect of variant histology on cancer specific, overall and recurrence-free survival (outcome) using multivariate Cox regression analysis (study design) in nonrandomized observational, randomized or cohort studies. We excluded reviews, letters, editorials, meeting abstracts, replies from authors, case reports and articles not published in English. In cases of duplicate publications either the higher quality or the most recent publication was selected. Bibliographies of included reports were scanned for additional studies of interest.

Data Extraction

Two investigators independently extracted from included articles the first author name, publication year, recruitment region, period of patient recruitment, number of patients, age, gender, study design, pathological T stage, oncologic outcome, followup duration, conclusion, number of VHs and variant type. Subsequently the hazard ratios and 95% confidence intervals of VH associated with each of the outcomes were retrieved. HRs were extracted from the multivariate analyses. All discrepancies regarding data extraction were resolved by consensus with a third investigator.

Quality Assessment

NOS was used to assess the quality of the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions for included nonrandomized studies.[16,17] The scale rates selection (1 to 4 points), comparability (1 to 2 points) and exposure (1 to 3 points), with total scores ranging from 0 (lowest) to 9 (highest). The main confounders were identified as the important prognostic factors of cancer specific, overall and recurrence-free survival. The presence of confounders was determined by consensus and review of the literature. We identified studies with scores above 6 as high quality choices.

Statistical Analyses

Forest plots were used to assess multivariate HRs and obtain summary HRs to describe the relationships between VH and overall, cancer specific and recurrence-free survival. Disease recurrence was defined as tumor relapse in the operative field or regional lymph nodes and/or distant metastasis. RFS did not include intravesical tumor recurrence in this analysis. In addition, VH was defined as nonpure UC, including UC with VH and pure VH in this analysis. Studies were not considered in the meta-analysis if they used only Kaplan-Meier log rank, univariable Cox proportional hazard regression or general logistic regression analysis without multivariable Cox proportional hazard regression model. In studies with only HRs and p values we calculated the

corresponding 95% CIs.[18,19] We also performed subgroup analyses of micropapillary, and squamous and/or glandular VHs.

Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using the Cochrane Q test and the I^2 statistic. Significant heterogeneity was indicated by $p < 0.05$ in Cochrane Q tests and ratio greater than 50% in I^2 statistics. We used fixed effects models for the calculation of pooled HRs for nonheterogeneous results.[20–22] Publication bias was assessed by funnel plots. All statistical analyses were performed using Stata®/MP 14.2, and statistical significance level was set at $p < 0.05$.

RESULTS

Study Selection and Characteristics

Our initial search identified 842 publications in PubMed, 1,003 in Scopus, 299 in Web of Science and 2 in the Cochrane Library. A total of 1,779 articles were excluded after screening the titles and abstracts, and a full text review was performed for 70 articles. After applying the selection criteria we identified 32 articles with 16,052 patients for the systematic review and 26 studies with 12,865 patients for the meta-analysis (fig. 1).[23–54] The extracted data from the 32 studies are outlined in tables 1 and 2.

All included studies had a retrospective design and were published between 2008 and 2019. Of the included studies 5 were from Europe or America and 27 were from Asia. VH in the pathological specimen was reported in 2,153 of 16,052 patients (13.4%). Median age was 59 to 74 years and median followup was 21 to 67.8 months. The studies had a median NOS score of 7 (range 6 to 7).

Meta-Analysis

Association of VH with CSS. A total of 23 studies including 11,381 patients provided data on the association of VH with CSS in patients with UTUC. The forest plot (fig. 2, *A*) showed that VH was significantly associated with CSS in UTUC (pooled HR 2.00, 95% CI 1.57 to 2.56, z-score 5.54). The Cochrane Q test (chi-square 87.00, $p = 0.000$) and I^2 test (71.3%) revealed significant heterogeneity. The funnel plot identified 7 studies over the pseudo-95% CI (fig. 2, *A*).

Association of VH with OS. A total of 10 studies including 5,238 patients provided data on the association of VH with OS in patients with UTUC. The forest plot (fig. 2, *B*) showed that VH was significantly associated with OS in UTUC (pooled HR 1.76, 95% CI 1.51 to 2.04, z-score 7.36). The Cochrane Q test (chi-square 15.52, $p = 0.078$) and I^2 test (42.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (fig. 2, *B*).

Association of VH with RFS. A total of 10 studies including 6,923 patients provided data on the association of VH with RFS in patients with UTUC. The forest plot (fig. 2, *C*) showed that VH was significantly associated with RFS in UTUC (pooled HR 1.64, 95% CI 1.42 to 1.89, z-score 6.64). The Cochrane Q test (chi-square 15.05, $p = 0.18$) and I^2 test (26.9%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (fig. 2, *C*).

Association of micropapillary VH with CSS. Four studies including 2,844 patients provided data on the association of micropapillary VH with CSS in patients with UTUC. The forest plot (fig. 3, *A*) showed that micropapillary VH was significantly associated with CSS in UTUC (pooled HR 3.02, 95% CI 1.71 to 5.34, z-score 3.80). The Cochrane Q test (chi-square 1.54, $p = 0.674$) and I^2 test (0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (fig. 3, *A*).

Association of squamous and/or glandular VH with CSS. Six studies including 4,055 patients provided data on the association of squamous and/or glandular VH with CSS in patients with UTUC. The forest plot (fig. 3, *B*) showed that squamous and/or glandular VH was significantly associated with CSS in UTUC (pooled HR 1.48, 95% CI 1.14 to 1.92, z-score 2.98). The Cochrane Q test (chi-square 2.05, $p = 0.842$) and I^2 test (0.0%) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (fig. 3, *B*).

DISCUSSION

This systematic review and meta-analysis investigated the prognostic value of VH in patients with UTUC. The results indicated that compared to pure UC, VH was significantly associated with poorer cancer specific, overall and recurrence-free survival. This result is consistent with the BCa literature.[12] UC with VH is usually associated with advanced stage, multifocality, sessile architecture, necrosis, lymphovascular invasion and lymph node metastasis. BCa with VH tends to be more aggressive in appearance and to have a poorer prognosis than pure BCa.[9–13,55]

It is noteworthy that all included studies used a retrospective design, which increases the risk of selection bias. In addition, pathological specimens were evaluated at each institution, and rather than conducting repeat reviews of all specimens, most studies depended on the individual pathologists for identification and reporting of VH. Furthermore, many studies failed to evaluate the percentage of VH in specimens, which may have influenced survival outcomes.

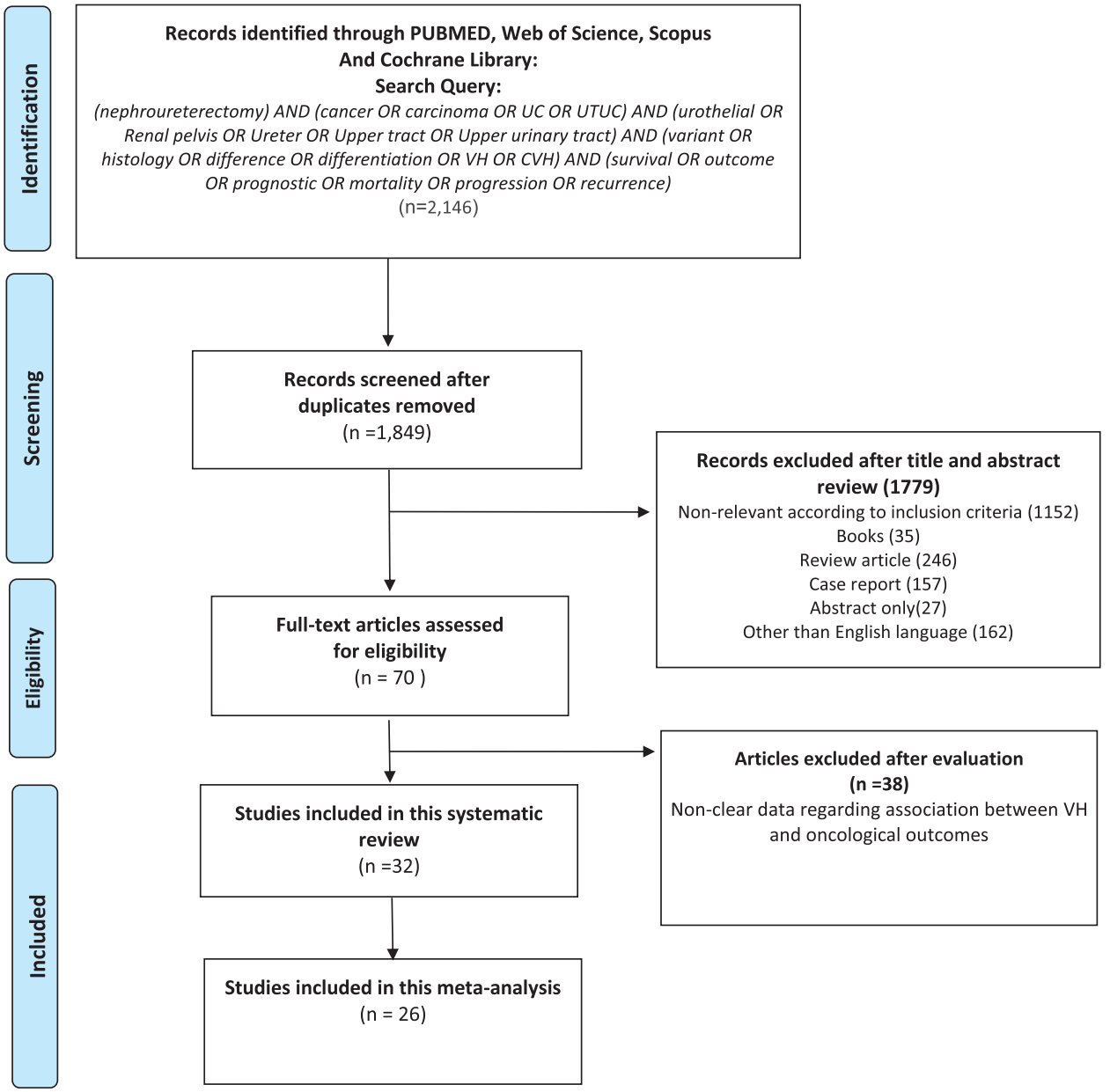

Figure 1. Identification of studies for systematic review and meta-analysis. *CVH,* concomitant variant histology.

It also proved rather difficult to compare pure VH and UTUC with VH for oncologic outcomes due to the paucity of reports available regarding pure VH. These factors could have resulted in misinterpretation of the pathological report and could have a varying impact on the oncologic outcomes. Nevertheless, the agreement between these studies and the same with BCa suggests a true prognostic value for VH in UTUC.[24,37,45–47,53] VH could potentially help improve the accuracy of postoperative nomograms and decision tools regarding followup strategies and, more importantly, adjuvant therapies.[56,57] UC can display a number of VHs.[58] However, not all VHs are similar with respect to biological, clinical and prognostic impact.

Interestingly the present study indicated that MP, and squamous and/or glandular VH subgroups were significantly associated with poor CSS. While few studies have assessed these subgroups, it appears that VH could be used to select patients who might benefit from more intensive therapy, such as adjuvant therapy in addition to standard RNU. Moreover, these results suggest that VH in UTUC requires a strict surveillance protocol. MP is morphologically defined as small nests and aggregates of tumor cells within lacunae without vascular cores.[9,59] The presence of a MP component indicates a risk of advanced stage at presentation consisting of either locally advanced disease or potentially metastatic disease. In patients with

Table 1. *Study characteristics of 32 retrospective series*

References	Region	Recruitment	No. Pts	Oncologic Outcome	NOS
Abe et al[23]	Japan	1990-2005	312	CSS	7
Chung et al[24]	Korea	2002-2016	1,173	OS, CSS, RFS	7
D'Andrea et al[25]	Austria	1990-2008	621	CSS	7
Ekmekçi et al[26]	Turkey	2000-2017	74	OS	7
Elawdy et al[27]	Oman	1983-2013	305	CSS	7
Fang et al[28]	China	1999-2011	612	CSS	7
Gao et al[29]	China	2005-2015	259	OS, CSS, RFS	7
Hara et al[30]	Japan	2005	1,172	RFS	7
Hashimoto et al[31]	Japan	1996-2014	144	IRFS	6
Hayakawa et al[32]	Japan	1994-2014	195	CSS, progression-free survival	6
Ikeda et al[33]	Japan	1990-2015	441	CSS, RFS	7
Inamoto et al[34]	Japan	1996-2009	103	CSS	6
Kawashima et al[35]	Japan	1999-2009	93	CSS	6
Kim DS et al[36]	Korea	1986-2006	238	RFS	7
Kim JK et al[37]	Korea	1991-2012	452	OS, CSS	7
Kuroda et al[38]	Japan	1999-2010	121	CSS, RFS	7
Li Y et al[40]	China	1999-2015	885	OS, CSS	7
Li T et al[39]	China	2008-2017	704	OS, CSS, RFS	7
Luo et al[41]	Taiwan	2004-2010	234	CSS, metastasis-free survival	7
Makise et al[42]	Japan	1996-2012	140	OS, CSS, RFS	7
Masson-Lecomte et al[43]	France	1995-2010	519	CSS, metastasis-free survival	6
Morizane et al[44]	Japan	2000-2012	345	CSS	6
Qin et al[45]	China	2012-2016	346	OS, CSS, IRFS	6
Rink et al[46]	Austria	1987-2007	1,648	CSS, RFS	6
Sakano et al[47]	Japan	1995-2009	502	CSS	7
Shibing et al[48]	China	2002-2012	795	OS, CSS, RFS	7
Shigeta et al[49]	Japan	Not reported	364	CSS, IRFS	7
Sung et al[50]	Korea	1994-2011	410	OS, CSS, RFS	7
Takahara et al[51]	Japan	1996-2009	103	CSS	7
Tang et al[52]	China	1999-2011	687	CSS	7
Zamboni et al[53]	Switzerland	1990-2016	1,610	CSS, RFS	6
Zeng et al[54]	China	2008-2018	445	CSS	7

urothelial carcinoma of the bladder MP VH is also shown to be a bad player, with the prevalence of this variant observed to be around 0.6% to 2.0% of all BCa cases.[9,60–62]

As yet, it remains difficult to account for the aggressive biological behavior of MP on the basis of molecular findings. However, while conventional UCs are categorized into basal, luminal and p53-like subtypes, a recent study on gene expression signatures indicated that MP tumors were predominantly of the luminal subtype.[60,63] Of conventional UCs the luminal subtype is usually associated with longer survival and less aggressive disease, whereas downregulation of miR-296 and upregulation of its target genes, including activation of the RUVBL1 pathway, have been suggested to drive the expression signature of MP. These differences may therefore account for a more aggressive disease course than conventional luminal UCs. Furthermore, a subset of MP VH has features of the p53-like subtype, which is associated with chemotherapy resistance in conventional UCs and is the most aggressive of all conventional and MP UCs.[60,63] Thus, molecular differences might also exist between MP UCs, depending on the presence of the p53-like subtype, which may lead to divergent outcomes in adjuvant chemotherapy.

Squamous variant is the most common histological entity of all variant subtypes, accounting for up to 20% to 40% of cases.[10,64] Glandular variant is the second most common variant and may be found in up to 18% of all invasive tumors. However, optimal management of either subtype remains controversial, given that squamous and glandular variants may coexist with other VHs, including MP and sarcomatoid types. The lower CI of this subgroup was 1.14, which still suggests poorer prognosis but a benefit with toxic systemic therapy. However, no other VH subgroups were subjected to analysis due to a lack of data available regarding their HRs from multivariate analyses.

It is also of interest to evaluate adjuvant chemotherapy for its effect on VH in patients with UTUC. Chung et al compared recurrence-free, cancer specific and overall survival between patients with pure UTUC vs UTUC with VH, demonstrating through Kaplan-Meier curve analysis lower survival ($p=0.011$, $p=0.002$ and $p=0.006$, respectively) in those with UTUC and VH vs pure UTUC.[24] However, among the 84 patients who underwent AC the recurrence-free, cancer specific and overall survival were not significantly different between the 2 groups ($p=0.562$, $p=0.060$ and $p=0.053$, respectively). These results suggest that AC improved survival in patients with UTUC and VH after RNU. Conversely Kim et al observed that patients with UTUC with VH who underwent AC had poorer survival outcomes than those with pure UTUC even after an

Table 2. *Patient characteristics*

References	Median Pt Age (yrs)	No. Gender (M:F)	% Smokers	No. Stage 3 or Greater (%)	No. VH (%)	Variant Type	No. Adjuvant Chemotherapy (%)	Median Followup (mos)	Conclusion
Abe et al[23,*]	70	207:105	Not reported	131 (42.0)	30 (9.6)	Not reported	36 (11.5)	47	Neg
Chung et al[24,*]	68.8	849:324	Not reported	483 (41.2)	93 (7.9)	G, microcystic, MP, SA, SC, SQ	357 (30.4)	38.9	Pos
D'Andrea et al[25,*]	70	340:281	Not reported	185 (29.8)	70 (11.3)	G, MP, neuroendocrine, PC, SA, SQ	0 (0)	35	Neg
Ekmekçi et al[26,†]	63.8	60:14	Not reported	41 (55.4)	22 (29.7)	G, SA, SQ	Not reported	43.5	Neg
Elawdy et al[27,*]	59	Not reported	Not reported	62 (20.3)	42 (13.8)	G, MP, SQ	0 (0)	34	Pos
Fang et al[28,*]	68	340:272	18.8	Not reported	93 (15.2)	G, SA, SQ	Not reported	64	Neg
Gao et al[29,*]	67.5	187:72	Not reported	88 (34.0)	23 (8.9)	Lymphoepithelioma-like, SA	Not reported	33.3	Pos
Hara et al[30,*]	71	806:336	44.4	510 (43.5)	112 (9.6)	Not reported	179 (15.3)	55.8	Neg
Hashimoto et al[31,†]	69	101:43	47.9	72 (50.0)	16 (11.1)	Not reported	Not reported	33.5	Neg
Hayakawa et al[32,†]	73	Not reported	Not reported	Not reported	30 (15.4)	Not reported	Not reported	53	Neg
Ikeda et al[33,*]	69	319:122	58.3	182 (41.3)	37 (8.4)	Not reported	100 (22.7)	35.7	Neg
Inamoto et al[34,†]	68.6	71:32	Not reported	47 (45.6)	11 (10.7)	Not reported	Not reported	29	Neg
Kawashima et al[35,*]	Not reported	68:25	Not reported	93 (100)	11 (11.8)	Not reported	38 (40.9)	Not reported	Pos
Kim DS et al[36,†]	64.1	164:74	Not reported	107 (45.0)	24 (10.1)	SQ	Not reported	53.4	Pos
Kim JK et al[37,*]	64	347:105	Not reported	188 (41.6)	41 (9.1)	Not reported	110 (24.3)	67.8	Pos
Kuroda et al[38,*]	68	92:29	Not reported	54 (44.6)	12 (9.9)	SQ	29 (24.0)	44.4	Neg
Li Y et al[40,†]	69	396:489	15.6	262 (29.6)	158 (17.9)	G, SA, SQ	Not reported	61	Pos
Li T et al[39,*]	66	401:303	28.4	345 (49.0)	162 (23.0)	Not reported	286 (40.6)	39	Pos
Luo et al[41,*]	Not reported	102:132	10.3	67 (28.6)	65 (27.8)	SQ	0 (0)	40.7	Neg
Makise et al[42,*]	Not reported	101:39	Not reported	68 (48.6)	23 (16.4)	SQ	42 (30.0)	53	Neg
Masson-Lecomte et al[43,*]	68.4	342:177	Not reported	Not reported	39 (7.5)	MP	80 (15.4)	27	Neg
Morizane et al[44,*]	74	234:111	Not reported	152 (44.1)	29 (8.4)	Not reported	80 (23.2)	39.9	Neg
Qin et al[45,*]	66.6	206:140	36.7	Not reported	50 (14.5)	G, PC, SA, SC, SQ	169 (48.8)	21	Pos
Rink et al[46,*]	Not reported	Not reported	Not reported	Not reported	398 (24.2)	G, MP, PC, SA, SC, SQ	169 (11.6)	48	Neg
Sakano et al[47,*]	72	344:158	Not reported	212 (42.2)	60 (12.0)	G, SA, SQ	164 (33.3)	41.4	Neg
Shibing et al[48,*]	Not reported	462:333	Not reported	405 (50.9)	162 (20.4)	Not reported	202 (25.4)	32	Pos
Shigeta et al[49,†]	71	278:86	Not reported	145 (39.8)	46 (12.6)	Not reported	75 (20.6)	51.1	Neg
Sung et al[50,†]	64	312:98	Not reported	178 (43.4)	6 (1.5)	MP	91 (22.2)	40.2	Pos
Takahara et al[51,†]	68.6	71:32	Not reported	47 (45.6)	11 (10.7)	Not reported	12 (11.7)	29	Neg
Tang et al[52,†]	Not reported	306:381	Not reported	173 (25.2)	81 (11.8)	G, SQ	Not reported	65	Neg
Zamboni et al[53,†]	69	1,096:512	Not reported	621 (38.6)	150 (9.3)	MP, SA, SQ	233 (14.5)	27.6	Neg
Zeng et al[54,†]	66.3	293:152	Not reported	148 (33.3)	46 (10.3)	Not reported	Not reported	33.5	Neg

* No patient underwent neoadjuvant chemotherapy.
† Number of patients undergoing neoadjuvant chemotherapy was not reported.

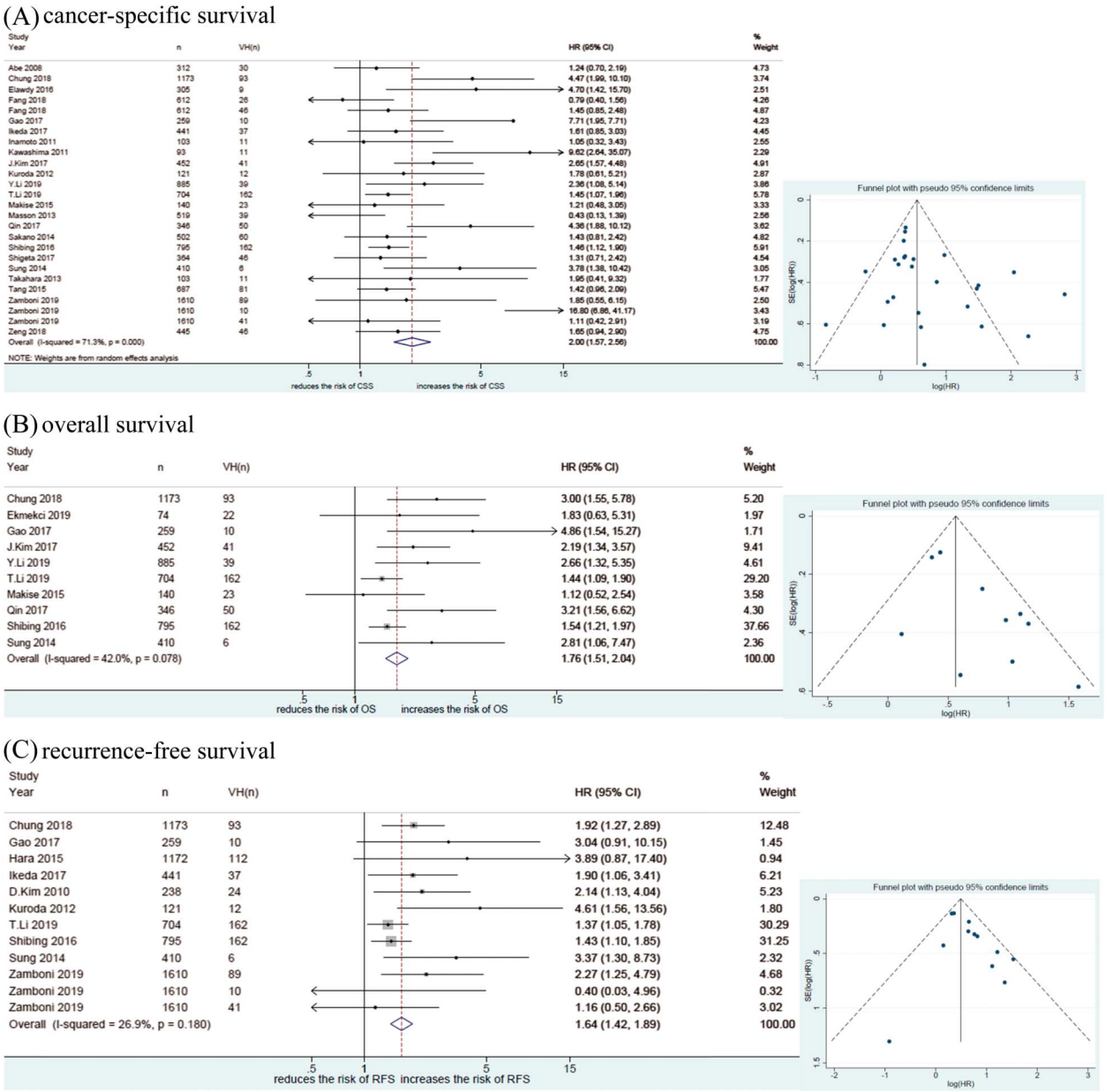

Figure 2. *A,* cancer specific survival. *B,* overall survival. *C,* recurrence-free survival.

adjustment for confounding factors through the propensity score matching analysis.[37]

Accordingly consideration needs to be given to adjuvant treatment modalities other than adjuvant chemotherapy in patients with UTUC with VH after RNU. Thus, the effect of AC on VH remains to be further examined. Moreover, no multivariate analysis data on VH were available for patients who underwent AC for inclusion in this systematic review, which made it difficult to evaluate the impact of AC on VH. Therefore, well designed prospective studies are needed to assess VH for its response to AC.

While our meta-analysis revealed a strong association between VH and UTUC recurrence and mortality, several study limitations exist. Reporting bias may have led to negative results not being published. In addition, heterogeneity was detected for CSS analysis, limiting the value of the results. Although the random effects model accounts for heterogeneity among studies, the conclusions should be interpreted with caution. In addition, the Cochrane Q test for MP may prove unreliable, given the small number of series available with data for MP VH. Furthermore, most patients in our study were confined to a population from a particular region of Asia, which may make it difficult to generalize the results. Therefore, well designed prospective studies with prolonged followup are needed to validate the prognostic value of VH in the clinical setting and to determine whether this factor may improve the current tools for risk

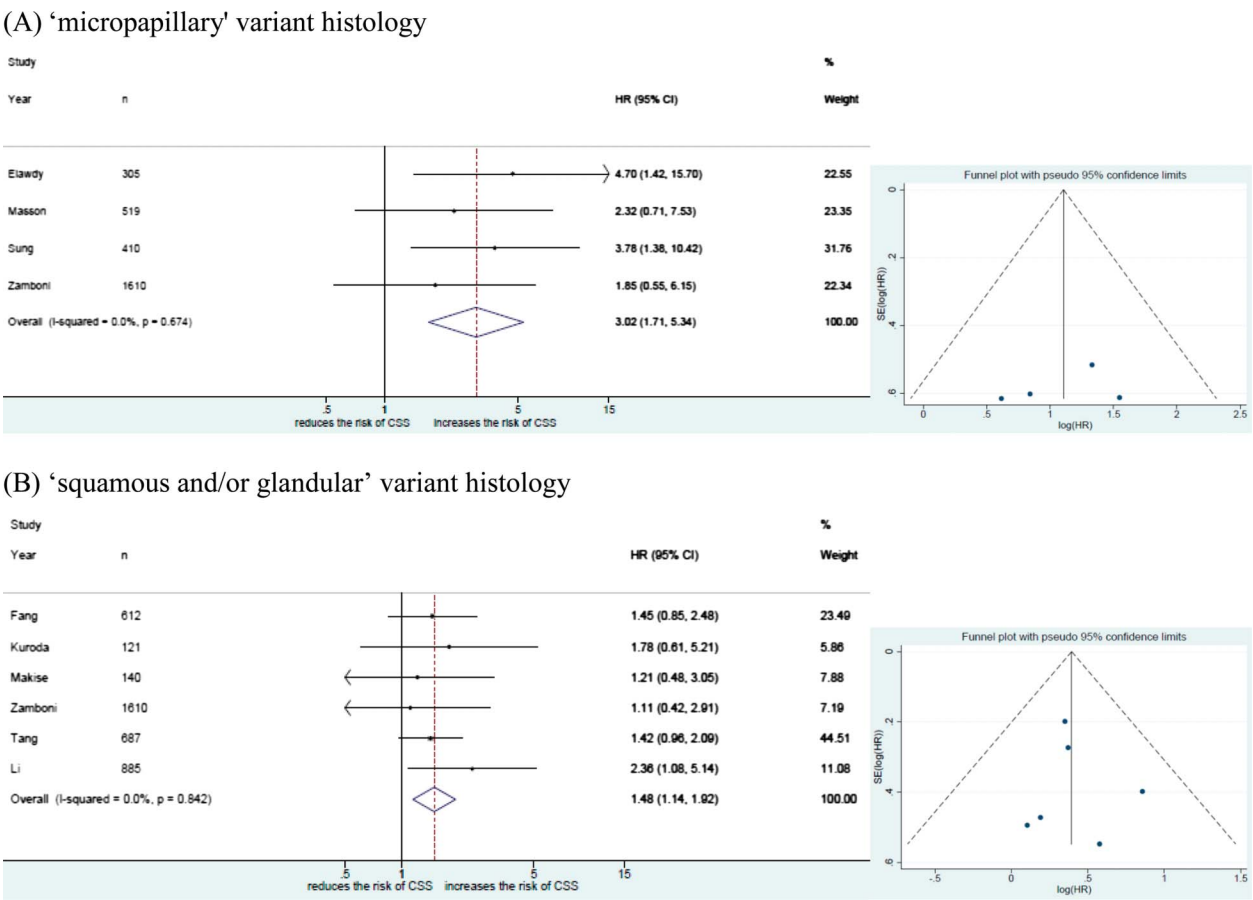

Figure 3. *A,* micropapillary variant histology. *B,* squamous and/or glandular variant histology.

stratification and thereby clinical decision making for patients with UTUC.

CONCLUSIONS

This meta-analysis revealed that VH in patients with UTUC is associated with increased risks of overall mortality, cancer specific mortality and disease recurrence. Furthermore, VH independently predicted CSS in patients with MP, and squamous and/or glandular VH subgroups. Therefore, it may be useful to incorporate VH into prognostic tools that help guide patients and physicians in selecting appropriate treatment and followup strategies after RNU for UTUC. MP VH had the highest HR, suggesting indirectly potentially stronger prognostic value than squamous and/or glandular VH.

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EDITORIAL COMMENTS

The presence of VH is a known prognostic indicator of a poor clinical outcome in patients with bladder urothelial carcinoma. However, due to the rarity of this disease entity, the prognostic significance of VH has not been established in the field of UTUC. Through a well designed systematic review and meta-analysis the authors demonstrate that the presence of VH in UTUC is significantly associated with lower cancer specific, overall and recurrence-free survival rates by identifying 26 articles describing more than 12,000 patients with UTUC treated with RNU. The information on the prognostic significance of VH in patients with UTUC treated with RNU may aid in patient counseling and help identify candidates for adjuvant therapy. Although additional evaluation is needed regarding whether the presence of VH in UTUC is also associated with intravesical recurrence, this study may be useful to optimize the followup regimen after RNU.

For routine clinical use of presence of VH as a prognostic indicator in RNU specimens future evaluations are needed to clarify the detailed basic and molecular mechanisms by which urothelial carcinoma with VH becomes malignant (reference 60 in article), the association between the volume and/or percentage of VH in RNU specimens and UTUC prognosis, and the effects of the presence of VH on chemotherapy, radiotherapy and/or immune checkpoint inhibitor treatment.[1]

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1. Berg S, D'Andrea D, Vetterlein MW et al: Impact of adjuvant chemotherapy in patients with adverse features and variant histology at radical cystectomy for muscle-invasive carcinoma of the bladder: does histologic subtype matter? Cancer 2019; **125:** 1449.

As for many other diagnostic and therapeutic aspects, the incidence and effect of histological variants on survival outcomes have been studied more extensively for BCa than for UTUC. In this field sparse data exist suggesting a potential detrimental effect of histological variants on survival outcomes compared to pure urothelial cancer (reference 53 in supplementary references).

In this meta-analysis the authors aimed to evaluate the existing literature on this topic, examining incidence and assessing the prognostic value of variant histology in patients with UTUC treated with radical nephroureterectomy. They identified 32 studies with 16,052 patients, observing that the presence of histological variants is associated with increased mortality compared to pure urothelial cancer.

These results confirm previous findings on BCa[1] and highlight the importance of histological variant evaluation in patients affected by UTUC. In this regard the authors should be praised for their important article, and further studies are needed to explore potential clinical and therapeutic consequences.

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