Surgical Oncology 28 (2019) 208–213

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

The impact of variant histological differentiation on extranodal extension and survival in node positive bladder cancer treated with radical cystectomy

Phillip Marks[a,1], Philipp Gild[a,1], Armin Soave[a], Florian Janisch[a], Sarah Minner[b], Oliver Engel[a], Malte W. Vetterlein[a], Shahrokh F. Shariat[c], Guido Sauter[b], Roland Dahlem[a], Margit Fisch[a], Michael Rink[a,*]

[a] University Medical Center Hamburg-Eppendorf, Department of Urology, Hamburg, Germany
[b] University Medical Center Hamburg-Eppendorf, Department of Pathology, Hamburg, Germany
[c] Medical University Vienna, Department of Urology, Vienna, Austria

ARTICLE INFO

Keywords:
Urinary bladder cancer
Histology
Urothelial carcinoma
Radical cystectomy
Lymph node metastasis
Extra nodal extension

ABSTRACT

Objective: To investigate the impact of variant urothelial carcinoma of the bladder (UCB) histologies on extra nodal extension (ENE) and survival in lymph node (LN) positive bladder cancer patients undergoing radical cystectomy (RC).

Material and methods: We meticulously reviewed all bladder specimens for presence of variant UCB histologies and LN specimen for presence and extent of ENE in 517 UCB patients treated with RC. Descriptive statistics, the Kaplan Meier method and multivariable Cox regression models evaluated the association between variant UCB histology, ENE and survival metrics including disease recurrence-free, cancer-specific, and overall survival, respectively.

Results: Overall, 138 patients had LN metastasis (27%), with a median number of 15 (IQR 9; 18) LNs removed. Among LN positive patients, 43 (31%) had ENE with a median length of 10 mm. Variant histology was present in 96 patients (18.6%) with squamous cell (12.0%) and sarcomatoid (2.5%) differentiation being the most common. In all patients, the presence of variant histology was neither associated with presence of LN metastasis nor ENE (all p-values = n.s.). In Kaplan-Meier analyses the presence of LN metastases and ENE in LN positive patients was significantly associated with disease recurrence and cancer-specific mortality, respectively (all $p < 0.001$). The presence of variant histology did not influence these outcomes (p = n.s.). In multivariable analyses, adjusted for standard UCB prognosticators, ENE, but not variant histology, independently predicted disease recurrence-free (hazard ratio (HR) 3.88, 95% confidence intervall (CI) 2.24–6.71, $p < 0.001$), cancer-specific (HR 4.60; 95% CI, 2.57–8.23, $p < 0.001$), and overall survival (HR 3.51; 95% CI, 2.10–5.86, $p < 0.001$).

Conclusion: Variant UCB histologies do not seem to increase the incidence of LN metastasis or ENE. This study confirms ENE being a powerful predictor for outcomes in node positive UCB patients - regardless of variant histological differentiation. Our findings warrant validation in larger cohort setting.

1. Introduction

With an estimated 81,190 new diagnoses and 17,240 deaths in 2017 urinary bladder cancer (UCB) is a leading cause of cancer related mortality [1]. Radical cystectomy (RC) with bilateral lymph node (LN) dissection is the gold standard surgical treatment for patients with high-risk non-muscle-invasive and muscle-invasive UCB, respectively. However, almost a quarter of patients harbor LN metastasis at the time of RC. While some of these patients can be cured with pelvic lymphadenectomy and adjuvant chemotherapy, the majority subsequently experiences a fatal course of disease, despite multimodal therapies [2].

To further risk-stratify this heterogeneous group of LN positive patients and thereby offer treatment modalities and surveillance on an individual level, several independent prognosticators have been identified in recent years [3]. Among these, extension of tumor tissue through the capsule into perinodal tissue (extranodal extension [ENE])

* Corresponding author. University Medical Center Hamburg-Eppendorf, Department of Urology, Martinistraße 52, D-20246, Hamburg, Germany.
E-mail address: m.rink@uke.de (M. Rink).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.suronc.2019.01.008
Received 11 August 2018; Received in revised form 20 December 2018; Accepted 27 January 2019
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might constitute an important factor for inferior survival outcomes, although findings have been controversial in the published literature [3–5]. Notably, while the majority of RC patients present with pure UCB histology, up to a quarter of patients exhibit variant UCB histology (i.e., the combination of urothelial carcinoma with other histologies) [6]. As such, variant histologies have been assumed to be associated with aggressive tumorbiological features and possibly unfavorable oncological outcomes compared to pure UCB [7]. Consequently, the WHO classification of the urothelial tract as of 2016 recommends reporting presence of variant UCB differentiation [8]. Interestingly, contradictory findings on variant UCB histologies and LN metastasis have been reported [6,7]. Particularly, the effect of variant UCB histologies on the incidence of LN metastasis, its effect on outcomes in this patient subpopulation and explicitly the association with ENE are currently undetermined.

Given the mounting evidence for limited efficacy of perioperative chemotherapy in some of the variant histologies [9], a number of authors have opted for personalized treatment and follow-up regimens in these patients [7,10]. Consequently, further detailed insight is warranted, particularly in a patient population that may be at highest risk for disease recurrence and most leading candidates for multimodal treatments. We sought to investigate the association of variant histologies on ENE and further, their predictive capacity on oncological outcome in LN positive patients with UCB following treatment with RC.

2. Materials and methods

2.1. Patient selection and data collection

We retrospectively collected data of 636 patients treated with RC and bilateral lymphadenectomy at University Medical Center Hamburg-Eppendorf between 1996 and 2011. Indications for RC were in conformity with international guidelines: muscle-invasive disease, recurrent non-muscle-invasive tumor, or Carcinoma in situ (CIS) refractory to transurethral resection of the bladder (TURB) with or without intravesical chemo- or immunotherapy. None of these patients had metastatic disease at the time of RC. Adjuvant systemic chemotherapy was administered to 101 patients, 93% were platin-based, decision depending on tumor stage, overall health status, renal function and patients desire. Due to the potential effect on LN metastasis and histological features, data of patients with neoadjuvant systemic chemotherapy or radiotherapy were not collected. A total of 55 patients were excluded because of missing clinico-pathologic data or follow-up. Nine patients with pure non-urothelial bladder cancer or incomplete histological specimen and 55 patients with histological pT0 disease were excluded. Finally, 517 patients were available for statistical analysis. This study was institutional review board approved.

2.2. Pathologic evaluation

RC and bilateral pelvic lymphadenectomy was performed standardized as previously described [11]. The surgical cystectomy and bilateral lymphadenectomy specimen were inked, multiple sections were obtained from the tumor, the bladder up to the ureters and all lymph nodes. Tumor stage and nodal status were assigned according to the tumor, lymph nodes and metastasis (TNM) system. Tumor grading was classified according to the 1998 World Health Organisation grading system [12]. Positive surgical margin was defined as presence of tumor cells at inked areas of soft tissue on the RC specimen [13]. Lymphovascular invasion was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular-tissue-walls [14]. The presence of concomitant carcinoma in situ (CIS) was defined as the presence in conjunction with another tumor other than CIS alone.

All pathological specimen were re-reviewed for presence of variant histologies. Presence of variant UCB histology was defined as UCB histology combined with any other type of histology [6]. Variant UCB histology types were classified according to the World Health Organisation classification of bladder tumors [8]. In addition, all LN metastases were histopathologically re-reviewed for presence and extent of ENE. ENE was defined as a clear-cut perforation of a microscopically visible lymph node capsule by tumor tissue infiltrating into perinodal tissue [3]. The extent of ENE was measured by meticulous microscopical evaluation of each single or consecutive slide. Lymph node density was calculated as ratio of the number of positive lymph nodes to the total number of lymph nodes removed.

2.3. Follow-up regimen

Follow-up work-up has been described in details previously [25]. In brief, patients were generally seen every 3–4 months after surgery within the first year, every 6 months for the second to the fifth year, and annually thereafter. Follow-up comprised clinical work-up, diagnostic imaging of the abdomen and pelvis including the urinary tract as well as chest radiography. Additional radiographic evaluations (e.g., bone or brain imaging) were performed when clinically indicated.

Definition of disease recurrence comprised tumor relapse at the operative site, regional lymph nodes, or any distant metastasis after RC. Upper tract urothelial carcinoma was considered a metachronous tumor and not disease recurrence. Patients not experiencing disease recurrence were censored at the time of last follow-up for recurrence-free survival analysis. Cancer-specific mortality was defined as death due to UCB. The cause of death was determined by a treating physician, medical chart review and death certificates, or death certificates alone [15]. Perioperative mortality was defined as death within the first 30 days after RC and censored at time of death for cancer-specific survival analyses.

2.4. Statistical analysis

Our analyses proceeded in the following steps. First, overall clinicopathological characteristics and distributions of the complete cohort, including age, sex, ASA score, pathological tumor stage and grade, presence of carcinoma in situ, number of lymph nodes removed, lymph node status and invasion, ENE status, soft tissue surgical margin status, administration of adjuvant chemotherapy and histological type (pure UCB, variant UCB, including Squamous and Non-squamous cell variant UCB) were listed. Second, patients were stratified according to lymph node status and differences in pathological features such as number of lymph nodes removed, extracapsular extension and histological type (as described above) were assessed. Similarly, lymph node positive patients were stratified by ENE status, and differences in additional pathological features, such as number of positive lymph nodes, lymph node density, diameter of LN metastasis, diameter of ENE were compared. Further, and in order to preclude an inherent bias due to differences in baseline comorbidities, the cohort was also compared with regard to ASA status among formerly mentioned strata. Continuous variables were reported using medians and interquartile ranges (IQR), frequencies and proportions used to describe categorical variables. The Mann-Whitney-U test (two categories) and the Kruskal-Wallis test (three or more categories), as well as Pearson's χ^2 test were used to compare differences in continuous, and categorical variables, respectively.

Next, the Kaplan Meier approach and log-rank test were used to depict and compare survival metrics, including disease recurrence and cancer-specific survival between LN negative and positive patients (stratified by ENE status), as well as histological differentiation (pure UCB, squamous, non-squamous UCB). Similarly, in the subgroup of lymph node positive patients, extend of ENE and histological subtypes were compared.

Last, multivariable Cox regressions adjusted for all available clinicopathological covariates assessed the impact of histological type and ENE on recurrence free and cancer-specific survival. All tests were two-

Table 1
Descriptive lymph node and histopathological characteristics of 517 patients undergoing radical cystectomy and bilateral lymphadenectomy for muscle-invasive or recurrent, high-risk bladder cancer. Subgroups stratified by a) lymph node status and b) presence of extranodal extension (ENE).

	All patients (n = 517)	Lymph node negative (n = 379)	Lymph node positive (n = 138)	p-value
Number LNs removed (median; IQR)	15 (9,18)	15 (10,18)	15 (9,20)	0.51
Extra nodal extension (%)				
negative	474 (92)	–	95 (68.8)	–
positive	43 (8)		43 (31.2)	
Histology (%)				
Pure UCB	421 (81)	310 (81.8)	111 (80.4)	0.47
Variant UCB Histology (total)	96 (19)	69 (18.2)	27 (19.6)	
Squamous-cell variant UCB histology	62 (12)	48 (12.7)	14 (10.1)	
Non-squamous cell variant UCB histology	34 (7)	21 (5.5)	13 (9.5)	
	Only LN + patients (n = 138)	**ENE negative** (n = 95)	**ENE positive** (n = 43)	**p-value**
Number LNs removed (median; IQR)	15 (9,20)	14 (9,18)	15 (9; 27)	0.18
Number of positive LNs (median; IQR)	2 (1,6)	2 (1,4)	5 (2,9)	**< 0.001**
LN density (median; IQR)	22 (10; 50)	15 (8; 44)	33 (17; 58)	**0.001**
Diameter of LN metastasis (largest per pat.) (in mm; median, IQR)	6 (3,12)	5 (2,10)	8 (5,12)	0.15
Diameter of ENE (in mm; median; IQR)	–	–	10 (6,10)	–
ENE < 10 mm (n; %)			16 (37.2)	
ENE > 10 mm (n; %)			27 (62.8)	
Histology (%)				
Pure UCB	111 (80.4)	77 (81.1)	34 (79.1)	
Variant UCB Histology (total)	27 (19.6)	18 (18.9)	9 (20.9)	
Squamous-cell variant UCB histology	14 (10.1)	12 (12.6)	2 (4.7)	
Non-squamous cell variant UCB histology	13 (9.5)	6 (6.3)	7 (16.3)	0.09

Abbreviations: IQR: Interquartile range; LN: Lymph Node; ENE: Extra Nodal Extension; UCB: Urothelial Carcinoma of the Bladder.
p-value in bold display significant results.

sided. Statistical significance was considered at $p < 0.05$. Analyses were performed with SPSS 20 (SPSS Inc., IBM Corp., Armonk, NY; U.S.).

3. Results

3.1. Characteristics of the study cohort

The median age of the study cohort was 67 years (interquartile range (IQR) 59–73 years) and 400 (77,4%) patients were male. 338 (65.3%) patients had muscle-invasive or locally advanced tumor stages (≥pT2). According to the ASA classification 64% of the patients had no or mild systemic disturbances (ASA 1–2) and 36% had severe systemic disturbances from any cause (ASA > 2) prior to surgery. The general characteristics are summarized in Supplemental Table 1.

Lymph node metastases were present in 138 (26.7%) patients, with 43 (8%) patients having ENE. The median number of removed lymph nodes was 15 (IQR 9–20) in the entire cohort. In total, 421 (81,4%) patients had pure UCB, whereas 96 patients (18.6%) showed variant UCB histologies (Table 1). Among these, squamous cell differentiation was the most common variant UCB histology followed by sarcomatoid, small cell and glandular differentiation in 62 (20%), 13 (2.5%), 10 (1.9%), and 7 patients (1.4%), respectively (Supplemental Table 1). Moreover, there were no statistically significant differences in presence of LN metastasis (pN0 vs pN+), presence of ENE (pN0 vs pN+,ENE-vs. pN+, ENE+) or presence of variant histology in relation to ASA scores (all p = n.s.).

3.2. Association of lymph node status, ENE, and variant UCB histology

The presence of variant UCB histology was not associated with presence of lymph node metastasis ($p = 0.47$). Among lymph node positive patients, ENE with a median length of 10 mm (IQR 6–10 mm) was present in 43 (31,1%). There was a positive correlation between an increased number of positive LNs ($p \leq 0.001$) as well as increasing LN density ($p = 0.001$) with presence of ENE. Variant UCB histology was not associated with the presence of ENE ($p = 0.09$) (Table 1).

3.3. Survival according to UCB histology and extranodal extension

At a median follow up of 45 months (IQR) disease recurred in 167 patients (32.3%) and 161 patients (31.1%) died of UCB. Of the deceasing patients, 36 patients (22.4%) had variant UCB histology.

In the overall cohort patients with presence of non-squamous variant UCB histology showed worse recurrence-free and cancer-specific survival compared to patients with pure UCB (pairwise p-values RFS: $p = 0.016$, CSS: $p = 0.006$). (Fig. 1A, B).

Within the cohort of LN positive patients no difference was observed between pure and variant histological subtypes regarding recurrence-free and cancer-specific survival (p-values = n.s.) (Fig. 1C, D).

LN positive patients with ENE exhibited significantly worse recurrence free ($p \leq 0.001$) and cancer specific survival ($p \leq 0.001$) compared to patients without ENE (Fig. 1E, F). Moreover, when categorized by diameter of ENE (> 10 mm vs. < 10 mm) patients with a larger diameter had worse recurrence-free ($p = 0.049$) but not cancer-specific mortality ($p = 0.062$) (Fig. 1G, H).

3.4. Adjusted survival analysis

In multivariable cox regression analyses adjusted for standard clinico-pathological UCB prognosticators, age, pathological tumor stage, soft tissue surgical margin status, and nodal status independently predicted survival (Table 2). Specifically, lymph node positive patients with/without presence of ENE compared to lymph node negative patients had greater odds of disease recurrence (Hazard Ratio (HR) 1.89, 95% confidence interval (CI) 1.15–3.12; $p = 0.012$ and HR 3.88; 95% CI 2.24–6.71, $p \leq 0.001$), cancer specific survival (HR 2.17, 95% CI 1.29–3.67; $p = 0.004$ and HR 4.60, 95% CI 2.57–8.23, $p \leq 0.001$), and overall mortality (HR 2.47, 95% CI 1.62–3.78, $p \leq 0.001$ and HR 3.51, 95% CI 2.10–5.86, $p \leq 0.001$). In contrast, the presence of variant UCB histology was not associated with disease recurrence, cancer specific-, and overall mortality (Table 2).

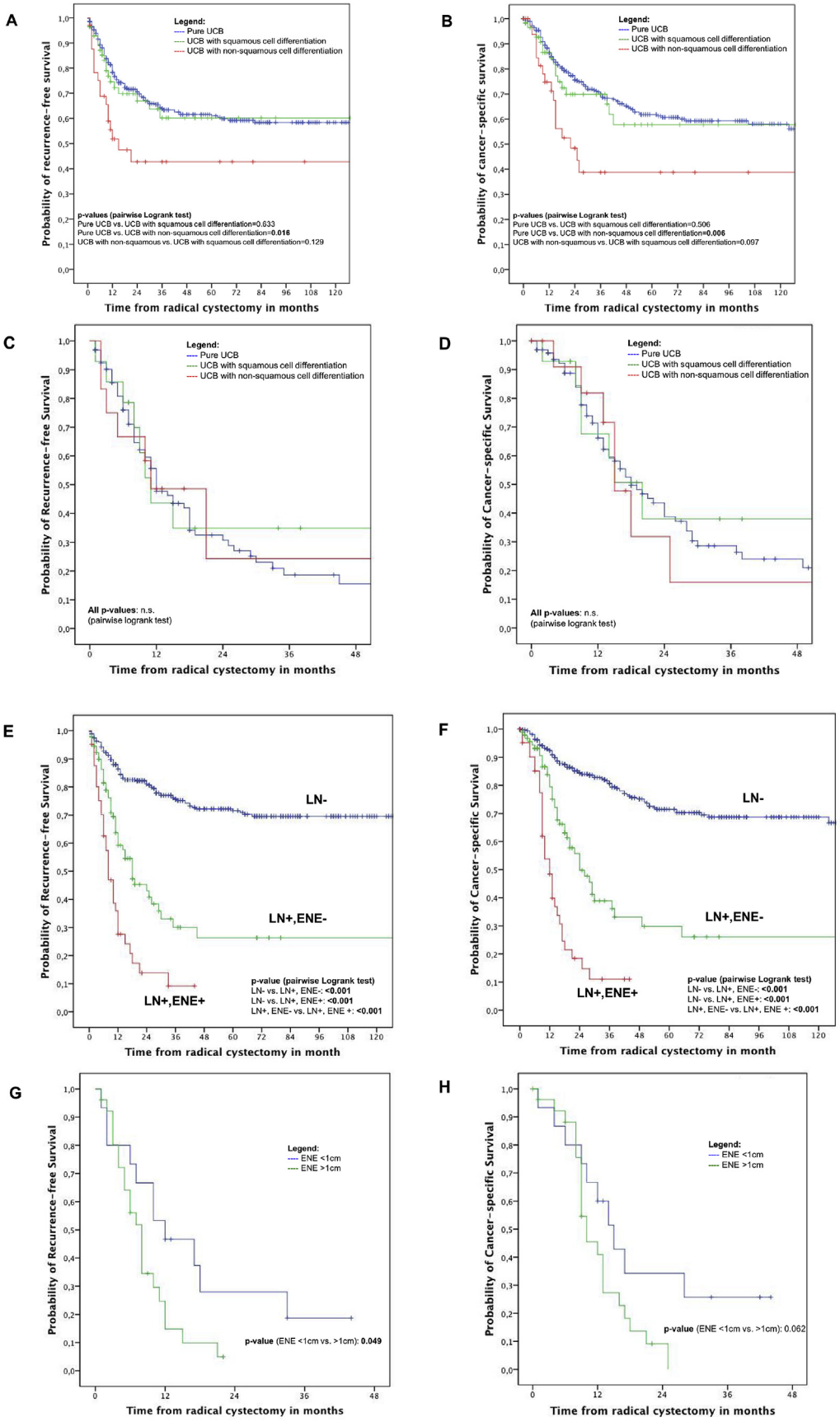

Fig. 1. Kaplan-Meier plots of recurrence-free and cancer-specific survival stratified by **A-B** pure and squamous/non-squamous variant UCB in the overall cohort, **C-D** pure and variant UCB among lymph node positive patients, **F-G** presence of lymph node positive disease ± extra nodal extension (ENE), **G-H** extent of ENE.

Table 2
Multivariable Cox regression analyses predicting recurrence-free, cancer-specific and overall survival in 517 urothelial carcinoma patients treated with radical cystectomy and bilateral lymphadenectomy.

Parameter	Recurrence-free Survival			Cancer-specific survival				Overall survival			
	HR	95% CI	p-value	HR	95% CI		p-value	HR	95% CI		p-value
Age (continuous)	1.02	1.07–1.04	**0.007**	1.02	1.01	1.04	**0.005**	1.03	1.02	1.05	< **0.001**
Female Gender	1.43	0.86–1.79	0.2	1.21	0.84	1.75	0.3	1.03	0.75	1.41	0.9
Pathologic Tumor Stage (Trend)							**0.001**				< **0.001**
pT1 vs. pTa/is	1.34	0.58–3.10	0.4	1.3	0.54	3.14	0.6	0.80	0.41	1.53	0.5
pT2 vs. pTa/is	1.74	0.81–3.76	0.1	1.93	0.90	4.22	0.1	1.02	0.57	1.81	1.0
pT3 vs. pTa/is	3.26	1.54–6.93	**0.002**	2.99	1.35	6.62	**0.007**	1.71	0.97	3.01	0.07
pT4 vs. pTa/is	4.93	2.22–10.93	< **0.001**	4.79	2.08	11.04	< **0.001**	2.74	1.50	5.03	**0.001**
Tumor Grade (continuous)	1.10	0.80–1.51	0.6	1.13	0.82	1.58	0.5	1.20	0.95	1.53	0.1
Concomitant Carcinoma in situ (Present vs. Absent)	0.97	0.67–1.39	0.8	0.79	0.54	1.16	0.2	0.75	0.54	1.05	0.1
Soft tissue surgical margin status (Positive vs. Negative)	1.67	1.11–2.56	0.2	1.72	1.12	2.65	**0.014**	1.55	1.07	2.27	**0.02**
Lymphovascular Invasion (Present vs. Absent)	0.89	0.58–1.38	0.6	0.85	0.54	1.34	0.5	0.98	0.67	1.43	0.9
Adjuvant Chemotherapy (Administered vs. Not Administered)	1.33	0.89–2.01	0.2	1.21	0.79	1.85	0.4	0.92	0.64	1.33	0.7
Histology type (Trend)			0.9				0.9				0.5
Squamous diff. vs. Pure UCB	1.11	0.67–1.82	0.7	1.11	0.67	1.85	0.7	1.27	0.84	1.94	0.3
Non-squamous diff. vs. Pure UCB	0.92	0.51–1.63	0.8	0.99	0.56	1.75	1.0	1.20	0.73	1.96	0.5
Nodal status (+/− ENE)											
LN pos. without ENE vs. LN neg.	1.89	1.15–3.12	**0.012**	2.17	1.29	3.67	**0.004**	2.47	1.62	3.78	< **0.001**
LN pos. with ENE vs. LN neg.	3.88	2.24–6.71	< **0.001**	4.60	2.57	8.23	< **0.001**	3.51	2.10	5.86	< **0.001**

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval; LN: Lymphnode; ENE: Extranodal Extension.
p-value in bold display significant results.

4. Discussion

Our analyses confirm presence and extent of ENE as a negative predictor of all analyzed survival metrics in unadjusted and adjusted outcome investigations. Interestingly, evidence regarding the impact of ENE on survival following RC is inconsistent [3–5,16]. Our findings are in line with those of Fajkovic et al., who demonstrated a significant association of ENE with decreased recurrence-free and cancer specific mortality, respectively, in a large multicenter study [3]. Notably, the presence of ENE in our study is comparable to previous reports, ranging between 1/3 and 2/3 of LN metastasis patients [3–5,16]. We found that patients with presence of ENE had almost twice the likelihood to experience disease recurrence and die from their disease compared to patients with LN metastasis without ENE. Importantly, differences in baseline comorbidities were unlikely an inherent bias to our analyses, as witnessed by the equal distribution of ASA scores among the patient strata. As such, and in line with previous authors, presence of ENE may outweigh the predictive capacity of number of positive lymph nodes and diameter of lymphnode metastasis in UCB (3–5,27). Notably, the tremendous impact of ENE as outcome predictor is accentuated by the limited number of patients with LN metastasis in our study, which otherwise may have masked this association.

Intriguingly, there is only limited evidence on the extent of ENE in UCB. Conversely, recent studies in other important malignencies, e.g. lymph node positive breast cancer, have demonstrated a prognostic benefit of stratifying patients by extent of ENE [17]. In our cohort, the median diameter of ENE was 10 mm, which intuitively may feel large. However, this dimension underscores the greater tumorbiological aggressiveness in patients exhibiting ENE. Moreover, a diameter above the median was associated with inferior outcomes. Taken together, the extent of ENE, may be an interesting issue for future investigations in larger prospective studies, especially in regards to adjuvant treatment for this poor prognosticator.

To our knowledge, previous studies did neither focus on analyzing the associations of variant UCB histologies with LN metastasis nor ENE. Our analyses did not reveal an association of variant histologies with neither LN status nor presence of ENE, respectively. The presence of non-squamous variant UCB histology was associated with survival in univariable Kaplan-Meier analysis, however, variant UCB histology was not associated with survival in multivariable analyses adjusted for standard clinicopathological predictors including LN parameters. Of note, the limited sample size in patients with variant histologies hampered more detailed analyses in this heterogeneous subgroup [6,18]. Overall, the impact of variant UCB histology on pathological features and survival metrics remains controversial. While a number of previous reports have found an association of variant UCB histology with adverse pathological features including lymph node status [3,7,18], this association did not indiscriminately translate into inferior survival in adjusted outcome analyses of contemporary series [6,7,19].

Our findings merit several clinical implications. Patients with LN metastasis and especially patients exhibiting ENE are at greatest risk for systemic spread and subsequently fatal course of disease - regardless of variant UCB differentiation. Thus, future efforts should focus on early identification of patients at risk for LN metastasis and identification of ENE incidence by genetic and molecular characterization. By this means individually tailored multimodal treatments may be offered, as already demonstrated in oral squamous carcinoma [20]. Similarly, given its association with survival, the presence and extent of variant histologies, especially non-squamous variants, merits reporting as part of individualized treatments [6]. All the more in respect of the growing understanding of the mutational landscape associated with variant urothelial differentiation [21–23]. Similarly, some recent investigations demonstrated the importance of molecular subtype identification, as this may seriously influence effectiveness of perioperative chemotherapy [24]. Beyond that, these effects may even gain greater future importance due to the growing treatment variability in the immune-oncologic checkpoint inhibitor era [25].

This study is not devoid of limitations. First and foremost are limitations inherent to the retrospective and single-center nature with its limited sample size. Additionally, due to the retrospective nature, we could not adjust for number of previous TURB, and intravesical instillation therapy, which could potentially have influenced results. Nevertheless, although limited, there is evidence for ineffectiveness of instillation therapy in some variant UCB histologies [26]. Similarly, some evidence suggests a benefit of neoadjuvant chemotherapy in some variant UCB histologies, which was not investigated in this study. Taken together, further validation of our results regarding ENE and the presence of variant histologies is warranted in larger cohorts and preferably prospective study design.

5. Conclusion

Neither incidence of LN metastasis nor ENE in LN positive patients seem to be increased in patients with variant UCB histologies. ENE represents a strong, independent predictor of inferior survival, with a high risk of early systemic disease and thus should be reported whenever present and included in adjuvant treatment counseling. Our findings merit validation in a larger, prospective cohort.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.01.008.

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