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Prognostic Implications of Variant Urothelial Carcinoma: Survival Outcomes and Risk Factors from a Single-Center Experience

Varyant Ürotelyal Karsinomun Prognostik Göstergeleri: Tek Merkezli Bir Deneyimden Sağkalım Sonuçları ve Risk Faktörleri

Short Title: Risk Factors in Variant Urothelial Carcinoma (Varyant Ürotelyal Karsinomda Risk Faktörleri)

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Abstract

Objectives: Variant urothelial carcinoma (VUC) represents a diverse group of bladder cancer subtypes with distinct clinical behaviors and prognostic implications. This study aims to evaluate survival outcomes and prognostic factors in patients diagnosed with VUC.

Materials and Methods: A retrospective analysis was conducted on 1844 bladder cancer patients treated at our center between 2018 and 2022. Among them, 59 patients with histologically confirmed VUC were included. Survival outcomes were assessed using Kaplan–Meier analysis, and prognostic factors were evaluated via multivariable Cox regression models.

Results: The most common VUC subtypes were squamous (39%), micropapillary (23.7%), and sarcomatoid (6.8%). The median overall survival (OS) was 11 months, while cancer-specific survival (CSS) was 7 months. Micropapillary and sarcomatoid variants exhibited significantly poorer CSS, with an approximately 8-fold and 7-fold increased mortality risk compared to squamous subtype, respectively. Age and the presence of metastases were key predictors of worse CSS. While radical cystectomy was performed in 30.5% of patients, it did not significantly improve survival.

Conclusion: Our findings underscore the aggressive nature of micropapillary and sarcomatoid VUC subtypes, highlighting the need for individualized treatment approaches. Age and metastatic status were significant determinants of survival, emphasizing the necessity for early diagnosis and targeted therapeutic strategies. Future research should explore molecular profiling and novel treatment modalities, including immunotherapies, to improve patient outcomes.
Keywords: variant urothelial carcinoma, bladder cancer, survival, prognosis, histological variants

Özet

Amaç: Varyant ürotelyal karsinom (VUC), farklı klinik davranışlar ve prognostik sonuçlar gösteren mesane kanseri alt tiplerinden oluşan heterojen bir gruptur. Bu çalışmanın amacı, VUC tanısı almış hastalarda sağkalım sonuçlarını ve prognostik faktörleri değerlendirmektir.

Gereçler ve Yöntemler: 2018-2022 yılları arasında merkezimizde tedavi edilen 1844 mesane kanseri hastasının retrospektif analizi gerçekleştirildi. Bunlar arasından histolojik olarak

doğrulanmış VUC tanısı alan 59 hasta çalışmaya dahil edildi. Sağkalım sonuçları Kaplan-Meier analizi ile değerlendirildi, prognostik faktörler ise çok değişkenli Cox regresyon modelleri kullanılarak analiz edildi.

Bulgular: En sık görülen VUC alt tipleri skuamöz (%39), mikropapiller (%23,7) ve sarkomatoid (%6,8) olarak tespit edildi. Ortanca genel sağkalım (OS) 11 ay, kanser spesifik sağkalım (CSS) ise 7 ay olarak bulundu. Mikropapiller ve sarkomatoid varyantlar, sırasıyla yaklaşık 8 kat ve 7 kat artmış mortalite riski ile belirgin şekilde daha kötü CSS sergiledi. Yaş ve metastaz varlığı, daha kötü CSS'nin temel belirleyicileri olarak tespit edildi. Hastaların %30,5'ine radikal sistektomi uygulanmış olmasına rağmen, sağkalım üzerinde anlamlı bir iyileşme sağlamadı.

Sonuç: Bulgularımız, mikropapiller ve sarkomatoid VUC alt tiplerinin agresif doğasını vurgulayarak bireyselleştirilmiş tedavi yaklaşımlarının gerekliliğini ortaya koymaktadır. Yaş ve metastatik hastalık durumu, sağkalım üzerinde önemli belirleyiciler olup erken tanı ve hedefe yönelik tedavi stratejilerinin önemini göstermektedir. Gelecekteki araştırmalar, hastaların sonuçlarını iyileştirmek amacıyla moleküler profilleme ve immünoterapiler de dahil olmak üzere yeni tedavi yöntemlerini keşfetmelidir.
Anahtar kelimeler: varyant ürotelyal karsinom, mesane kanseri, sağkalım, prognoz, histolojik varyantlar

Introduction

Bladder cancer ranks as the 10th most common malignancy worldwide, with an estimated 573,000 new cases and 213,000 deaths reported annually, according to recent global cancer statistics [1]. Approximately 90% of bladder cancers are classified as urothelial carcinoma (UC), yet a subset exhibits histological variants collectively referred to as "variant histologies (VH)." These include micropapillary, squamous differentiation, adenocarcinoma, and neuroendocrine carcinoma, which comprise approximately 5–25% of all bladder tumors depending on the studied population and diagnostic criteria [2]. These variants are often associated with advanced disease stages, aggressive clinical behavior, and distinct treatment responses.

Emerging evidence from international studies highlights significant heterogeneity in survival outcomes among patients with these VH. For instance, the five-year overall survival

rates for patients with micropapillary and neuroendocrine variants are reported to be as low as 35% and 25%, respectively, compared to nearly 60% in those with pure UC [3,4]. This variation underscores the need for an in-depth understanding of the prognostic differences among these subtypes to inform clinical management strategies.

Despite these findings, much of the existing literature lacks direct comparative analyses of survival metrics across VH. Furthermore, factors such as cohort heterogeneity, variability in diagnostic practices, and limited representation of rare subtypes often impede the generalizability of results. This study aims to bridge these gaps and contribute to the literature to guide treatment approaches by systematically examining survival outcomes across variant bladder tumor histologies.

Our study aimed to determine the survival of patients with variant UC (VUC) and to analyze the factors affecting survival. Understanding these differences could yield critical insights into disease biology and improve prognostication and therapeutic decision-making.

Materials and Methods

After obtaining ethics committee approval from the institution where the study was conducted (protocol identification date and number: 26.01.2022/2011-KAEK-25 2022/01-19), the pathology results of 1844 patients who underwent transurethral resection or radical cystectomy for bladder tumor in our hospital between January 2018 and December 2022 were retrospectively analyzed. Of the 78 patients with VH other than pure UC, 19 were excluded from the study due to the unavailability of their radiological images. The remaining 59 patients were included in the study.

The specimens of patients diagnosed with VUC were independently confirmed by a pathologist, with patient information and original pathological diagnoses blinded. Demographic, radiological, and pathological characteristics of the patients were recorded. All patients with visceral metastasis identified on cross-sectional imaging also had lymph node metastasis. Patients with isolated lymph node metastasis were categorized into the "cN+" group, while those with both lymph node and visceral metastasis were included in the "cM+" group. Survival data were obtained using the records from the central population registry system.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0. The data are expressed as mean ± standard deviation (SD). Differences in categorical

variables were assessed with the Chi-square test, while Student's t-test was employed for continuous variables. Kaplan–Meier curves were utilized to estimate overall survival, and the log-rank test was applied to determine statistical significance. Binomial regression analysis was conducted to identify predictors of mortality. A p-value of less than 0.05 was deemed statistically significant.

Results

Of the patients with VH, 23 patients (39%) were diagnosed with squamous cell carcinoma, 14 patients (23.7%) with micropapillary carcinoma, and 4 patients (6.8%) with sarcomatoid tumors. Additionally, 3 patients each had a plasmacytoid, nested pattern, and clear cell carcinomas. Two patients each were diagnosed with adenocarcinoma and microcystic pattern tumors. Finally, single cases of lymphoepithelioma-like carcinoma, lipid cell variant, osteoclastic giant cell variant, glandular differentiation, and small cell carcinoma were identified. Microscopic images of some rare types of VH are shown in **Figure 1**. Of these patients, 53 were male (89.8%) and 6 were female (10.2%). The mean age at diagnosis was 72.1 ± 11.5 years. The baseline characteristics of patients with squamous, micropapillary, sarcomatoid, and other VH are summarized in **Table 1**. No statistically significant differences were observed between the groups in the evaluated parameters. However, subgroup analysis revealed that patients with tumors other than the three most common types had a statistically significantly higher likelihood of visceral metastasis compared to those with squamous differentiation (45% vs. 4%, p=0.003).

Radical cystectomy was performed in 18 (30.5%) patients after the initial diagnosis. Systemic chemotherapy was planned for 14 (23.7%) patients with lymph nodes and 13 (22.1%) patients with solid organ metastasis. 14 (23.7%) patients did not accept early radical cystectomy at the non-muscle invasive stage.

In our study with a mean follow-up period of 29 months, the median overall survival (OS) of the patients was 11 [interquartile range (IQR):34, min-maximum (min-max):1-97] months. Cancer-specific survival (CSS) was 7[IQR:10, min-max:1-65] months. Overall and cancer-specific survival graphs of variant subgroups are shown in **Figure 2**. The median OS (95% confidence interval) of squamous, micropapillary, sarcomatoid, and other variant subtypes were 13(9-19), 12(5-65), 3(2-3) and 10(3-20) months, respectively. Cancer-specific survival was 40(11-40), 12(5-65), 3(2-3), 14(4-54) months in the same order.

Age was a risk factor for cancer-specific survival (HR: 1.05; 95% CI 1.01-1.11; p0.045), but not for overall survival (HR: 1.03; 95% CI 0.98-1.07; p0.153). The cancer-specific mortality risk for the micropapillary variant was nearly eightfold higher compared to the squamous subtype. Cancer-related mortality was 7 times higher in the sarcomatoid variant and 5 times higher in the other variants. Detection of lymph node or solid organ metastasis on cross-sectional imaging did not affect overall survival but was found to affect cancer-specific survival **(Table 2)**.

Discussion

The diverse histological variants of UC present significant challenges, as they exhibit differing clinical behaviors that can markedly affect patient outcomes and prognoses. Understanding these differences is crucial for effective diagnosis and treatment planning. Many VUCs may be muscle-invasive or even metastatic at diagnosis [5]. On the other hand, considering that in a study where 589 transurethral bladder resection (TURBT) specimens were re-evaluated by expert genitourinary pathologists, VH was not reported in 44% of cases, its detection becomes even more significant in terms of prognostic importance [6]. Many studies have shown that VUC is more aggressive and OS and CSS are shorter [7-9].

In this study, we evaluated the outcomes of patients diagnosed with VH of bladder cancer and showed that micropapillary and sarcomatoid types, in particular, had worse cancer-specific survival than the most common squamous type. These findings are consistent with the existing literature, which highlights the prognostic importance of histological variants and their correlation with adverse pathological features. When evaluating VUC, it is necessary to consider that each variant may have a very different prognosis from each other as each variant has different dynamics.

The squamous variant of UC, while less aggressive than micropapillary or sarcomatoid types, presents a variable prognosis depending on the extent of the disease. In our study, the squamous variant accounted for 39% of all variant cases and was predominantly associated with localized disease at diagnosis. Cancer-specific survival for squamous variants in our cohort was similar to that reported in other studies, with 5-year survival rates ranging from 40% to 60%, depending on the stage at diagnosis [10]. The literature suggests that squamous differentiation frequently arises in response to chronic inflammation or infection, such as recurrent urinary tract infections or prolonged catheterization, which may explain its localized presentation in many cases [11]. However, conflicting data exist, with some studies indicating

worse outcomes for higher-stage squamous variants, including a significant association with lymphovascular invasion and advanced pathological staging [12].

Micropapillary UC is a rare yet notably aggressive variant, constituting 0.6-2.2% of all UCs. This variant is characterized by early lymph node involvement and high-stage disease at diagnosis. In our cohort, micropapillary UC exhibited an approximately eight-fold higher cancer-specific mortality risk compared to squamous cell carcinoma (SCC). These results align with existing literature, which identifies micropapillary UC as having significantly worse survival outcomes than conventional UC, with five-year overall survival rates as low as 35% in some studies [13,14]. The clinical management of micropapillary UC remains a challenge. Radical cystectomy with pelvic lymphadenectomy is the cornerstone of treatment. However, the high propensity for early metastasis underscores the need for neoadjuvant chemotherapy. However, evidence supporting this approach is limited, and future prospective studies are needed to evaluate its efficacy [15,16] In our study, according to the literature, in 5 (35%) patients who could undergo radical cystectomy, the operation did not provide a statistically significant contribution in terms of OS or CSS.

The sarcomatoid variant of UC, as demonstrated in our study, represents one of the most aggressive histological subtypes. This variant accounted for 6.8% of all cases and was characterized by advanced pathological features, including a 75% rate of visceral metastasis at diagnosis. Multivariable analyses revealed that the sarcomatoid variant was associated with a seven-fold increased risk of cancer-specific mortality (HR: 7.1; 95% CI: 1.02–48, p=0.047). In comparison, literature reports indicate a similarly poor prognosis, with 5-year survival rates often below 20% and a high likelihood of lymphovascular invasion and systemic spread [17]. Tumor size and unifocal presentation were notable features in our cohort, with all sarcomatoid tumors measuring ≥3 cm and 75% being unifocal, aligning with reports that highlight their rapid growth and localized dominance [18]. Sarcomatoid UC poses distinct challenges due to its aggressive nature and frequent metastasis at diagnosis. Standard therapies such as radical cystectomy are often inadequate due to the aggressive nature of the disease and its metastatic nature at the time of diagnosis. New therapies, including immune checkpoint inhibitors, show promise, especially given the high tumor mutation burden observed in upper urinary tract UC, especially in sarcomatoid variants. However, further research is needed to establish standardized treatment protocols and to evaluate the efficacy of new therapeutic approaches [19].

Other rare variants, including plasmacytoid, nested, and clear cell subtypes, were also analyzed. The plasmacytoid variant is associated with high metastatic potential, while the nested variant often poses diagnostic challenges due to its resemblance to benign lesions. In our study, patients with these subtypes showed varied survival outcomes, reflecting the heterogeneity of these entities. Nested UC, for instance, can mimic non-invasive UC, complicating early detection and treatment [18,20].

Our analysis identified age as a significant risk factor for cancer-specific survival but not for overall survival. This finding is consistent with studies suggesting that even elderly patients with pure UC have diminished physiological reserves to withstand aggressive disease and treatment regimens [21]. Additionally, the presence of lymph nodes or solid organ metastases at diagnosis adversely affected cancer-specific survival. Kim et al. analyzed 424 patients who underwent radical cystectomy+lymph node dissection for VUC and found that 92 patients (21.7%) had histological positive lymph node involvement. In the LN positive group, histological variants of UC were a significant independent prognostic factor of overall survival (hazard ratio (HR) 3.54; 95% confidence interval (CI) 1.77-7.08, $p < 0.001$) and cancer-specific survival (HR 3.66; 95% CI 1.69-7.90, $p = 0.001$) in both uni-variate and multivariate Cox regression analyses [22]. Our study is consistent with literature highlighting metastasis as a critical determinant of prognosis.

A key strength of our study lies in the detailed sub-analysis of variant UC subtypes, enabling a nuanced understanding of their prognostic implications. Furthermore, the confirmation of diagnoses by an independent pathologist enhances the reliability of our findings. However, the study's retrospective design and relatively small sample size, particularly for rare subtypes, limit the generalizability of the results. Larger multicenter studies are needed to validate our findings and explore potential therapeutic targets.

Conclusion

This study analyzed the effects of different subtypes of VUC on survival outcomes and showed that micropapillary and sarcomatoid variants in particular were associated with worse cancer-specific survival. Micropapillary and sarcomatoid variants were associated with an approximately eightfold and sevenfold increased risk of cancer-specific mortality, respectively. Our study revealed that age and the presence of metastases were the main factors affecting survival, while lymph node and visceral metastases significantly worsened cancer-specific survival. Our findings highlight the importance of molecular profiling and individualized

therapeutic approaches in the management of these aggressive tumors, as each of these tumors behaves differently. Our findings emphasize the need for future research to assess the efficacy of immunotherapies and emerging treatment modalities.

Ethics Committee Approval: Ethical approval for this study was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Ethics committee approval date and number: 26.01.2022/2011-KAEK-25 2022/01-19.
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
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Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – M.K., A.E.; Design – M.K., A.E.; Supervision – M.D.; Resources – M.Ö.; Materials – M.Ö.; Data Collection and/or Processing – M.K., M.Ö.; Analysis and/or Interpretation – A.E.; Literature Search – M.K., D.B.; Writing Manuscript – M.K., D.B., A.E.; Critical Review – M.B.
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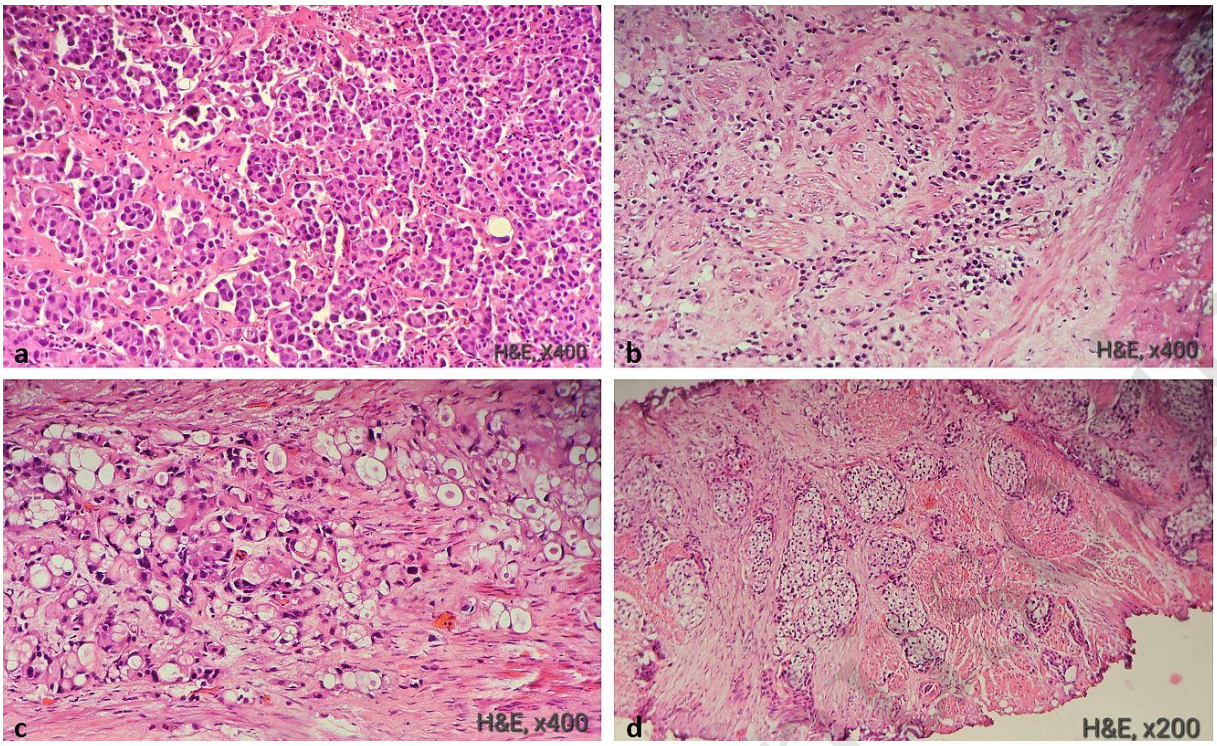

Figure 1. Microscopic specimen images of some variant histologies. a: micropapillary variant, b: plasmacytoid variant, c: lipid cell variant, d: clear cell variant

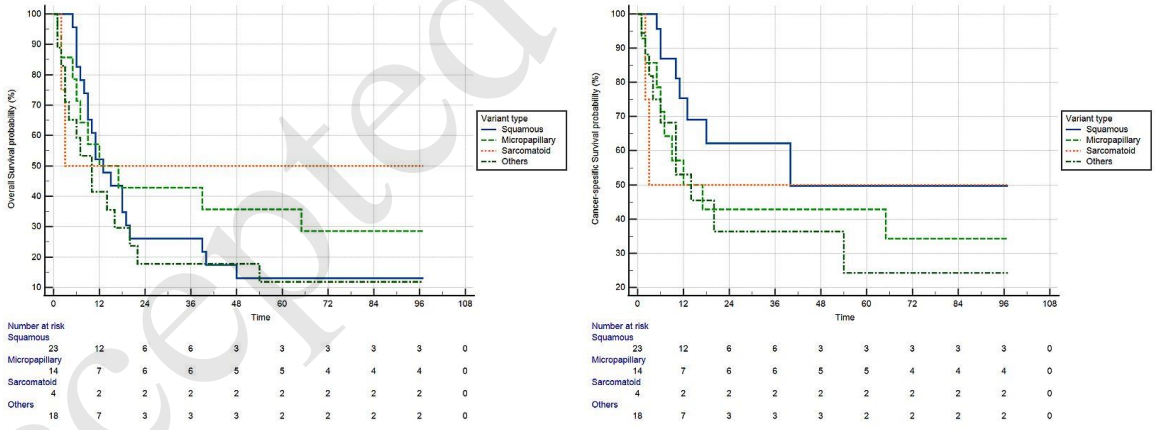

Figure 2. Kaplan-Meier plots stratified by histologic variants of urothelial carcinoma

Table 1. Baseline characteristic of patients according to type of variant histology

	Squamous (n=23)	**Micropapillary (n=14)**	**Sarcomatoid (n=4)**	**Diğer VH(n=18)**	**P-value**
Age	73.9±9	73.5±8.1	70±16.8	69.1±15.3	0.888
Gender n (%)					
Male	20 (87%)	13 (93%)	4 (100%)	16 (89%)	0.845
Female	3 (13%)	1 (7%)	-	2 (11%)	
Initial Surgery n (%)					
TUR-tm	23 (100%)	12 (86%)	4 (100%)	17 (94%)	0.179
Radical cystectomy	-	2 (14%)	-	1 (6%)	
Tumor size					
<3 cm	-	2 (14%)	-	-	0.084
≥3 cm	23 (100%)	12 (86%)	4 (100%)	18 (100%)	
Number of tumors					
Unifokal	7 (30%)	6 (42%)	3 (75%)	9 (50%)	0.319
Multifokal	16 (70%)	8 (58%)	1 (25%)	9 (50%)	
pT n (%)					
pT1	8 (35%)	2 (14%)	1 (25%)	3 (17%)	0.607
pT2	15 (65%)	10 (72%)	3 (75%)	14 (77%)	
pT3	-	1 (7%)	-	1 (6%)	
pT4	-	1 (7%)	-	-	
Presence of lymph node metastasis n (%)					
cN-	16 (70%)	11 (78%)	4 (100%)	14 (77%)	0.598
cN+	7 (30%)	3 (22%)	-	4 (23%)	
Presence of visceral organ metastases n (%)					
cM-	22 (96%)	13 (93%)	1 (25%)	10 (55%)	**0.003***
cM+	1 (4%)	1 (7%)	3 (75%)	8 (45%)	

VH: variant histology; TUR: transurethral resection; pT: pathological tumour stage; cN: clinically detected lymph node positivity; cM: clinically detected visceral organ metastasis positivity; *: indicates clinically significant

Table 2. Multivariable Cox proportional hazards regression models testing the association between demographic, pathological features, and CSS, OS

	Overall Survival			Cancer-specific Survival		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**P-value**
Age	1.03	0.98-1.07	0.153	1.05	1.01-1.11	**0.045***
Gender (male vs female)	1.28	0.48-3.4	0.611	0.89	0.22-3.6	0.881
Presence of muscle invasion at diagnosis	0.99	0.44-2.22	0.989	1.53	0.58-4.02	0.383
Radical cystectomy after diagnosis	1.41	0.62-3.22	0.406	1.15	0.36-3.65	0.811
Variant histology						
Squamous	Ref.			Ref.		
Micropapillary	0.8	0.36-1.77	0.582	7.73	2.16-27.6	**0.001***
Sarcomatoid	0.99	0.19-5.11	0.997	7.1	1.02-48	**0.047***
Other VH	1.52	0.67-3.42	0.312	5.46	1.31-22.8	**0.019***
Lymph node positivity at diagnosis	1.38	0.71-2.71	0.344	4.63	1.07-20	**0.039***
Visceral organ metastasis positivity at diagnosis	0.98	0.39-2.45	0.977	11.6	1.39-96	**0.023***

HR: Hazard ratio; 95% CI: 95% confidence interval; VH: variant histologies; *: indicates clinically significant