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Unfavourable cancer specific survival after neoadjuvant chemotherapy and radical cystectomy in bladder cancer patients with squamous-cell variant: A multi-institutional study

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Abstract

Background: Non-urothelial carcinoma (UC) malignancies are traditionally considered to yield a more aggressive clinical course and little is known about their response to neoadjuvant therapy. We examined the effect of neoadjuvant chemotherapy (NAC) on a large population of bladder cancer (BCa) patients with histological variant (HV).

Methods: We relied on a retrospective, multicentre database including 2,858 patients with BCa, who received radical cystectomy (RC) +/- NAC, between 1990 and 2017. Pure and mixed HVs were grouped into six categories: squamous cell carcinoma (SCC) (n=283, 45%), other subtypes (n=95, 15%), micropapillary (n=85, 14%), adenocarcinoma (n=65, 10%), small-cell (n=54, 8.6%) and sarcomatous (n=47, 7.6%). Kaplan-Meier and Cox regression analyses examined the cancer-specific survival (CSS) according to HVs, using pure UC as reference. Logistic regression models examined the odds of clinic-pathological downstaging after NAC according to HV.

Results: Overall, we identified 2,229 pure UC and 629 BCa with HV at RC. Among neoadjuvant chemotherapy-treated patients (N=450), only patients with SCC (44, 9.8%) were associated with worse CSS (median CSS: 33 vs. 116 months, $p<0.001$) and higher mortality rates (hazard ratio: 2.1, $p=0.03$) compared to pure UC (328, 72.9%). Analyses were also confirmed when pure and mixed cases were considered separately. After adjusting for NAC, only SCC showed lower rate of clinical-to-pathological downstaging (odds ratio: 0.4, $p=0.03$) compared to UC.

Conclusions: SCC was the variant histology exhibiting the lowest effect of NAC in terms of activity and CSS. In comparison with pure UC, SCC seems to be insensitive to traditional NAC regimens.

MICROABSTRACT

Little is known about the response to neoadjuvant therapy of non-urothelial carcinoma (UC) bladder malignancies. Using a retrospective, multicentre database, we found that squamous-cell

carcinoma (SCC) was the histology exhibiting the lowest effect of neoadjuvant chemotherapy in terms of activity and cancer specific survival. Among the non-UC histologies, SCC seems to be insensitive to traditional neoadjuvant chemotherapy regimens.

Keywords

Squamous-cell carcinoma; Neoadjuvant chemotherapy; Bladder cancer; Genomic profile; Immunotherapy

Introduction

Cisplatin-based neoadjuvant chemotherapy (NAC) is the standard of care in the management of patients with bladder cancer (BCa) who are candidates for radical cystectomy (RC) [1,2]. During the past few decades, several efforts have been spent to identify more active chemotherapy regimens and to enable appropriate patient selection through the use of clinical and genomic predictors of response to chemotherapy[3]. The majority of studies in the field focused on pure or predominant urothelial carcinoma (UC), the latter being conventionally defined as cases presenting with 50% of UC component within the tumour specimen. Altogether, these cases comprise about 90% of BCa, whereas little is known about non-urothelial histologies, and their appropriate management is still unknown [4,5]. Interestingly, UC has a propensity for divergent differentiations, ranging from 7% to 81% [6–8]. Taken together, non-UC malignancies are traditionally considered to yield a more aggressive clinical course, resulting in a dismal prognosis for the majority of patients [9–11]. Nevertheless, caution should be applied to generalize these findings to all variant histologies[12,13]. For instance, cisplatin-based chemotherapy regimens have shown to improve survival in patients with neuroendocrine variants [14], while the beneficial role of neoadjuvant chemotherapy in the other histological variants has yet to be proven. In this context, the primary aim of the present study was to examine the efficacy of NAC on cancer-specific survival (CSS) across different HVs in BCa. We attempted to identify whether one or more BCa VHs were associated with modified/reduced NAC activity in comparison with pure UC histology, in terms of CSS.

Patients and Methods:

Study design and clinical database characteristics

This multi-institutional database includes data gathered from hospitals in the United States, Europe, Israel, and Canada. Overall, 4,807 patients with non-metastatic BCa treated with RC between January 1990 and September 2017 were included. The criteria for initial patient selection included: any histology, clinical T_{any}N_{any} M0 stage, and radical cystectomy performance with or without neoadjuvant chemotherapy. Clinical TN stages were defined according to TURB and preoperative CT scan. For those patients who received neoadjuvant chemotherapy, administration of at least 2 cycles of any regimen was required (Figure 1). The administration of any new drug, either alone or combined with neoadjuvant chemotherapy, was not allowed. The histological diagnosis was obtained from the radical cystectomy specimens, rather than from TURB specimens. Histological

evaluation was not centralized but performed independently at each institution relying on expert uro-pathologists. The study was approved by the Institutional Review Board from all participating institutions that constitute this multi-institutional database.

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuous variables. The statistical significance of differences in medians and proportions was respectively tested with the Kruskal-Wallis and Chi-square tests. Analyses were performed by grouping histological variants into 6 categories, where pure and mixed cases of each histological variant were respectively combined. Furthermore, we analysed data by separating pure from mixed cases of each variant histology. Here, 11 histological subgroups were tested as independent predictors. For example, squamous cell carcinoma (SCC) was analysed combining pure and mixed cases, and also as pure SCC vs. UC with SCC component, separately. The primary study endpoint was CSS, which was analysed across all different histological variants and according to treatment delivered. Here, UC was used as reference category while all others histological variants were compared with. CSS was defined as the time from RC to cancer-specific death. Data were censored if the patients were alive at last follow-up, or if they died for other causes. The secondary endpoint was the clinical-to-pathological downstaging, which was defined as a pathologic nodal stage (N stage) that was at least one stage lower than the pre-NAC clinical N stage[15]. Whether no variation of the N stage occurred, we used the above-mentioned criteria using the tumour stage (pre-NAC cT and pT). Kaplan-Meier method was used for estimation of CSS. Logistic regression and Cox regression models were used to analyse the effect of NAC. Subgroup analyses specifically focused on cN0 and cisplatin-only treated patients. The reverse Kaplan-Meier method was used for follow-up quantification. All statistical tests were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics.

Results:

Study population

We identified 2,858 patients with cT_{any}N_{any}M0 bladder cancer treated with RC $\pm$ NAC who were suitable for the study purposes. (Table 1). Overall, 2,229 (78%) had pure UC, while 629 (22%) exhibited pure or predominant histological variant. The most frequently represented histological variant was SCC (n=283, 45%) followed by other subtypes (n=95, 15%), micropapillary tumours (n=85, 14%), adenocarcinoma (n=65, 10%), small-cell/neuroendocrine (n=54, 8.6%) and sarcomatous components (n=47, 7.6%). NAC was administered in 450 (16%) patients. However, NAC was variably administered according to different histological variants. Specifically, small-cell carcinomas (35.4%) and micropapillary tumours (35.1%) were the histologies most frequently treated with NAC, followed by SCC (19.4%), UC (18.5%), adenocarcinoma (17%), other subtypes (14.3%), and sarcomatous variants (12.1%). Cisplatin-based chemotherapy was the preferred NAC regimen in UC, SCC, sarcoma, micropapillary and other subtypes, ranging from 73 to 57% (Supplementary Table 1).

CSS outcomes

The median follow-up was 29 months (IQR: 12–57 months). Overall, we recorded 751 (33%) cancer-related death events. Median CSS rates for each histological variant and stratified according to received treatment are reported in Table 2. Noteworthy, we found that SCC (n=44, 9.8%) was the only histological variant associated with worse CSS compared to UC (with a median of 33 vs. 116 months, 95% confidence interval [CI]: 17-NA months, $p<0.001$), when only NAC-treated patients (n=450, being the 15.7% of all study population) were considered (Figure 2). Within the 450 NAC-treated patients, SCC variant exhibited higher cancer specific mortality (CSM) rates after multivariable adjustment (HR: 2.1, 95% CI: 1.1–4.2, $p=0.03$) compared to UC (Table 3). Similar results were obtained in the subgroup of patients who showed a bladder-confined tumour (pN0) on final (RC specimens) pathological examination (Supplementary Table 2 and Supplementary Table 3). Subgroup analyses including cN0 and cisplatin-only treated patients showed that SCC was the only histological variant associated with higher CSM after uni- and multi- variable adjustments, when only patients treated with NAC were considered (results not shown).

Clinical-to-pathological downstaging

After either univariable (odds ratio [OR]: 0.4, 95% CI: 0.2–0.7, $p=0.01$) or multivariable (OR: 0.4, 95% CI: 0.1–0.8, $p=0.03$) adjustment for NAC administration and Charlson comorbidity index [CCI], SCC was the only histological variant associated with significant lower odds of clinical-to-pathological downstaging compared to UC (Supplementary Table 4).

Effect of neoadjuvant chemotherapy regimen on CSS

After NAC-regimen stratification, patients with SCC still exhibited worse CSS rates compared to UC both in cisplatin-based (33 vs. NA months, $p=0.009$) and other regimens-based (5 vs. 49 months, $p<0.0001$) groups. In contrast, no CSS rate difference (29 vs. 76 months, $p=0.7$) was found between SCC and UC patients who received a carboplatin-based chemotherapy. On multivariable models, SCC exhibited higher CSM rates in cisplatin-treated patients (HR: 2.5, 95% CI: 1.2–5.2, $p=0.02$) after adjustment for age, CCI, gender and lymph node dissection, but not after pTN stage adjustment (HR: 1.6, 95% CI: 0.8–3.2, $p=0.2$). Furthermore, SCC exhibited higher CSM rates in the other-based regimen group after adjustment for age, CCI, gender and lymph node dissection (HR: 3.3, 95% CI: 2.1–NA, $p=0.001$) or pTN stages (HR: 4.6, 95% CI: 4–NA, $p=0.002$).

Discussion:

SCC of the bladder has been considered an aggressive form of BCa, frequently diagnosed in advanced stages and characterized by rapid progression[16]. Moreover, it has been postulated that this specific histology might exhibit a remarkable resistance to traditional platinum-based regimens in either neoadjuvant[17] or adjuvant[18] settings[19]. In our report, we integrated different sources to comprehensively characterize bladder SCC, and we reported several key findings. Firstly, we found that SCC was the only histological variant associated with worse CSS after NAC and RC, confirming previous results on the overall poor effectiveness of chemotherapy in SCC [21–23]. Indeed, our large, multi-institutional

dataset allowed us to achieve a level of data granularity which is not possible in population-based dataset, as previously reported by other authors[9,18,20]. For instance, we were able to correctly capture the chemotherapeutic regimen in both the neoadjuvant and adjuvant settings, and to stratify our analyses for such variables. Thus, we found that CSS differences may occur in patients with SCC when different NAC regimens are considered. Taken together, our study can be considered a strong, although retrospective, evidence of overall poor efficacy of traditional NAC in patients with SCC.

Data from the PURE-01 study, which is investigating neoadjuvant immunotherapy in patients with MIBC, showed a potential benefit of immunotherapy in terms of pathologic response in the sub-group of patients with SCC variant treated with neoadjuvant pembrolizumab[21]. The identification of predictive biomarkers underlying response to immunotherapy[22], as well as chemotherapy resistance, is required to better stratify patients at the diagnosis of a VH. For example, the role of PI3K-AKT-mTOR signalling pathway, to which PIK3CA gene belong, has been robustly characterized in cancer and it is known to regulate most hallmarks of cancer, including proliferation, survival, and genomic instability[23], as well as chemotherapy resistance[24]. Interestingly, there is increasing evidence that this network also regulates the immunosuppressive microenvironment. For instance, PI3K pathway inhibition enhanced CD8+ T cell infiltration within tumour tissue in various preclinical models, resulting in significant survival benefit[25,26]. Therefore, it is clear that therapeutic inhibition of the PI3K-AKT-mTOR axis may have the dual benefit of putting the brakes on tumour progression and also increasing local tumour immunotherapy surveillance. Such therapeutic strategy may also be implemented in the clinics, either as single- or multiple-agent regimens, as already proved for SCC in the metastatic settings[27]. Taken together, data elaborated from this multi-institutional database suggest that SCC histology is associated with inferior neoadjuvant chemotherapy sensibility, as compared to UC. Such findings may justify the lower clinical-to-pathological downstaging and shorter cancer-specific survival, which have been captured by our analyses. Our study is not devoid of limitations. First and foremost, collapsing pure and mixed SCC cases might have introduced a bias related to the heterogeneity of the SCC cohort. On the other hand, sub-analyses were provided keeping SCC and UC with SCC component separated. Here, pure SCC remained significantly associated with worse CSS after NAC in either overall and localized (pN0) cohorts. Additionally, in support of our methodology, previous results of a retrospective study, investigating the potential CSS differences between pure and mixed SCC histologies, did not find differences between the two groups[28]. Another similar limitation is the lack of quantification of the percentage of VH in mixed cases. Thirdly, the inclusion of muscle invasive and non-muscle invasive BCa may increase the heterogeneity of our cohorts. However, no defined guidelines are available in SCC BCa and no uniform treatment protocol exists that specify the correct and appropriate use of chemotherapy and/or RC according to clinical stage in histological variants. Consequently, wider inclusion criteria should be chosen, where guidelines are lacking. For this reason, we focused on patients with BCa who were treated with RC rather than on muscle invasive BCa only, excluding those patients with recurrent, BCG resistant or multifocal non-muscle invasive BCa that may be associated with adverse prognosis when associated with histological variants[29]. Fourth, it is also important to highlight that some HVs were probably poorly represented in the current

analyses. Indeed, we probably lacked of adequate power to identify statistically significant differences in the NAC treated groups between UC and non-SCC patients. This seems the case for the sarcomatoid variant, which showed absolute inferior CSS compared to UC, although not statistically significant. Taken together, it should be kept in mind that HVs are rare entities and that adequate power is difficult to reach even in large multi-institutional studies, such as our one. Five, the definition of clinical TN stage was also subjected to a certain degree of bias. Under-staging derived from incomplete TURB or variable slide thickness of the CT scans should be taken into account when examining our data. Six, the time frame of the current study crossed the past three decades, when surgical techniques, NAC regimens, lymph node dissection templates, as well as management of BCa patients have evolved and changed. Unfortunately, we could not adjust for all these confounding factors, which have undoubtedly affected the results of the present study. Last but not least, being a retrospective multi-institutional study, there was no centralized pathology revision, standardized chemotherapy regimens, and homogeneous imaging surveillance protocol after treatment. These limitations should be acknowledged, since they might have markedly influenced our results and their reproducibility.

Conclusions:

When treated with traditional neoadjuvant chemotherapy, squamous-cell bladder cancer variant is characterized by lower clinical-to-pathological downstaging and shorter cancer-specific survival compared to pure UC histology, representing the variant histology with the lowest activity of NAC in our multicenter database. For this group of patients, new therapeutic strategies should be explored, including neoadjuvant immunotherapy. Coming trials, including detailed biomarker analyses, are largely awaited, to better address the specific role of neoadjuvant modalities in bladder cancer variant histologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL PRACTICE POINTS

- The efficacy of chemotherapy on non-urothelial bladder cancer has never been examined accurately.
- Using a multicentre, international dataset, it was shown that squamous-cell bladder cancer variant is characterized by low clinical-to-pathological downstaging and short cancer-specific survival when treated with traditional neoadjuvant chemotherapy (NAC), representing the variant histology with the lowest activity of NAC.
- For this group of patients, new therapeutic strategies should be explored, including neoadjuvant immunotherapy.

Figure 1.
Inclusion and exclusion criteria flow-chart.

Figure 2. Cancer-specific survival rates according to BCa histologies in 2,858 cT_{any}N_{any}M0 patients treated with radical cystectomy + neoadjuvant chemotherapy.

Table 1.

Overall patient characteristics of 2,858 non-metastatic (cM0pM0) bladder cancer (BCa) patients (cT_{any}N_{any}) treated with radical cystectomy at 27 tertiary care centers.

Variables		Rate (%)
Overall	N	2858 (100)
Age at cystectomy (years)	Median	68yrs
	Range	61–75 yrs
Gender	Female	527 (18.4)
	Male	2331 (81.6)
Smoke habits	Never smoked	673 (23.5)
	Current smoker	690 (24.1)
	Former smoker	1144 (40)
	Unknown	351 (12.3)
Surgical Margins status	Negative	2454 (85.9)
	Positive	319 (11.2)
	Unknown	85 (3)
Charlson Comorbidity Index (CCI)	≥2	1077 (37.7)
	0	731 (25.6)
	1	347 (12.1)
	Unknown	703 (24.6)
Ethnicity	Not Hispanic/Latino, White	2520 (88.2)
	Asian	23 (0.8)
	Hispanic or Latino	106 (3.7)
	Not Hispanic/Latino, Black	47 (1.6)
	Other or mixed	162 (5.7)
Histology at RC specimens	UC	2229 (78)
	Adenocarcinoma	65 (2.3)
	Pure	38 (58.5)
	UC with Glandular component	27 (41.5)
	Micropapillary	85 (3)

Variables		Rate (%)
	Other subtypes	95 (3.3)
	Pure other/mixed non UC	63 (66.3)
	UC with others component	32 (33.7)
	Sarcoma	47 (1.6)
	Pure	17 (36.2)
	UC with sarcomatoid component	30 (63.8)
	SCC	283 (9.9)
	Pure	127 (44.9)
	UC with squamous component	156 (55.1)
	Small-Cells	54 (1.9)
Clinical T stage	Pure	41 (75.9)
	UC with small-cell component	13 (24.1)
	<cT2	506 (17.7)
	cT2	1632 (57.1)
Clinical N stage	cT3–4	357 (12.5)
	Unknown	363 (12.7)
	cN0	1247 (43.6)
	cN1	153 (5.4)
	cN2	103 (3.6)
	cN3	11 (0.4)
NAC	cNX	462 (16.2)
	Unknown	882 (30.9)
	No	2207 (77.2)
NAC Regimen	Unknown	201 (7)
	Yes	450 (15.7)
	Carboplatin based	45 (1.6)
	CMV/MVEC	19 (0.7)
	Gemcitabine + cisplatin	197 (6.9)
	MVAC	96 (3.4)
	No NAC	2205 (77.2)

Variables		Rate (%)
	Others	95 (3.3)
	Unknown	201 (7)
RT to the primary	Yes	143 (5)
	No	1638 (57.3)
AC	Unknown	720 (25.2)
	Yes	500 (17.5)
AC Regimen	Carboplatin based	69 (2.4)
	CMV/MVEC	7 (0.2)
	Gemcitabine + cisplatin	198 (6.9)
	MVAC	57 (2)
	No AC	1637 (57.3)
	Others	170 (5.9)
	Unknown	720 (25.2)
LND	LND	1655 (57.9)
	no LND	49 (1.7)
	Unknown	1154 (40.4)
pT stage	pT0	123 (4.3)
	pT1	241 (8.4)
	pT2	540 (18.9)
	pT3	1214 (42.5)
	pT4	527 (18.4)
	pTa-is	213 (7.5)
pTN stage	<pT2N0M0	399 (14)
	pT0N0M0	110 (3.8)
	pT2N0M0	355 (12.4)
	pT3–4N0M0	787 (27.5)
	pTanyN+M0	1066 (37.3)
	pT anyNX	141 (4.9)

Variables		Rate (%)
Treatment received	NAC + RC + no AC	366 (12.8)
	NAC + RC + AC	35 (1.2)
	no NAC + RC + AC	434 (15.2)
	RC alone	1244 (43.5)
	Unknown	779 (27.3)

Abbreviations:

UC: Urothelial carcinoma

SCC: Squamous-cell carcinoma

RC: Radical cystectomy

NAC: Neoadjuvant chemotherapy

AC: Adjuvant chemotherapy

Table 2
Median Cancer-specific Survival Stratified by Histologic Type and Perioperative Treatment (Compared With UC as Reference)

Histologic Variant	Median CSS (IQ), mo; P Value				
	Overall (n = 2858)	NAC + RC (n = 450)	RC Alone (n = 1244)	RC + AC (n = 500)	RC + Perioperative CHT (n = 915)
Pure and mixed combined					
UC	116 (103–133)	116 (64-NR)	127 (115–179)	103 (88–145)	112 (98–145)
Adenocarcinoma	76 (30-NR); .8	107 (30-NR); .64	NR (NR); .36	74 (23-NR); .23	76 (30-NR); .57
Micropapillary	65 (31-NR); .056	28 (22-NR); .23	65 (33-NR); .2	31 (23-NR); .091	31 (23-NR); .056
Small cell	41 (30-NR); .15	46 (34-NR); .4	33 (30-NR); .073	NR (NR); .35	46 (34-NR); .61
Other subtype	74 (33-NR); .11	NR (22-NR); .48	33 (10-NR); .012 ^a	132 (42-NR); .77	132 (42-NR); .64
Sarcoma	14 (9-NR); < .0001 ^a	12 (12-NR); .98	9 (8-NR); < .0001 ^a	9 (4-NR); < .0001 ^a	12 (9-NR); .035 ^a
SCC	47 (33-NR); .00034 ^a	33 (17-NR); .00059 ^{a, b}	268 (47-NR); .16	38 (23-NR); .093	34 (25-NR); .0016 ^a
Pure and mixed separated					
UC	116 (103–133)	116 (64-NR)	127 (115–179)	103 (88–145)	112 (98–145)
Pure adenocarcinoma	104 (76-NR); .77	107 (NR-NR); .5	NR (28-NR); .9	76 (11-NR); .06	107 (76-NR); .55
Micropapillary	65 (31-NR); .056	28 (22-NR); .23	65 (33-NR); .2	31 (23-NR); .091	31 (23-NR); .056
Pure small cell	41 (33-NR); .2	46 (34-NR); .38	33 (30-NR); .1	NR (NR); .35	46 (34-NR); .65
Pure other/mixed non-UC	100 (48-NR); .7	NR (22-NR); .87	NR (10-NR); .38	132 (100-NR); .39	132 (100-NR); .3
Pure sarcoma	9 (8-NR); < .0001 ^{a, b}	12 (NR); .0098 ^a	9 (8-NR); .00024 ^{a, b}	9 (NR-NR); .00052 ^{a, b}	10.5 (9-NR); < .0001 ^{a, b}
Pure SCC	70 (40-NR); .13	20.5 (8-NR); .0016 ^{a, b}	268 (70-NR); .78	107 (15-NR); .52	29 (15-NR); .082
UC with glandular component	74 (24-NR); .94	30 (NR); .87	NR (NR); .13	74 (23-NR); .92	74 (30-NR); .83
UC with other component	33 (24-NR); .016 ^a	24 (6-NR); .42	25 (6-NR); .002 ^a	42 (21-NR); .24	42 (24-NR); .4

Histologic Variant	Median CSS (IQR), mo; P Value				
	Overall (n = 2858) 25 (14-NR); .011 ^{a, b}	NAC + RC (n = 450) NR (NR); .34	RC Alone (n = 1244) 14 (4-NR); < .0001 ^{a, b}	RC + AC (n = 500) 14.5 (4-NR); .0011 ^{a, b}	RC + Perioperative CHT (n = 915) 25 (25-NR); .51
UC with sarcomatoid component	NR (16-NR); .48	NR (16-NR); .89	30 (14-NR); .36	NA	NR (16-NR); .82
UC and SCC component	34 (25-NR); 0.00017 ^{a, b}	33 (17-NR); .014 ^a	NR (22-NR); .014 ^{a, b}	38 (23-NR); .084	34 (24-NR); .0053 ^a

Abbreviations: AC = adjuvant chemotherapy; CHT = chemotherapy; CSS = cancer-specific survival; IQR = interquartile range; NA = not applicable; NAC = neoadjuvant chemotherapy; NR = not reached; RC = radical cystectomy; SCC = squamous cell carcinoma; UC = urothelial carcinoma.

^aStatistically significant.

^bStatistically significant also on multivariable analysis.

Multivariable logistic regression testing for the effect of histological variant on cancer specific mortality (CSM) according to treatment protocol in the overall population.

Table 3.

Histological variant	Overall	NAC+RC	RC+AC	RC only	RC+perioperative CHT
Adenocarcinoma	0.91 (0.49–1.67) p=0.75	0.36 (0.08–1.65) p=0.19	5.20 (1.74–15.52) p=0.003	0.39 (0.10–1.58) p=0.19	1.03 (0.42–2.51) p=0.95
Pure Adenocarcinoma	0.66 (0.27–1.63) p=0.37	0.19 (0.02–1.56) p=0.12	9.28 (1.99–43.28) p=0.005	0.61 (0.15–2.48) p=0.49	0.95 (0.29–3.15) p=0.93
UC with glandular component	1.30 (0.57–2.94) p=0.53	1.95 (0.22–17.03) p=0.54	3.75 (0.85–16.56) p=0.08	NA	1.87 (0.57–6.15) p=0.31
Micropapillary	1.31 (0.84–2.04) p=0.24	1.24 (0.49–3.15) p=0.65	2.48 (1.11–5.56) p=0.03	1.02 (0.51–2.02) p=0.96	1.69 (0.90–3.15) p=0.10
SCC	1.36 (1.03–1.79) p=0.03	2.10 (1.07–4.15) p=0.03	2.36 (1.32–4.23) p=0.004	0.94 (0.62–1.42) p=0.77	1.95 (1.25–3.04) p=0.003
Pure SCC	0.98 (0.63–1.52) p=0.92	3.38 (1.19–9.59) p=0.02	3.27 (1.15–9.31) p=0.03	0.48 (0.25–0.95) p=0.03	3.36 (1.60–7.03) p=0.001
UC and SCC component	1.74 (1.22–2.46) p=0.002	1.61 (0.68–3.80) p=0.28	2.11 (1.06–4.17) p=0.03	1.73 (1.05–2.85) p=0.03	1.67 (0.98–2.82) p=0.06
Small cell	1.20 (0.65–2.21) p=0.55	2.50 (0.85–7.32) p=0.09	NA	1.13 (0.46–2.78) p=0.79	1.47 (0.57–3.81) p=0.43
Pure Small-cells	1.24 (0.58–2.66) p=0.57	3.00 (0.90–10.04) p=0.07		1.30 (0.32–5.31) p=0.71	1.40 (0.51–3.84) p=0.52
UC with small-cell component	1.17 (0.43–3.16) p=0.76	2.03 (0.27–15.46) p=0.49		1.09 (0.34–3.47) p=0.89	2.02 (0.27–14.82) p=0.49
Sarcoma	4.67 (2.79–7.82) p<0.0001	1.86 (0.23–14.89) p=0.56	21.72 (4.79–98.56) p=0.004	3.97 (2.11–7.48) p<0.0001	6.96 (2.41–20.13) p=0.0003
Pure Sarcoma	9.02 (3.98–20.91) p<0.0001	4.84 (0.58–40.62) p=0.14	36.86 (3.01–452.64) p=0.005	7.88 (2.33–26.67) p=0.001	9.86 (2.16–45.01) p=0.003
UC with sarcomatoid component	3.66 (1.92–6.97) p=0.0001	NA	16.46 (2.45–110.56) p=0.004	3.48 (1.67–7.28) p=0.001	5.11 (1.16–22.39) p=0.03
Other subtypes	1.35 (0.84–2.17) p=0.21	1.23 (0.28–5.39) p=0.78	0.99 (0.39–2.56) p=0.99	1.79 (0.85–3.79) p=0.13	0.95 (0.41–2.19) p=0.90

adjusted for pTN stages + LND+ RT to primary tumor + surgical margins status + age at cystectomy + gender + smoke habits + CCI.

Abbreviations:

UC: Urothelial carcinoma

SCC: Squamous-cell carcinoma

RC: Radical cystectomy

NAC: Neoadjuvant chemotherapy

AC: Adjuvant chemotherapy

CHT: Chemotherapy