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# Tumor multifocality associated with poor prognosis in patients with upper urinary tract urothelial carcinoma after radical nephroureterectomy

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**Background:** Upper urinary tract urothelial carcinoma (UTUC) accounts for approximately 5% in all urothelial tumors. While several independent risk factors have been reported, a potential prognostic variable would be the multifocality within the upper urinary tract.
**Objective:** The aim of this study was to assess the impact of tumor multifocality for clinical outcomes in patients treated with a radical nephroureterectomy (RNU) for a UTUC.
Methods: This study included 195 patients who had been diagnosed with a UTUC based on the pathological examination. From January 1975 through April 2014, we retrospectively reviewed the association of tumor location with clinical outcomes in the consecutive patients with a UTUC treated with an RNU.
**Results:** Overall, 110 tumors were located in the renal pelvis and 49 in the ureter. Thirty-six tumors were classified as multifocal UTUCs. Fifty-seven patients were treated with a laparoscopic RNU, and 138 patients underwent an open RNU. The Kaplan-Meier analysis showed that tumor multifocality was associated with worse cancer-specific survival (CSS) (P = 0.038). On a multivariate analysis, tumor multifocality (hazard ratio [HR] 4.60, P = 0.03), grade (HR 5.65, P = 0.03), and lymph node status (HR 4.6, P = 0.01) were independent prognostic factors for CSS. Surgical procedures such as laparoscopic RNU and open RNU were not prognostic factors in the same analysis (HR 0.5, P = 0.39).
**Conclusions:** Tumor multifocality in UTUC was an independent prognostic factor for CSS. Patients with multifocal UTUC would be candidates for requiring adjuvant therapy and may need to be closely followed up.

**Key words:** tumor multifocality, upper urinary tract urothelial carcinoma, radical nephroureterectomy, survival

## Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon disease. Although UTUC arises from the urothelium including the calyces, renal pelvis, and ureter, it accounts for only 5% of all urothelial malignancies.[1,2] UTUCs are generally considered aggressive, and diagnosed as advanced stages in over 50% of cases.[3-5] Radical nephroureterectomy (RNU) with excision of the distal ureter with a bladder cuff is the gold standard treatment for invasive, non-metastatic UTUCs; however, prognosis of invasive UTUCs is still poor.[3,4] Invasive UTUCs were associated with worse prognosis with 5-year survival data ranging from 30－60%.[4,5]

Although several prognostic factors for UTUC have been identified, primary tumor location represents a controversial risk factor. Recently, large, multicenter and population based studies failed to show that tumor location (renal pelvis vs. ureter) had a significant effect on cancer specific outcomes after adjusting for the effects of established features of disease severity including pathologic stage, grade, and lymph node metastases.[6,7]

However, multifocal UTUC, defined as the synchronous occurrence of multiple tumors in the renal pelvis and ureter, have not been considered in these studies

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because tumor locations have been divided into two groups, the renal pelvis or the ureter, based on the location of the dominant tumor site as identified in the pathologic specimen. Although Chromecki et al.[8] suggested that multifocal UTUC would have a more aggressive biologic behavior and clinical benefit, the impact of tumor multifocality in UTUC on cancer prognosis is still poorly understood. In the present study, we investigated to determine the association between tumor multifocality and clinical outcomes in patients treated with RNU for UTUC.

## Patients and Methods

This study was approved by the ethics committee of Kitasato University School of Medicine and Hospital (B15-25) and was conducted in accordance with the Declaration of Helsinki. All clinical data were retrieved from a surgery database in our institution. This study included 195 Japanese patients who were pathologically diagnosed with UTUC and treated with open or laparoscopic RNU between January 1975 and April 2014. The database included the following parameters: age at the time of RNU, gender, a history of previous bladder cancer, surgical procedure (open or laparoscopic), distal ureter management (intravesical or extravesical), cancer grade, pathologic tumor (pT) stage, lymph node status, tumor location (the renal pelvis, ureter, or both), the follow-up period, and the oncologic outcomes. Tumor multifocality was defined as the synchronous presence of tumors with two or more distinct locations within both the renal pelvis and the ureter in the upper urinary tract with evidence from pathological examinations of those surgical specimens. The presence of CIS (carcinoma *in*

**Table 1.** Association between tumor multifocality and clinical and pathological characteristics

| Variables | | Tumor location | | P value | Tumor multifocality | P value |
|---|---|---|---|---|---|---|
| | | Renal pelvis | Ureter | | | |
| N | | 110 | 49 | | 36 | |
| Age at RNU | <70 | 73 | 28 | 0.26 | 20 | 0.38 |
| | ≥70 | 37 | 21 | | 16 | |
| Gender | Male | 89 | 38 | 0.63 | 28 | 0.78 |
| | Female | 21 | 11 | | 8 | |
| Previous bladder cancer | Yes | 10 | 6 | 0.54 | 6 | 0.78 |
| | No | 100 | 43 | | 30 | |
| Distal ureter management | Open | 78 | 37 | <0.01 | 23 | 0.02 |
| | Laparoscopic | 32 | 12 | | 13 | |
| | Intravesical | 5 | 9 | | 8 | |
| | Extravesical | 105 | 40 | | 28 | |
| Grade | G1/G2 | 88 | 37 | 0.52 | 24 | 0.13 |
| | G3 | 22 | 12 | | 12 | |
| LVI | Positive | 35 | 10 | 0.25 | 17 | 0.11 |
| | Negative | 60 | 28 | | 18 | |
| Pathologic stage | <pT1 | 43 | 17 | 0.60 | 12 | 0.62 |
| | pT2 | 19 | 19 | | 8 | |
| | pT3 | 42 | 10 | | 15 | |
| | pT4 | 6 | 3 | | 1 | |
| Lymph node dissection | Yes | 52 | 28 | 0.49 | 29 | <0.01 |
| | No | 58 | 21 | | 7 | |
| Lymphatic stage | N0 | 46 | 24 | 0.72 | 25 | 0.86 |
| | N1/2 | 6 | 4 | | 4 | |
| FU (m [median, IQR]) | | 61 (20.5－127.4) | 35.8 (14.6－80.6) | | 19.7 (9.7－42) | |

RNU, radical nephroureterectomy; LVI, lymph node vascular invasion; IQR, interquartile range; FU, follow-up

*situ*) was not defined as tumor multifocality.

All patients were followed up after an initial surgical treatment, every 3 months in the first 2 years, then every 6 months for the following 3 years, and annually thereafter. The follow-ups consisted of a physical examination, complete blood test, urine cytology, and cystoscopic/ultrasound evaluation of the urinary bladder. Computed tomography was generally performed annually. Magnetic resonance imaging was performed when clinically indicated. Death from UTUC was coded as a cancer specific event.

*Statistical analysis*

Fisher exact and $\chi^2$ tests were used to evaluate the association between categorical variables. Differences in continuous variables were analyzed using the Mann-Whitney U or Kruskal-Wallis test. Kaplan-Meier analyses were performed and categories compared with log-rank test. Multivariate analyses were assessed using Cox proportional hazard regression model. All tests were two sided, with values of $P < 0.05$ considered significant. Statistical analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC, USA).

## Results

One hundred fifty-five men and 40 women were included with a median follow-up of 45.8 months (interquartile range [IQR]: 14.6－100.3). The median age at the time of RNU was 66 years (IQR: 59－72). Overall, 110 patients had renal pelvic tumors, and 49 had ureteral tumors. Thirty-six patients had multifocal tumors. Open RNU was performed in 138 patients, and 57 patients underwent laparoscopic RNUs.

There were no statistically significant differences in tumor multifocality with respect to grade, pT stage, or lymph node status (Table 1). Patients with tumor multifocality more frequently underwent intravesical bladder cuff removal and lymphadenectomy ($P = 0.02$ and $P < 0.01$, respectively).

Kaplan-Meier analysis revealed cancer specific survival (CSS) following RNU stratified by tumor location (Figure 1). The Kaplan-Meier analysis showed that tumor multifocality was associated with worse CSS ($P = 0.038$). On a multivariate analysis, tumor multifocality (hazard ratio [HR] 4.60, $P = 0.03$), grade (HR 5.65, $P = 0.03$), and lymph node status (HR 4.6, $P = 0.01$) were independent prognostic factors for CSS. Surgical procedures such as laparoscopic RNU and open RNU were not prognostic factors in the same analysis (HR 0.5, $P = 0.39$). The 5-year CSS rates were 65.1%, 54.5%, and 33.7% for renal pelvis tumors, ureteral tumors, and multifocal tumors, respectively. Tumor multifocality was associated with worse CSS ($P = 0.038$, log rank test). Moreover, grade, lymph node status, and tumor multifocality were associated with CSS in a multivariable analysis ($P = 0.027$, $P = 0.009$ and $P = 0.029$, respectively) (Table 2). Surgical procedure was not associated with CSS in the same analysis ($P = 0.39$).

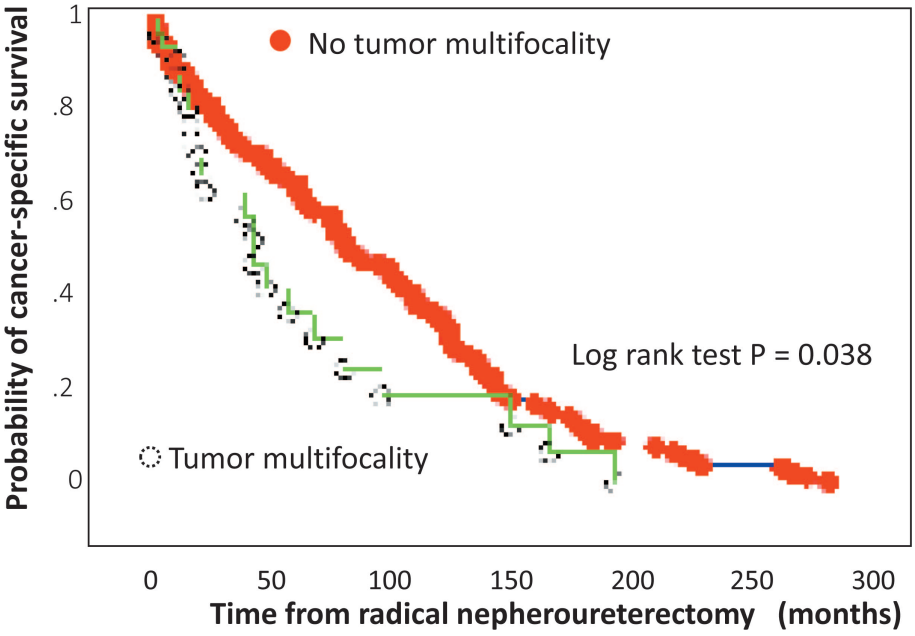


**Figure 1.** Kaplan-Meier analysis of cancer-specific survival stratified by tumor multifocality in 195 patients with UTUCs treated with RNUs

**Table 2.** Multivariate analysis predicting CSS in 195 patients with UTUCs treated with RNUs

| | HR (95% CI) | P value |
|---|---|---|
| Tumor multifocality | 4.60 (1.17－18.05) | 0.03 |
| Age | 0.42 (0.11－1.17) | 0.23 |
| Gender | 1.54 (0.32－7.45) | 0.59 |
| History of previous bladder cancer | 2.96 (0.64－13.60) | 0.16 |
| Surgical procedure | | |
| Open vs. laparoscopic | 0.50 (0.11－2.41) | 0.39 |
| Management of distal ureter | | |
| Intravesical vs. extravesical | 8.42 (0.70－102.97) | 0.10 |
| Grade | 5.65 (1.22－26.16) | 0.03 |
| Pathologic tumor stage | 2.03 (0.52－7.92) | 0.31 |
| Lymph node status | 4.60 (1.17－18.10) | 0.01 |

CSS, cancer-specific survival; UTUC, upper urinary tract urothtelial carcinoma; HR, hazard ratio; CI, confidence interval

## Discussion

The association of tumor location in UTUC with prognosis has been in question for some years.[6-11] Park et al.[10] demonstrated that patients diagnosed with ureteral tumors had a worse prognosis than did those diagnosed with renal pelvic tumors and were associated with significantly higher survival rates than those diagnosed with stage pT3 ureteral tumors. They found that ureteral tumors in advanced stages, which invaded periureteral fat, had higher local failure and worse survival rates than did renal pelvis tumors, which invaded the renal parenchyma. Conversely, van der Poel et al.[11] reported that patients diagnosed with renal pelvis tumors were 2.5 times more likely to die of disease compared to those with ureteral tumors. Contrary to those previous reports, Roman et al.,[6] in their large multicenter study of 1,249 patients, found that tumor location was not significantly related to the patients' prognoses after adjusting for the effects of tumor stage and lymph node metastasis. In another analysis of 2,842 patients, tumor location was not statistically significant for CSS after multivariable adjustments.[7] According to these findings, tumor location in UTUC is no longer considered as an independent predictor of CSS.

Unfortunately, tumor multifocality was not assessed in these studies. The primary location of multifocal tumors was only attributed to that of the index lesion, in either the renal pelvis or the ureter, based on the location of dominant tumor, according to its stage or grade, as identified in the pathologic specimen. In cases in which the renal pelvic and ureteral tumors were of the same stage, tumor size was used to identify the dominant lesion. Thus, they were concerned that consideration of the unavailable variables in their study such as tumor mutifocality might modify their findings regarding prognostic factors for UTUC.[7]

In the present series, tumor multifocality in UTUC was an independent predictor associated with increased risk of CSS, irrespective of surgical procedures, in a multivariate analysis. This finding is in accordance with those of several other independent investigators.[8,12-15] Chromecki et al.[8] reported, in their multivariate analyses, that tumor multifocality was an independent prognostic factor in patients with organ confined UTUC treated with open or laparoscopic RNU. However, they failed to find this association in all patients including those diagnosed with advanced UTUCs. On the contrary, Novara et al.[12] found, in their study, which included a higher rate of multifocal UTUCs (42%), that tumor multifocality was associated with worse CSS in all patients with UTUCs treated with RNUs. Ouzzane et al.[14] evaluated the impact of tumor location in UTUC on survival in their study of 609 patients including 18% of multifocal UTUCs, which is nearly the same as that in the present study (18.5%). In Ouzzane et al.'s multivariate analysis,[14] tumor multifocality appeared as a prognostic factor for CSS as it did in the present series. In Yeh et al.'s study[15] of 90 patients with 17.9% of multifocal UTUC, multifocal UTUC was marginally associated with worse overall survival (P = 0.057); however, the small size of that series would not be sufficient to indicate a significant difference. On the other hand, field cancerization is presumed to be the cause for multifocal tumor development in the oral cavity and upper aerodigestive tract, although there is molecular evidence for widespread

expansion of a single malignant clone populating extensive areas of the mucosa.[16] Heney et al.[17] have proposed a hypothesis that there may be a field effect of urothelial carcinogens that results in the independent malignant transformation of spatially distinct urothelial cells. Additionally, in their multivariate analysis, Krabbe et al.[13] demonstrated that tumor multifocality increased intravesical recurrence. Although intravesical recurrence was considered not to affect CSS, taken together, these findings may strongly reconfirm the panurothelial nature of the disease and could result from a more aggressive biologic potential of tumor multifocality in UTUC.

There is the growing evidence that lymphadenectomy may play an important role in UTUC treatments.[18] Intravesical bladder cuff removal and chemotherapy may also be important to prevent cancer-specific mortality.[13,19] Tumor multifocality, along with other factors for worse survival, may help refine clinical decision making regarding the treatments of UTUC to identify patients who may be candidates for lymphadenectomy, intravesical bladder cuff removal, and future neoadjuvant and/or adjuvant chemotherapy. Patients with multifocal UTUC may need to be followed up closely.

This study has several limitations. The main limitations were the small sample size, that fact that it was a retrospective study on a single center database, and that all the patients were Japanese. Also, we did not include certain patient characteristics including smoking status or the details of multifocality such as the number of tumors at each site and the tumor sizes. These factors may likely affect prognoses. Although several factors would be associated with biological aggressiveness of urothelial carcinoma, there is still controversy in terms of the prognostic role of such factors.[3-5,7,20] Further, accumulation of evidence is needed, however, the low incidence of UTUC hinders randomized and prospective studies.

Based on these findings, we suggest that tumor multifocality in UTUC should be considered as a prognostic factor of survival. Patients with tumor multifocality in UTUC may be candidates for lymphadenectomy, intravesical bladder cuff removal, and neoadjuvant and/or adjuvant chemotherapy. Although further studies are warranted, to validate these findings, they are in accordance with the most recent retrospective studies.[8,12-15,19,20]

**Conflicts of Interest:** None

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