Prognostic Significance of Tumor Necrosis in Primary Transitional Cell Carcinoma of Upper Urinary Tract

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Objective: We investigated the prognostic significance of tumor necrosis in primary transitional cell carcinoma (TCC) of upper urinary tract.

Methods: We retrospectively analyzed the records of 119 patients who received surgical management for primary TCC of upper urinary tract. The presence or absence of tumor necrosis was evaluated based on the macroscopic description of the tumor. Along with pathologic features of tumor necrosis, we assessed the impacts of various prognostic factors previously reported for TCC of upper urinary tract.

Results: Tumor necrosis was identified in 19 (16.0%) patients. Patients with tumor necrosis were more likely to have higher local stage, nodal involvement, higher tumor grade, lymphovascular invasion (LVI), and recurrence of disease. Among all subjects, disease-specific survival rates at 5 years after surgery for patients with and without macroscopic tumor necrosis were 36.7 and 83.2%, respectively (P = 0.0001). In multivariate analysis, only pathologic T stage, LVI and tumor necrosis were shown to be independent predictors for disease-specific survival. For solely the invasive tumors, variables including age, surgical margin and tumor necrosis were observed to be independent prognostic factors for disease-specific survival in multivariate analysis, with tumor necrosis showing the highest rank order of statistical significance.

Conclusions: Our results suggest that macroscopic tumor necrosis may be a useful prognostic indicator for primary TCC of upper urinary, especially for invasive tumors. Further investigation would be warranted for the prognostic implications of tumor necrosis in TCCs of upper urinary tract and on actual pathogenesis of tumor necrosis in upper tract TCC.

Key words: transitional cell carcinoma – kidney – ureter – prognosis – tumor necrosis

INTRODUCTION

Transitional cell carcinoma (TCC) of the upper urinary tract is a relatively rare cancer, accounting for only 5% of all urothelial carcinomas (1). Prognosis for advanced upper tract TCCs is still generally poor. Survival at 5 years has been reported to be less than 50% for stage T2–T3 tumors and less than 10% for T4 or metastatic cases (1). Previously, factors such as age, tumor stage, grade, tumor location, lymph node involvement, lymphovascular invasion (LVI) and extent of surgery have been reported in the literature to be associated with prognoses of patients with upper tract TCC (1–3). Nevertheless, most of the reported series on upper tract TCCs involved limited number of cases with discrepancies existing among the data presented.

In tumors within specimens taken from operations for various solid tumors, necrotic areas can often be observed grossly. Recently, the pathologic feature of tumor necrosis has been gaining attention as being a potential prognostic factor for some types of solid tumors (4–6). Currently, it is hypothesized that tumor necrosis is representative of high proliferative activity in aggressive tumors. It has been suggested that when tumors are exposed to hypoxia as a result of rapid growth beyond existing blood supplies,
portions of tumors turn necrotic (4). Indeed, hypoxia-inducible factor (HIF) has been recently reported to be associated with aggressiveness of tumor and poor prognosis in TCCs of bladder and upper urinary tract (7,8). To the best of our knowledge, however, the prognostic significance of tumor necrosis in upper tract TCC has not been documented in any published reports until now.

Thus, we tried to investigate the prognostic significance of tumor necrosis in primary upper urinary tract TCC by reviewing the records of patients managed at our institution.

PATIENTS AND METHODS

Among the 138 patients who received surgical management for TCC of the upper urinary tract at our institution from January 1994 to December 2003, 119 were included in the current study. Exclusion criteria were: history of urothelial tumor or other malignancies; distant metastasis at diagnosis; concomitant invasive bladder tumor; upper tract TCC managed by endo-urological procedure; pre-operative needle biopsy (owing to inconclusive radiologic diagnosis); pre-operative systemic therapy; and incomplete data. We performed a retrospective study of the aforementioned 119 patients, who were treated for primary TCC of the upper urinary tract, by reviewing their records upon approval from our institutional review board. In reviewing the patients’ records, we assessed clinical and pathologic findings along with the post-operative follow-up evaluations including clinical and radiologic findings. Patients were followed post-operatively with urine cytology and cystoscopy every 3 months for the first 2 years, every 6 months for a subsequent 3 years and annually thereafter. Computed tomography and/or excretory urography were performed annually. Median follow-up was 41 months (mean 45, range 2–164).

Among the total patients included in our study, 113 (94.9%) patients received nephro-ureterectomy with removal of the bladder cuff. Nephrectomy and renal sparing surgery of partial ureterectomy were performed in three and three, respectively. In patients who had enlarged lymph nodes on pre-operative evaluation or in those who were suspected of having nodal involvement on intra-operative examination, regional lymphadenectomy was performed. Extended lymphadenectomy was not routinely performed. Post-operatively, cisplatin-based adjuvant chemotherapy was performed in 40 (33.6%) patients.

Tumors were staged according to the UICC classification staging system and graded according to the WHO classification (9,10). LVI was defined as unequivocal presence of tumor cells within endothelial lining of lymphatic and/or vascular channels (11). The presence of tumor necrosis was evaluated based on macroscopic description of tumor, and tumors were considered necrotic only if they exhibited >10% macroscopic necrosis which would be apparent to the experienced pathologists on gross examination of specimens (Fig. 1) (12). As shown in Fig. 1, tumor necrosis is generally observed grossly as a circumscribed area within tumors showing up as a pale yellow color and with granular friable consistency. Degenerative lesions such as fibrosis and old hemorrhages certainly have different appearances (more whitish or rather much more blackish lesions frequently accompanying old clots with tissue defects). The tumors were considered necrotic only when necroses were macroscopically remarkable and the distinction between necroses and non-necrotic tumor cut surfaces was grossly apparent. Diffuse friability of the papillary tumor caused by long ischemic time or delayed fixation was considered as degeneration, not necrosis. Diffuse congestion or hemorrhage of the tumor, not accompanied by apparent necrosis, was also excluded. All gross findings of tumor necrosis were confirmed by microscopic examination, thus gross findings of fibrosis or simple hemorrhages within a tumor were not mistaken for tumor necrosis. With our study being a retrospective one, we did not try to analyze cases with microscopic tumor necrosis only, because we obviously did not have full control over initial sectioning of the tumor for microscopic evaluation. In assessing the variable of tumor size as the greatest dimension of tumor mentioned in the pathologic report, we designated mean value (3.2 cm) as the cutoff to dichotomize the variable.

STATISTICAL ANALYSES

Survival was determined from time of surgery to the time of last follow-up. To examine potential differences between patients with and without macroscopic tumor necrosis, the \( \chi^2 \) test was applied. Disease-specific and progression (recurrence)-free survival was estimated using the Kaplan–Meier method. Deaths from causes other than TCC were censored. In assessing recurrence-free survival, recurrence of disease was defined as local failure or distant metastasis. Since bladder recurrence was observed to have no significant effect towards survival among our subjects, it was not

Figure 1. Tumor necrosis (pale yellowish area) identified grossly in surgical specimen of renal pelvis transitional cell carcinoma along with its microscopic feature. Please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.
considered as disease recurrence. Of the total subjects, 41 (34.5%) eventually experienced bladder recurrence. Log-rank tests were used to compare survival curves. Multivariate analysis was performed according to the Cox proportional hazards regression model to identify significant prognostic factors. All P values were two-sided and P < 0.05 was significant. All statistical analyses were performed with the SPSS (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Ill., USA) programs.

RESULTS

The median age of patients (92 men and 27 women) was 62 years (range 36–90). For patients who died from TCC-related cause, median time to death was 20.5 months (range 4–67) whereas for those who are still alive, median duration of follow-up was 47 months (range 2–164). Among the patients who had disease recurrence, median time to recurrence of disease was 11 months (range 3–48). Characteristics of patients and tumors along with associations of tumor necrosis with various factors are as listed in Table 1. Among the total patients, macroscopic tumor necrosis was identified in 19 (16.0%) patients. Patients with macroscopic tumor necrosis were more likely to have higher local stage, nodal involvement, higher tumor grade, non-papillary morphology, and recurrence of disease. LVI, which has recently been reported to be an adverse pathological prognostic factor for TCC, was assessed to be more prevalent in tumors with macroscopic necrosis. The relationship between tumor size and presence of necrosis also approached statistical significance as larger tumors tended to accompany tumor necrosis more commonly.

For all subjects, estimated disease-specific survival rates at 5 and 10 years following surgery were 75.9 and 69.2%, respectively. Comparing survival rates according to local pathological stage, patients with superficial (pTa–pT1) disease showed 5-year disease-specific survival rate of 100% while those with invasive (pT2–pT4) disease demonstrated 64.5% (Fig. 2). As for the association of macroscopic tumor necrosis with patient outcome, patients with macroscopic tumor necrosis had noticeably worse disease-specific survival than those who did not present this feature among the total subjects. Disease-specific survival rates at 5 years after surgery for patients with and without macroscopic tumor necrosis were 36.7% and 83.2% respectively (Fig. 3).

In univariate analysis, variables such as age, pT stage, tumor grade, nodal involvement, tumor’s gross appearance, surgical margin, and LVI along with macroscopic tumor necrosis were all shown to have significant prognostic impact on disease-specific survival for total subjects included in our study (Table 2). In multivariate analysis, only pathological T stage, LVI, and tumor necrosis were retained as independent predictors of disease-specific survival.

As nearly all cases with tumor necrosis were found to be of invasive tumors (pT2–pT4) rather than superficial tumors, univariate and multivariate analyses of prognostic variables were also performed separately for invasive tumors only (Table 3). In multivariate analyses of prognostic factors for invasive tumors only, variables including age, surgical margin and tumor necrosis were observed to be independent prognostic factors for disease-specific survival with tumor necrosis having the highest rank order of statistical significance. Compared with the results of multivariate analysis performed among the total subjects, only tumor necrosis was observed to maintain its prognostic significance as an independent prognostic variable even when subjects were limited to invasive tumors only.

DISCUSSION

The presence of tumor necrosis may reflect tumor biology and may also provide additional prognostic information. In solid tumors such as malignant mesothelioma and renal cell carcinoma, tumor necrosis has been suggested to be representative of tumors outgrowing their blood supply and has been proposed to be a sign of tumor aggressiveness, which generally leads to poor prognosis (4,5).

Meanwhile, as can be seen from the review of the literature, tumor necrosis has not received much attention in the investigations of prognostic indices in upper tract TCC. Few have looked into the prognostic significance of tumor necrosis in TCC. In 1991, Portillo Martin et al. (13) reported that tumor necrosis was observed to influence survival for both superficial and infiltrating TCCs of bladder. They suggested that wide areas of tumor necrosis correlated with a lower survival rate for those with bladder TCC. Apart from that, we could not identify other studies performed in recent years, which demonstrated that tumor necrosis has any prognostic implications for TCC of the bladder or upper urinary tract.

The lack of recognition of tumor necrosis as a prognostic indicator for TCC may be at least in part explained by the fact that there is still no established criteria for defining tumor necrosis. In the current retrospective investigation, we investigated whether tumor necrosis was observed macroscopically because we did not have full control over initial sectioning of specimens to produce slides for microscopic analyses. Certainly, an exact verification of a lesion grossly suspected to be tumor necrosis would require microscopic examination. Detection of microscopic foci of necrosis is extremely difficult if they are not seen grossly within tumor diameters which can be several centimeters long.

In our study, tumor necrosis was observed to be predominantly common among the invasive tumors rather than superficial tumors, demonstrating prognostic significance for invasive upper tract TCC. Such a finding should be
considered significant because the prognoses for invasive TCCs of upper urinary tract have been known to be poor (1). As adjuvant treatment such as radiotherapy with concurrent chemotherapy has been reported to improve ultimate outcome in patients with locally advanced upper tract TCC, a prognostic factor such as tumor necrosis may prove useful in the selection of candidates for adjuvant therapy (14).

Despite the fact that tumor necrosis has recently garnered increasing attention as a prognostic indicator for some types of solid tumors, exact explanation is still currently not available for tumor necrosis having a significant prognostic implication. The pathogenesis of tumor necrosis in various tumors remains poorly understood. Meanwhile, it has been suggested that necrosis within tumors may be the result of the tumor rapidly proliferating and outgrowing its blood supply. In several types of tumor, the presence of tumor necrosis has been correlated with staining for carbonic anhydrase IX (CA IX) (15,16). Such a phenomenon in many

| Table 1. Clinicopathological characteristics of patients with or without tumor necrosis |
|--------------------------------------------------|------------------|------------------|------------------|------------------|
| All pts                                      | Pts with tumor necrosis (%) | Pts without tumor necrosis (%) | P-value |
| No. pts                                      | 119               | 19 (16.0)         | 100 (84.0)       | 0.313 |
| Gender                                       |                   |                   |                  |
| Male                                         | 92                | 13 (14.1)         | 79 (85.9)        |      |
| Female                                       | 27                | 6 (22.2)          | 21 (77.8)        |      |
| Age                                          |                   |                   |                  |
| <60 yrs                                      | 46                | 7 (15.2)          | 39 (84.8)        | 0.859 |
| ≥60 yrs                                      | 73                | 12 (16.4)         | 61 (83.6)        |      |
| pT stage                                     |                   |                   |                  |
| pTa–T1                                       | 38                | 1 (2.6)           | 37 (97.4)        | 0.006 |
| pT2–T4                                       | 81                | 18 (22.2)         | 63 (77.8)        |      |
| Grade                                        |                   |                   |                  |
| 1 or 2                                       | 76                | 7 (9.2)           | 69 (90.8)        | 0.007 |
| 3                                            | 43                | 12 (27.9)         | 31 (72.1)        |      |
| Tumor size (greatest dimension)              |                   |                   |                  |
| <3.2 cm                                      | 62                | 6 (9.7)           | 56 (90.3)        | 0.051 |
| ≥3.2 cm                                      | 57                | 13 (22.8)         | 44 (77.2)        |      |
| Lymph node involvement                      |                   |                   |                  |
| N0                                           | 47                | 0 (0)             | 47 (100.0)       | <0.001 |
| Nx                                           | 46                | 9 (19.6)          | 37 (80.4)        |      |
| N+                                           | 26                | 10 (38.5)         | 16 (61.5)        |      |
| Location of tumor                            |                   |                   |                  |
| Renal pelvis                                 | 54                | 10 (18.5)         | 44 (81.5)        | 0.488 |
| Ureter                                       | 65                | 9 (13.8)          | 56 (86.2)        |      |
| Surgical margin                              |                   |                   |                  |
| Positive                                     | 6                 | 1 (16.7)          | 5 (83.3)         | 1.000 |
| Negative                                     | 113               | 18 (15.9)         | 95 (84.1)        |      |
| Gross appearance of tumor                   |                   |                   |                  |
| Papillary                                    | 45                | 3 (6.7)           | 42 (93.3)        | <0.001 |
| Non-papillary                                | 74                | 16 (21.6)         | 58 (78.4)        |      |
| Recurrence                                   |                   |                   |                  |
| None                                         | 95                | 9 (9.5)           | 86 (90.5)        | <0.001 |
| Local or distant recurrence                  | 22                | 10 (45.5)         | 12 (54.5)        |      |
| Lymphovascular invasion                     |                   |                   |                  |
| Present                                      | 30                | 11 (36.7)         | 19 (63.3)        | <0.001 |
| Absent                                       | 89                | 8 (9.0)           | 81 (91.0)        |      |
tumor types has been explained by the observation that CA IX is regulated by HIF, a transcription factor which is upregulated in the presence of hypoxia (17). When tumors are exposed to hypoxia as a result of rapid proliferation beyond their blood supply, their furthest front is believed to become necrotic (4). In the more proximal perinecrotic area, hypoxia contributes to production of HIF which in turn stimulates increased production of CA IX (17). Subsequently, CA IX optimizes extracellular milieu for growth and invasion of cancer. In studies with specimens of breast, head and neck cancers, high expression of CA IX was reported in perinecrotic areas (15,16). As for TCC of bladder, Hoskin et al. (18) reported that CA IX, which also showed a correlation with tumor proliferation marker of Ki-67, was an independent predictor for cause-specific survival. Also, Hussain et al. (19) observed that patients with CA IX positive invasive bladder TCC had shorter survival compared with those who had CA IX negative tumors. Regarding HIF, its protein expression has already been shown to be associated with tumor aggressiveness and poor prognosis in a variety of tumors including carcinomas of cervix, colon, ovary, lung, oropharynx, breast and bladder (8). Theodoropoulos et al. (7) performed immunohistochemical examination in 93 patients with bladder TCC and found that those with HIF-1α protein overexpression had significantly worse overall and disease-free survival rates in multivariate analysis. In the upper tract TCC, Nakanishi et al. (8) recently demonstrated that HIF-1α protein expression has significant correlation with overall and disease-free survival in patients who received surgical management for upper tract TCC. They also showed a significant correlation between the expression of HIF-1α protein and that of p53 oncoprotein, overexpression of which has been related to increased tumor proliferation and eventual long-term survival in patients with the upper tract TCC. Nevertheless, we could not identify any published reports which dealt with potential relationship between tumor necrosis and molecules such as HIF and CA IX in TCC. Based on the informations above and our findings, tumor necrosis, which can be regarded as a product of relative hypoxia resulting from rapid proliferation of tumor cells, may indeed be a sign of rapid proliferation and aggressiveness. However, such an hypothesis should be validated through further investigation such as immunohistochemical study on relevant molecules and proteins. Considering the observed prognostic impact of tumor necrosis in the current study and in other solid tumors, further basic research is justified on the actual pathogenesis of tumor necrosis in the upper tract TCC and it may even lead to elucidation of the pathogenesis of TCC.

Admittedly, our study is limited because it is retrospective in nature and traditionally accepted prognostic variables such as tumor grade and lymph node involvement were not observed to be independent prognostic factors for survival. Such results may be due to the limited number of subjects included in the study and the fact that lymph node dissection was not routinely performed at our institution. In addition, even though macroscopic tumor necrosis is not much difficult to detect for pathologists, pathologists’ efforts in trying to detect tumor necrosis may have been inconsistent during past years, because it was not considered as a significant prognostic factor. The observed findings in the present study were not complemented with further evaluation of possibly associated molecular markers. Nevertheless, we believe that the results of our analysis demonstrate potential significance of tumor necrosis as a legitimate prognostic indicator for upper tract TCC, justifying further investigation.

In conclusion, our results suggest that macroscopic tumor necrosis may be a useful prognostic indicator for upper tract TCC, especially for invasive tumors. Further investigation would be warranted to define the prognostic implications of tumor necrosis in TCCs of upper urinary tract and to further elucidate the actual pathogenesis of tumor necrosis in upper tract TCC.

Figure 2. Kaplan–Meier curves using log rank test for disease-specific survival of total subjects with primary transitional cell carcinoma of upper urinary tract stratified by the pathological T stage.

Figure 3. Kaplan–Meier curves using log rank test for disease-specific survival of total subjects with primary transitional cell carcinoma of upper urinary tract stratified by the presence of tumor necrosis.
tract TCC through a prospective study with a larger cohort of patients.

Conflict of interest statement
None declared.

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Table 2. Univariate and multivariate analysis of prognostic variables for disease-specific survival among the total subjects

| Factors                  | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | Hazard ratio (95% confidence interval) | P value | Hazard ratio (95% confidence interval) | P value |
| Age                     | 2.46 (1.03–5.87) | 0.043 | 1.46 (0.53–4.03) | 0.464 |
| Gender                  | 1.40 (0.62–3.14) | 0.420 | 0.701 (0.26–1.87) | 0.482 |
| pT stage                | 8.15 (1.75–26.8) | 0.004 | 3.30 (1.16–9.37) | 0.025 |
| Grade                   | 3.98 (1.48–10.71) | 0.006 | 2.58 (0.84–7.94) | 0.096 |
| Lymph node involvement  | 5.58 (2.48–12.57) | <0.001 | 4.16 (0.88–19.54) | 0.072 |
| Tumor location          | 1.44 (0.69–3.03) | 0.335 | 1.33 (0.58–3.03) | 0.503 |
| Gross appearance of tumor | 3.52 (1.33–11.31) | 0.010 | 2.95 (0.83–10.99) | 0.108 |
| Margin positivity       | 3.20 (1.24–8.25) | 0.016 | 2.32 (0.79–6.83) | 0.126 |
| Lymphovascular invasion | 3.73 (1.82–7.66) | <0.001 | 2.59 (1.07–6.31) | 0.035 |
| Tumor necrosis          | 6.85 (3.32–14.14) | <0.001 | 4.29 (1.70–10.86) | 0.002 |

Table 3. Univariate and multivariate analysis of prognostic variables for disease-specific survival among the invasive tumor (pT2–pT4) cases only

| Factors                  | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | Hazard ratio (95% confidence interval) | P value | Hazard ratio (95% confidence interval) | P value |
| Age                     | 3.17 (1.07–9.39) | 0.038 | 3.37 (1.24–9.15) | 0.017 |
| Gender                  | 1.40 (0.62–3.19) | 0.419 | 0.71 (0.26–1.97) | 0.513 |
| pT stage (pT2 vs higher) | 1.42 (0.58–3.51) | 0.443 | 0.86 (0.34–2.21) | 0.753 |
| Grade                   | 1.17 (0.56–2.47) | 0.675 | 0.89 (0.39–2.06) | 0.797 |
| Lymph node involvement  | 3.84 (1.68–8.74) | 0.001 | 2.41 (0.76–7.62) | 0.134 |
| Tumor location          | 1.12 (0.52–2.39) | 0.770 | 0.79 (0.31–2.08) | 0.642 |
| Margin positivity       | 3.05 (1.23–7.52) | 0.016 | 2.67 (1.01–7.07) | 0.048 |
| Lymphovascular invasion | 3.21 (1.51–6.80) | 0.002 | 1.68 (0.58–4.85) | 0.341 |
| Tumor necrosis          | 5.05 (2.38–10.72) | <0.001 | 3.43 (1.32–8.90) | 0.012 |
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