



ORIGINAL ARTICLE

The association between gender and outcome of patients with upper tract urothelial cancer

Yii-Her Chou ^a, Wei-Chiao Chang ^b, Wen-Jeng Wu ^a, Ching-Chia Li ^a, Hsin-Chih Yeh ^a, Ming-Feng Hou ^c, Ping-Song Chou ^d, Mei-Hui Lee ^a, Wei-Pin Chang ^e, Wei-Ming Li ^{f,g,*}

^a Department of Urology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

^b Department of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei, Taiwan

^c Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

^d Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

^e Department of Healthcare Management, Yuanpei University, Hsinchu, Taiwan

^f Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

^g Pingtung Hospital, Department of Health, Executive Yuan, Pingtung, Taiwan

Received 15 November 2011; accepted 8 February 2012

Available online 7 October 2012

KEYWORDS

Gender;
Nephroureterectomy;
Outcome;
Upper tract urothelial cancer;
Urothelial cancer

Abstract The incidence of upper tract urothelial cancer (UTUC) has gradually increased over the past 30 years. Although most reports have shown that UTUC occurs more frequently in men than in women, women have been found to have a worse prognosis than men. In Taiwan, a high incidence of UTUC has been reported, with an unusual minor predominance of female cases. The purpose of this study was to determine the influence of gender on the outcome of patients with UTUC after nephroureterectomy and bladder cuff excision. From January 1990 to December 2007, 301 patients diagnosed with UTUC were admitted at our institution. A retrospective analysis of the effect of gender on the clinical outcome was performed. We compared the 5-year bladder recurrence-free, progression-free, and disease-specific survival rates. While we did not observe any differences between men and women in bladder recurrence-free, progression-free, or disease-specific survival rates, we found that female patients had a significantly higher percentage of contralateral recurrence than the males (5.9% vs. 0.8%, $p = 0.019$).

Copyright © 2012, Kaohsiung Medical University. Published by Elsevier Taiwan LLC. All rights reserved.

* Corresponding author. Department of Urology, Kaohsiung Medical University Hospital, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan.
E-mail address: yihech@kmu.edu.tw (W.-M. Li).

Introduction

Upper tract urothelial cancer (UTUC), including renal pelvis and ureter diseases, is a rare disease, representing only 5% of all urothelial cancers (UCs). In developed countries, UC is a common malignancy in men. However, it is less common in women in most regions of the world, especially in Southern European countries; for example, a male-to-female ratio of 7:1 for UC incidence has been reported in Spain [1–3].

Although bladder cancer is less common in women, they have been reported to have a worse prognosis than men. Mungan et al. demonstrated that this difference in prognosis is not entirely explained by the fact that a higher proportion of this disease is at an advanced stage at the time of diagnosis in women [4,5]. In Taiwan, a high incidence of UTUC has been reported, with an unusual minor predominance of female cases [6].

Nephroureterectomy with bladder cuff excision (radical nephroureterectomy) remains the standard therapy for UTUC [7]. However, even after undergoing this surgery, tumor recurrence is still common. Patients may develop the signs and symptoms of recurrence in the urinary bladder, local retroperitoneal space, or contralateral upper urinary tract (UT) [8]. To date, the definite risk factors for disease recurrence and patient survival after radical nephroureterectomy have not been elucidated. The purpose of this study was to investigate whether there are gender-related prognostic factors associated with UTUC.

Materials and methods

From January 1990 to December 2007, 414 patients were diagnosed with UTUC and underwent radical nephroureterectomy at our institution. Among the 414 patients, 113 were excluded from this study—59 had previous or concomitant urinary bladder tumors, 23 had lymph node or distant metastasis at the time of diagnosis, 5 had bilateral synchronous UTUC, and 26 provided incomplete data. The remaining 301 patients, who received radical nephroureterectomy for primary UTUC, were included in this study. The study was approved by the Institutional Review Board.

The clinicopathological data were recorded retrospectively. The tumors were staged according to the 2002 American Joint Committee on Cancer classification and were graded according to the 1998 World Health Organization classification. Postoperative follow-up involved recording of interval history, physical examination, urinalysis, urine cytology, radiography of the chest, abdominal ultrasonography, excretory urography, and computed tomography of the abdomen. Cystoscopy was performed at intervals of 3 months for the first 2 years, 6 months for the next 2 years, and annually thereafter. Excretory urography or computed tomography was performed annually during follow-up or when clinically indicated. The treatment method and follow-up policy were completely the same for both men and women.

The predictive value of the clinicopathological prognostic factors was analyzed with respect to disease-specific or recurrence-free survival rates. Recurrence-free survival was calculated as the time interval between the date of

nephroureterectomy and the date of first documented clinical recurrence. Disease progression was defined as local retroperitoneal space, contralateral upper UT, and distant-organ metastasis. Disease-specific survival was defined as the time interval between the date of nephroureterectomy and the end point, including death or censoring. Bladder recurrence was included only in disease recurrence but not in disease progression. Progression-free survival was defined as the time interval between the date of nephroureterectomy and the observation of disease progression. Categorical data were analyzed using Pearson Chi-square or Fisher exact test. Univariate and multivariate analyses were performed using the Kaplan–Meier method, using the log rank test and Cox proportional hazards regression model. A p value <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

In this study, we observed 131 men and 170 women whose median age was 66 years (range: 23–87 years), with a median follow-up time of 33 months (range: 1–196 months). The clinical characteristics of these patients are summarized in Table 1. The overall male-to-female ratio was 1:1.3. Tumor arising from the renal pelvis or calyx was found in 105 patients (34.9%), tumor from the ureter in 142 patients (47.2%), and tumor from both areas in 54 cases (17.9%). In the 301 patients studied, pathological stages were distributed as follows: 36 (12%) patients had pTa/pTis tumors, 86 (28.5%) had pT1 tumors, 88 (29.2%) had pT2 tumors, 77 (25.6%) had pT3 tumors, and 14 (4.7%) had pT4 tumors. In total, 122 patients (40.5%) had nonmuscle-invasive tumors, while 179 (59.5%) had muscle-invasive tumors; 130 tumors (43.2%) were low grade, and 171 (56.8%) were high grade.

Segregating the study population according to gender revealed that the female patients were not older than the male ones at the time of performing the surgery. The percentage of female smokers was significantly lower than that of male smokers (12.9% vs. 40.5%, $p < 0.001$). There was no significant difference between male and female patients in other variables, such as gross hematuria, tumor side (right, left), tumor location (calyx, pelvis, ureter), multiplicity, type of nephroureterectomy (open, laparoscopic), type of bladder cuff excision (transurethral incision, open), tumor stage (Ta/Tis/T1, T2, T3, T4), and grade (low, high). Compared with men, women had similar proportions of high-grade, high-stage, and multiple tumors.

In the overall oncologic outcomes of patients with UTUC, women had a significantly higher rate of contralateral recurrence than men (5.9% vs. 0.8%, $p = 0.019$). This difference could not be explained by the difference of adherence to medication. There was no statistically significant difference between men and women with regard to percentage of bladder recurrence, local recurrence, distant metastasis, disease progression, and death from disease-related causes. The bladder recurrence-free survival was not different between men and women ($p = 0.137$), Progression-free and disease-specific survivals were significantly associated with tumor stage (both

Table 1 Characteristics of 301 patients with upper tract urothelial cancer.

| Variables | Total (n = 301) | Male (n = 131) | Female (n = 170) | p |
|------------------------|-----------------|----------------|------------------|--------|
| Age | | | | 0.924 |
| ≤65 | 141 (46.8%) | 54 (41.2%) | 71 (41.8%) | |
| >65 | 160 (53.2%) | 77 (58.8%) | 99 (58.2%) | |
| Smoking | | | | <0.001 |
| Yes | 75 (24.9%) | 53 (40.5%) | 22 (12.9%) | |
| No | 226 (75.1%) | 78 (59.5%) | 148 (87.1%) | |
| Gross hematuria | | | | 0.658 |
| Yes | 233 (77.4%) | 103 (78.6%) | 130 (76.5%) | |
| No | 68 (22.6%) | 28 (21.4%) | 40 (23.5%) | |
| Tumor side | | | | 0.355 |
| Right | 147 (48.8%) | 60 (45.8%) | 87 (51.2%) | |
| Left | 154 (51.2%) | 71 (54.2%) | 83 (48.8%) | |
| Tumor location | | | | 0.849 |
| Renal pelvis or calyx | 105 (34.9%) | 45 (34.4%) | 60 (35.3%) | |
| Ureter | 142 (47.2%) | 64 (48.9%) | 78 (45.9%) | |
| Multiple | 54 (17.9%) | 22 (16.8%) | 32 (18.8%) | |
| Type of NU | | | | 0.778 |
| Open | 246 (81.7%) | 108 (82.4%) | 138 (81.2%) | |
| Laparoscopy | 55 (18.3%) | 23 (17.6%) | 32 (18.8%) | |
| Type of BCE | | | | 0.244 |
| Open | 210 (69.8%) | 96 (73.3%) | 114 (67.1%) | |
| Transurethral incision | 91 (30.2%) | 35 (26.7%) | 56 (32.9%) | |
| pT stage | | | | 0.331 |
| Ta/Tis | 36 (12.0%) | 10 (7.6%) | 26 (15.3%) | |
| T1 | 86 (28.5%) | 37 (28.2%) | 49 (28.8%) | |
| T2 | 88 (29.2%) | 42 (32.1%) | 46 (27.1%) | |
| T3 | 77 (25.6%) | 36 (27.5%) | 41 (24.1%) | |
| T4 | 14 (4.7%) | 6 (4.6%) | 8 (4.7%) | |
| Tumor grade | | | | 0.082 |
| Low | 130 (43.2%) | 64 (48.9%) | 66 (38.8%) | |
| High | 171 (56.8%) | 67 (51.1%) | 104 (61.2%) | |

Data are presented as n (%).

Abbreviations: BCE = bladder cuff excision; NU = nephroureterectomy.

$p < 0.001$) and tumor grade ($p = 0.006$ and $p = 0.002$, respectively). In a multivariate analysis after adjusting for tumor stage and tumor grade, gender did not significantly affect progression-free and disease-specific survivals ($p = 0.297$ and $p = 0.679$, respectively). Five-year progression-free survival rates of men and women were 81.3% and 79.5%, respectively ($p = 0.371$, Fig. 1A). Five-year cancer-specific survival rates of men and women were 81.5% and 86.7%, respectively ($p = 0.450$, Fig. 1B).

Discussion

The standard procedure for treating UTUC is nephroureterectomy with bladder cuff excision. However, UC sometimes recurs after standard surgery in the bladder, either in the previous surgical area or in the contralateral upper UT. Previous studies demonstrated that 25–69% of

the patients who underwent nephroureterectomy for UTUC had subsequent bladder tumor recurrence [9,10]. Recurrence in the local retroperitoneal space is rare; several studies reported a 3–9% local recurrence [11,12]. Similarly, contralateral UT recurrence rates are low, ranging from 3.1% to 11.3% [13]. Several factors, including patient age, tumor size, tumor location, history of bladder UC, tumor multifocality, tumor grade, and tumor stage, are well-known risk factors for cancer-specific survival of patients with UTUC [14]. However, in most studies, gender was not considered as a variable in prognostic analyses.

The importance of gender in the development and prognosis of UC is currently unknown. A majority of reports in the current literature suggest that UTUC is about three times more common in men than in women in countries other than Taiwan [15]. Excessive exposure to cigarette smoke and industrial chemicals in men have been suggested to have a causative role [16]. In bladder UC, Mungan et al.

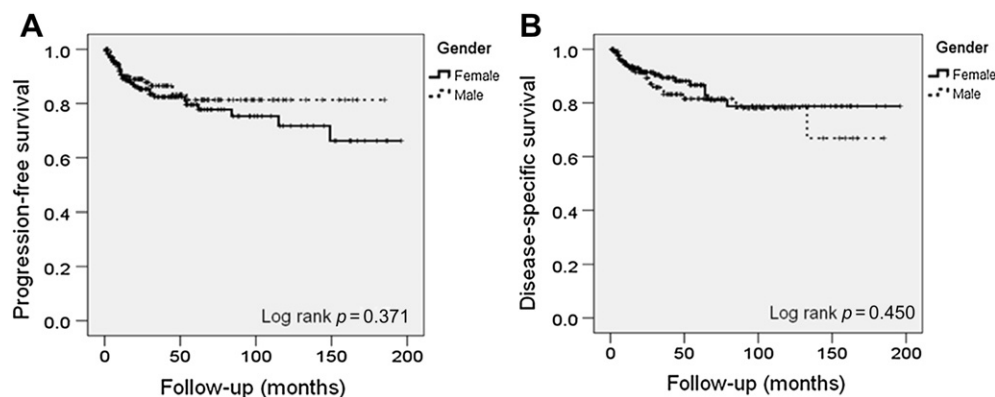


Figure 1. Kaplan–Meier survival analysis showing (A) progression-free survival and (B) disease-specific survival in patients of upper tract urothelial carcinoma treated with nephroureterectomy.

showed that female patients had poorer outcomes than males, even after adjusting for tumor stage [4]. Among patients with UTUC, Lughezzani et al. reported that women undergoing nephroureterectomy had a higher proportion of pT3 UTUC, and a higher proportion of grade III/IV UTUC, with respect to men. After accounting for other causes of mortality, cancer-specific mortality rates were higher in women than in men. However, in multivariate competing risks regression models, no statistically significant difference in survival was recorded between men and women [17–19]. Another study reported that women neither had more advanced tumor stage at nephroureterectomy nor had demonstrated worse survival than men [20]. The fact that male UTUC patients have a better prognosis than female patients with the same disease may be explained by inequalities in health care between men and women and inferior quality of care for women, for example, because of reduced inpatient length of stay and disparities in referral patterns for hematuria [21].

The impact of gender on the prognosis of UTUC is unknown. There are no evidence-based recommendations to guide health-care professionals. Moreover, in Taiwan, UTUC presents with two unusual characteristics: the first being the high incidence of urinary upper tract compared with lower tract cancers and the second is the prevalence of UTUC among women, which is higher than anywhere else in the world. In fact, the incidence of UTUC is slightly higher in Taiwanese women than in men, as we first reported in 1999 [6].

The Taiwan Cancer Registry published that, from 1995 to 2003, the incidence of UTUC ranged from 3.37 to 4.62 per 100,000 women (ICD-9 189.1 and 189.2). During those 9 years, there were 3178 female and 2970 male patients, with a female-to-male ratio of 1.07, demonstrating a slight female predominance. This study emphasizes the prognosis of UTUC within the Taiwanese population. Our study demonstrates that women had a significantly higher percentage of contralateral recurrence than men. There were no significant differences between men and women in the percentage of bladder recurrence, local recurrence, distant metastasis, disease progression, or deaths from disease-related causes. Our results thus show that the female gender is not a harmful factor with regard to survival, but is a risk factor for contralateral recurrence.

This finding of gender-related contralateral recurrence of UTUC has clinical implications. Besides cystoscopy, examination of the upper UT by renal ultrasonography and intravenous or retrograde pyelography should be performed during follow-up of female patients after an initial nephroureterectomy.

There is no uniform theory to explain the differential incidence, severity, and prognosis of UTUC between genders. Differences between genders in carcinogenic exposures, routes of entry, or enzymatic processing of environmental substances may account for the clinical discrepancies. Excessive environmental exposure to carcinogens, such as tobacco and industrial chemicals, in men has been suggested to play a role. However, a previous study showed that the gender-related differential risk of developing bladder UC persisted even after controlling these factors [12]. Little effort has been spent exploring other environmental factors or biological pathways that could underlie the heterogeneity between genders. Another possible explanation for the differential behavior of UC between genders has been postulated to be a relationship with sex steroids and their receptors [22–25]. Because UC is more common in men than in women, androgen or androgen receptors may be one of the etiological factors for the development of UC. Consequently, estrogen or antiandrogen steroids may act as protective factors. Experimental studies have demonstrated that androgens either promote or do not inhibit the growth of UC, and that estrogens have the opposite effect [26]. Female patients, therefore, may theoretically be expected to have better outcomes than males as a result of the protective effect of estrogens or antiandrogens. In patients with UTUC, establishing a link between hormone status and clinical outcomes would require additional basic mechanistic and clinical studies.

Tobacco consumption is an important risk factor for UC. However, in Taiwan, most smokers are men, and very few women smoke: among people aged 60–69 years, the rates of current smoking in men and women are 40.9% and 3.2%, respectively [27]. This suggests that although cigarette smoking has been repeatedly shown to confer a significant risk of bladder UC, smoking is not a major risk factor for women in Taiwan. Female patients may thus develop UC as a result of other etiological factors.

Another possible reason for the high female predominance in our study may be difference in exposure to carcinogen. Environmental carcinogens, other than tobacco smoke, might explain the high incidence of UTUC in Taiwan. First, people living in blackfoot disease areas of southern Taiwan have a higher risk of UC because of arsenic intoxication from water [28]. Second, many people regularly consume herbal medicines in Taiwan. Some studies have reported a high prevalence of UC in patients with Chinese herb nephropathy, which is associated with the use of carcinogenic remedies containing aristolochic acid [29,30]. Aristolochic acid-mediated UC is characterized by renal failure and UTUC, and has an unusual female predominance. Other, yet unidentified factors may contribute to the unusual presentation of female patients with UTUC in Taiwan. Further studies are needed to explore whether aristolochic acid or other compounds in herbal preparations or folk food remedies are responsible for the development of end-stage renal disease and UTUC. We believe that the etiology of UTUC in Taiwanese female patients is different from that of UC in other countries. Differences in the pathogenesis of the development may also result in a different clinical course of UTUC.

This study has several limitations. The data were collected retrospectively, and the study is therefore prone to all the biases of a retrospective report. In addition, the results are limited to experience in Taiwan, an area with an unusually high prevalence of women with UTUC. Moreover, although this study included a relatively large case series, it may not have been statistically powerful enough to detect small differences in survival and tumor recurrence in relation to some variables such as renal function and arsenic exposure. Despite these limitations, the results of this relatively large cohort study provide a better understanding of the role of gender in the prognosis of UTUC in patients treated with radical nephroureterectomy and bladder cuff excision.

In conclusion, a high incidence of UTUC has been reported in Taiwan, with an unexpected female predominance. Women had a significantly higher rate of contralateral recurrence than men. Female patients did not have worse outcomes than males after long-term follow-up.

References

- [1] Raman JD, Messer J, Sietatycki JA, Hollenbeak CS. Incidence and survival of patients with carcinoma of the ureter and renal pelvis in the USA, 1973–2005. *BJU Int* 2011;107:1059–64.
- [2] Shariat SF, Favaretto RL, Gupta A, Fritsche HM, Matsumoto K, Kassouf W, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. *World J Urol* 2011;29:481–6.
- [3] Puente D, Malats N, Cecchini L, Tardón A, García-Closas R, Serra C, et al. Gender-related differences in clinical and pathological characteristics and therapy of bladder cancer. *Eur Urol* 2003;43:53–62.
- [4] Mungan NA, Aben KK, Schoenberg MP, Visser O, Coebergh JW, Witjes JA, et al. Gender differences in stage-adjusted bladder cancer survival. *Urology* 2000;55:876–80.
- [5] Mungan NA, Kiemeny LA, van Dijck JA, van der Poel HG, Witjes JA. Gender differences in stage distribution of bladder cancer. *Urology* 2000;55:368–71.
- [6] Chou YH, Huang CH. Unusual clinical presentation of upper urothelial carcinoma in Taiwan. *Cancer* 1999;85:1342–4.
- [7] Cai G, Liu X, Wu B. Treatment of upper urinary tract urothelial carcinoma. *Surg Oncol* 2011;20:43–55.
- [8] Li CC, Chang TH, Wu WJ, Ke HL, Huang SP, Tsai PC, et al. Significant predictive factors for prognosis of primary upper urinary tract cancer after radical nephroureterectomy in Taiwanese patients. *Eur Urol* 2008;54:1127–34.
- [9] Latchamsetty KC, Porter CR. Treatment of upper tract urothelial carcinoma: a review of surgical and adjuvant therapy. *Rev Urol* 2006;8:61–70.
- [10] Kume H, Teramoto S, Tomita K, Nishimatsu H, Takahashi S, Takeuchi T, et al. Bladder recurrence of upper urinary tract cancer after laparoscopic surgery. *J Surg Oncol* 2006;93:318–22.
- [11] Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG. Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology* 1998;52:594–601.
- [12] Muntener M, Schaeffer EM, Romero FR, Nielsen ME, Allaf ME, Brito FA, et al. Incidence of local recurrence and port site metastasis after laparoscopic radical nephroureterectomy. *Urology* 2007;70:864–8.
- [13] Kang CH, Yu TJ, Hsieh HH, Yang JW, Shu K, Huang CC, et al. The development of bladder tumors and contralateral upper urinary tract tumors after primary transitional cell carcinoma of the upper urinary tract. *Cancer* 2003;98:1620–6.
- [14] Novara G, De Marco V, Gottardo F, Dalpiaz O, Bouygues V, Galfano A, et al. Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional dataset from 3 European centers. *Cancer* 2007;110:1715–22.
- [15] Lughezzani G, Sun M, Perrotte P, Shariat SF, Jeldres C, Budäus L, et al. Gender-related differences in patients with stage I to III upper tract urothelial carcinoma: results from the Surveillance, Epidemiology, and End Results database. *Urology* 2010;75:321–7.
- [16] Sakauchi F, Mori M, Washio M, Watanabe Y, Ozasa K, Hayashi K, et al. Dietary habits and risk of urothelial cancer incidence in the JACC Study. *J Epidemiol* 2005;15:S190–5.
- [17] Lughezzani G, Sun M, Perrotte P, Shariat SF, Jeldres C, Budaus L, et al. Should bladder cuff excision remain the standard of care at nephroureterectomy in patients with urothelial carcinoma of the renal pelvis? A population-based study. *Eur Urol* 2010;57:956–62.
- [18] Lughezzani G, Jeldres C, Isbarn H, Shariat SF, Sun M, Pharand D, et al. A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. *Urology* 2010;75:118–24.
- [19] Lughezzani G, Jeldres C, Isbarn H, Sun M, Shariat SF, Alasker A, et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. *Eur J Cancer* 2009;45:3291–7.
- [20] Fernández MI, Shariat SF, Margulis V, Bolenz C, Montorsi F, Suardi N, et al. Evidence-based sex-related outcomes after radical nephroureterectomy for upper tract urothelial carcinoma: results of large multicenter study. *Urology* 2009;73:142–6.
- [21] Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH. The effect of age and gender on bladder cancer: a critical review of the literature. *BJU Int* 2010;105:300–8.
- [22] Tuygun C, Kankaya D, Imamoglu A, Sertcelik A, Zengin K, Oktay M, et al. Sex-specific hormone receptors in urothelial carcinomas of the human urinary bladder: a comparative analysis of clinicopathological features and survival outcomes according to receptor expression. *Urol Oncol* 2011;29:43–51.

- [23] Liu CH, Huang JD, Huang SW, Hour TC, Huang YK, Hsueh YM, et al. Androgen receptor gene polymorphism may affect the risk of urothelial carcinoma. *J Biomed Sci* 2008;15:261–9.
- [24] Mir C, Shariat SF, van der Kwast TH, Ashfaq R, Lotan Y, Evans A, et al. Loss of androgen receptor expression is not associated with pathological stage, grade, gender or outcome in bladder cancer: a large multi-institutional study. *BJU Int* 2011;108:24–30.
- [25] Birtle AJ, Freeman A, Munson P. The androgen receptor revisited in urothelial carcinoma. *Histopathology* 2004;45:98–9.
- [26] Kihara K, Fukui I, Higashi Y, Oshima H. Inhibitory effect of testosterone on gap junctional intercellular communication of human transitional cell carcinoma cell lines. *Cancer Res* 1990;50:2848–52.
- [27] Wen CP, Levy DT, Cheng TY, Hsu CC, Tsai SP. Smoking behaviour in Taiwan, 2001. *Tob Control* 2005;14:i51–5.
- [28] Yang CY, Chiu HF, Chang CC, Ho SC, Wu TN. Bladder cancer mortality reduction after installation of a tap-water supply system in an arsenious-endemic area in southwestern Taiwan. *Environ Res* 2005;98:127–32.
- [29] Nortier JL, Martinez MC, Schmeiser HH, Arlt VM, Bieler CA, Petein M, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med* 2000;342:1686–92.
- [30] Colin P, Koenig P, Ouzzane A, Berthon N, Villers A, Biserte J, et al. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. *BJU Int* 2009;104:1436–40.