

# Racial differences in the outcome of patients with urothelial carcinoma of the upper urinary tract: an international study

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## OBJECTIVE

- To assess the impact of differences in ethnicity on clinico-pathological characteristics and outcomes of patients with upper urinary tract urothelial carcinoma (UTUC) in a large multi-center series of patients treated with radical nephroureterectomy (RNU).

## MATERIALS AND METHODS

- We retrospectively collected the data of 2163 patients treated with RNU at 20 academic centres in America, Asia, and Europe.
- Univariable and multivariable Cox regression models addressed recurrence-free

## What's known on the subject? and What does the study add?

The differential effect of ethnicity on clinico-pathological features and cancer-related outcomes remains uninvestigated in upper tract urothelial carcinoma.

Ethnicity was not an independent predictor of either recurrence or cancer-related death in upper tract urothelial carcinoma.

survival (RFS) and cancer-specific survival (CSS).

## RESULTS

- In all, 1794 (83%) patients were Caucasian and 369 (17%) were Japanese. All the main clinical and pathological features were significantly different between the two ethnicities.
- The median follow-up of the whole cohort was 36 months. At last follow-up, 554

patients (26%) developed disease recurrence and 461 (21%) were dead from UTUC.

- The 5-year RFS and CSS estimates were 71.5% and 74.2%, respectively, for Caucasian patients compared with 68.8% and 75.4%, respectively, for Japanese patients.
- On univariable Cox regression analyses, ethnicity was not significantly associated with either RFS ( $P = 0.231$ ) or CSS ( $P = 0.752$ ).

- On multivariable Cox regression analyses that adjusted for the effects of age, gender, surgical type, T stage, grade, tumour architecture, presence of concomitant carcinoma *in situ*, lymphovascular invasion, tumour necrosis, and lymph node status, ethnicity was not associated with either RFS (hazard ratio [HR] 1.1;  $P=0.447$ ) or CSS (HR 1.0;  $P=0.908$ ).

## CONCLUSIONS

- There were major differences in the clinico-pathological characteristics of Caucasian and Japanese patients.
- However, RFS and CSS probabilities were not affected by ethnicity and race was not an independent predictor of

either recurrence or cancer-related death.

## KEYWORDS

race, prognosis, urinary tract cancer, urothelial carcinoma, nephroureterectomy, recurrence

## INTRODUCTION

The incidence of cancer and its biological behaviour varies considerably among ethnicities and between geographic areas [1–3]. For example, epidemiological studies originating from the USA show that tumour stage and mortality rates for many cancers including those arising from breast, colon and rectum, kidney, prostate, and lung are highest in African-Americans followed by Whites and are lowest in Asians/Pacific Islanders [4–6]. Similarly, for bladder urothelial carcinoma (UC), African-Americans have worse overall survival when compared with Caucasian patients [7–10]. Although much of this difference has been attributed to higher stage at presentation in African-Americans [8,9], outcome disparities still persist after controlling for tumour stage, grade, treatment effect, and other cause mortality [10]. Potential differences contributing to these disparities among ethnicities and geographic locations include delays in presentation/diagnosis, inherent biological behaviour of the tumour, socioeconomic status, lack of adequate health care access, differences in exposure to environmental risk factors such as smoking, and social support. For upper urinary tract UC (UTUC), to our knowledge, the differential effect of ethnicity on clinico-pathological features and cancer-related outcomes remains uninvestigated.

Therefore, the purpose of the present study was to assess the effect of differences in ethnicity on clinico-pathological characteristics and outcomes of patients with UTUC in a large multi-center series of patients treated with radical nephroureterectomy (RNU) in three continents (America, Asia, and Europe), encompassing nine countries (USA, Canada, Japan, Austria, France, England, Germany, Italy, and Spain).

## PATIENTS AND METHODS

This was an Institutional Review Board-approved study with all participating sites providing the necessary institutional data sharing agreements before initiation of the study. In all, 20 academic centres worldwide provided data. A computerized databank was generated for data transfer. After combining the datasets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen, and the final data set was produced for the present analysis.

The database comprised 2217 patients who underwent RNU with ipsilateral bladder cuff resection between 1987 and 2008. After exclusion of patients in whom ethnicity was unknown (six patients), and of the few patients that were African-American (27) or Hispanic (21), the 2163 patients left were the subjects of the present analysis.

Surgery was performed by several surgeons according to the standard criteria for RNU, i.e. extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. The hilar and regional LNs adjacent to the ipsilateral great vessel generally were resected together with enlarged LNs if abnormal on preoperative CT or palpable intraoperatively. Extended lymphadenectomy was not routinely performed.

All surgical specimens were processed according to standard pathological procedures at each institution. Tumours were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification. [11]. Tumour grading was assessed according to the 1998 WHO/International Society of

Urologic Pathology consensus classification [12].

Patients were generally followed-up every 3–4 months for the first year after RNU, every 6 months from the second through to the fifth year, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scan, chest CT, and MRI were performed when clinically indicated.

Disease recurrence was defined as local failure in the operative site, regional LNs, or distant metastasis. Bladder recurrences were not considered in the analysis of the recurrence-free survival (RFS) rate. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died from UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (i.e. death within 30 days of surgery) were censored at time of death for cancer-specific survival (CSS) analyses.

The Fisher's exact test and the chi-square test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann–Whitney *U*-test. The Kaplan–Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as  $P \leq 0.05$ . All reported *P* values are two-sided.

RESULTS

ASSOCIATION OF ETHNICITY WITH CLINICAL AND PATHOLOGICAL FEATURES

In all, 1794 (83%) patients were Caucasian and 369 (17%) were Japanese. Table 1 shows the association of clinical and pathological features with ethnicity. Patients' age, gender, tumour stage, tumour grade, prevalence of lymphovascular invasion, tumour architecture, prevalence of tumour necrosis, presence of concomitant carcinoma *in situ* (CIS), and use of adjuvant chemotherapy were significantly different between the two ethnicities (all  $P < 0.05$ ). Moreover, also follow-up duration from RNU was slightly longer in Japanese patients ( $P = 0.039$ ).

ASSOCIATION OF RACE WITH CLINICAL OUTCOMES

The median (interquartile range, IQR) follow-up of the whole cohort was 36 (15.3–71.1) months. At last follow-up, 554 patients (26%) had developed disease recurrence and 461 (21%) were dead from UTUC. Moreover, 301 patients (14%) had noncancer-related deaths. The median (IQR) follow-up for patients alive at last follow-up was 45 (20–81) months. The overall 5- and 10-year RFS estimates were 71% (standard error, SE 1.1%) and 67% (SE 1.3%) respectively. The overall 5- and 10-year CSS estimates were 74.4% (SE 1.1%) and 69.1% (SE 1.4%), respectively.

The 5-year RFS and CSS rates were 71.5% (SE 1.2%) and 74.2% (SE 1.2%), respectively, for Caucasian patients compared with 68.8% (SE 2.7%) and 75.4% (SE 2.6%), respectively, for Japanese patients (Fig. 1A,B, respectively;  $P$  value 0.23 for RFS and 0.75 for CSS).

Tables 2 and 3 summarize univariable and multivariable analyses for prediction of RFS and CSS, respectively. On univariable Cox regression analyses, ethnicity was not significantly associated with either RFS ( $P = 0.231$ ) or CSS ( $P = 0.752$ ). On multivariable Cox regression analyses that adjusted for the effects of age, gender, surgical type, T stage, grade, tumour architecture, presence of concomitant CIS, lymphovascular invasion, tumour necrosis, and lymph node (LN) status, ethnicity was not associated with either RFS (hazard ratio [HR] 1.1;  $P = 0.447$ ) or CSS (HR 1.0;  $P = 0.908$ ).

TABLE 1 Association of race with clinical and pathological characteristics of 2163 patients treated with RNU and bladder-cuff excision for UTUC

Variable	Cases	Race		P
		Caucasian	Japanese	
Number of patients (%)	2163 (100)	1794 (83)	369 (17)	
Median (IQR) age, years	69 (61–76)	69.9 (62–76)	66.3 (58.3–74)	<0.001
Gender, n (%)				<0.001
– Male	1478 (68)	1186 (66)	292 (79)	
– Female	685 (32)	608 (34)	77 (21)	
Type of RNU, n (%)				0.821
– Open	1790 (83)	1486 (83)	304 (82)	
– Laparoscopic	373 (17)	308 (17)	65 (18)	
LN dissection, n (%)				0.162
– Performed	604 (28)	490 (27)	114 (31)	
– Not performed	1559 (72)	1304 (73)	255 (69)	
Pathological stage, n (%)				0.003
– pT0	10 (0.5)	10 (0.5)	0	
– pTa	450 (21)	382 (21)	68 (18)	
– pTis	36 (2)	26 (1.5)	10 (3)	
– pT1	488 (23)	426 (24)	62 (17)	
– pT2	401 (18.5)	330 (18)	71 (19)	
– pT3	667 (31)	535 (30)	132 (36)	
– pT4	111 (5)	85 (5)	26 (7)	
Grade, n (%)				<0.001
– Low	655 (30)	587 (33)	68 (18)	
– High	1508 (70)	1207 (67)	301 (82)	
Lymphovascular invasion, n (%)				0.001
– Absent	1682 (78)	1372 (77)	310 (84)	
– Present	481 (22)	422 (23)	59 (16)	
Tumour architecture, n (%)				<0.001
– Papillary	1660 (77)	1351 (75)	309 (84)	
– Sessile	503 (23)	443 (25)	60 (16)	
Tumour necrosis, n (%)				<0.001
– Absent	1667 (77)	1354 (76)	313 (85)	
– Present	496 (23)	440 (24)	56 (16)	
Concomitant CIS, n (%)				0.014
– Absent	1671 (77)	1368 (76)	303 (82)	
– Present	492 (23)	426 (24)	66 (18)	
Median (IQR) no. removed LNs	4 (2–8)	4 (2–8)	3 (2–7)	0.147
LN stage, n (%)				0.247
– N0	419 (19)	336 (19)	83 (23)	
– Nx	1559 (72)	1304 (73)	255 (69)	
– N+	185 (9)	154 (8)	31 (8)	
Adjuvant chemotherapy*, n (%)				<0.001
– no	1928 (89)	1629 (91)	299 (81)	
– yes	224 (10)	154 (9)	70 (19)	
Median (IQR) follow-up, months	36 (15.3–71.1)	35.1 (15.5–69)	38 (15–84)	0.039

Re-analysis of the data after exclusion of 224 patients who received adjuvant chemotherapy yielded consistent statistical patterns of H.R. and  $P$  values for ethnicity (HR 1.1;  $P = 0.685$  for RFS; H.R. 0.9;  $P = 0.730$  for CSS). Further subgroup analyses in patients with pathologically localized, locally-advanced, N0/Nx, or N positive disease yielded

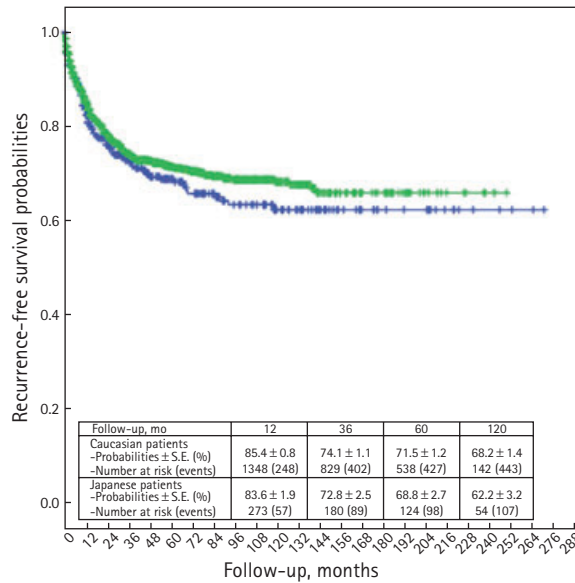
consistent statistical patterns (data not shown).

DISCUSSION

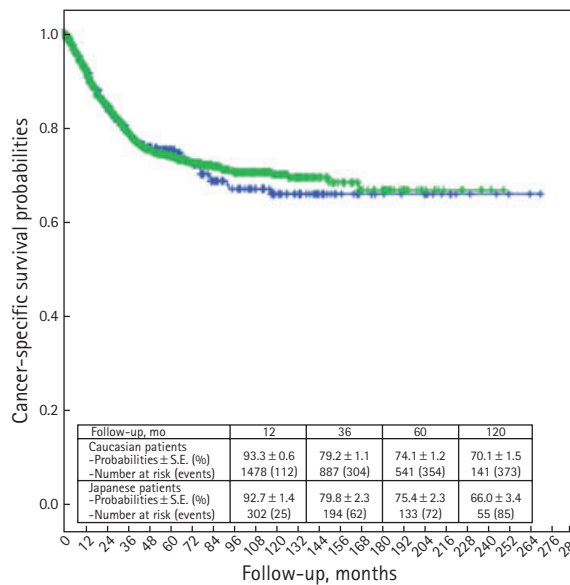
In the present multi-institutional study involving about 2200 patients with UTUC

FIG. 1. A

Kaplan–Meier curves of RFS and CSS stratified by patients' race in 2163 patients treated with RNU and ipsilateral bladder-cuff excision for UTUC. Green, Caucasian patients; blue, Japanese patients. Log-rank P values 0.23 for RFS and 0.75 for CSS.



B



undergoing RNU there were major differences in the clinico-pathological characteristics of Caucasian and Japanese patients. However, RFS and CSS probabilities were not affected by ethnicity and race was not an independent predictor of either recurrence or cancer-related death, once adjusted for the effects of other clinical and pathological covariates.

It is well established by epidemiological studies that rates of cancers incidence and deaths vary considerably among racial groups. Data from the National Center for

Health Statistics concerning statistics collected from 1930 to 2006 in the USA showed that African-Americans had incidence and death rates that were consistently higher than in Whites for all cancer sites, excluding breast, lung and kidney cancers [4,5]. Specifically, all site incidence and mortality rates were 651.5 and 313 per 100 000 in male African-Americans and 389 and 186.7 per 100 000 in female African-Americans, respectively, compared with 551.4 and 230.7 per 100 000 in male White and with 423.6 and 159.2 per 100 000 in female White,

respectively. Significantly lower figures, indeed, were shown for Asian-American and Hispanic, compared with both African-American and White [4].

However, specific epidemiological data for UTUC are missing, due to the low prevalence of the disease and, above all, to the lack of a specific code able to distinguish RCC and renal pelvis UTUC in the International Classification of Diseases. However, figures for bladder UC reconfirmed a similar trend, with significantly higher incidence and mortality rates in White patients (22.8 and 4.5 per 100 000, respectively), compared with African-American (12.8 and 3.7 per 100 000, respectively), Asian-American (9.3 and 1.7 per 100 000, respectively), and Hispanic patients (11.4 and 2.4 per 100 000, respectively) [6]. In the present analysis, there was a high prevalence of non-organ confined (43%) and high-grade (82%) disease in Asiatic patients, which is in agreement with previous report from Taiwan [13,14], where pT3–4 disease might be as frequent as 50%. Several hypotheses can be made to explain the differences in the clinical and pathological characteristics of UTUC at presentation. For example, environmental and occupational exposures, lifestyle choices such as smoking and nutrition, and socioeconomic and cultural factors involving access to and the willingness to seek care may account for such differences [15]. However, despite the large number of patients, we were unable to find any statistically significant differences in RFS and CSS probabilities, between these two racial groups. Moreover, the few African-American and Hispanic patients in our dataset prevented us from including them in the analysis.

For the other predictors of RFS and CSS, in our multivariable models we showed that patients' age at surgery, pathological stage of the primary tumour, tumour grade, presence of lymphovascular invasion, tumour architecture, and LN stage were independent predictors of both recurrence and survival, while type of surgery was significantly associated only with cancer-related death. The data of the present study reproduced and validated those previously available on pT stage and grade [16,17], lymphovascular invasion [18,19], architecture [20], and LN stage [21]. Notably, patients undergoing laparoscopic RNU had worse CSS once adjusted for the effects of the other covariates. The data echoes the findings of

Simone *et al.* [22], who showed that laparoscopic surgery may jeopardize the outcome of patients with locally advanced disease. However, similar data were not reproduced in large multi-institutional comparative studies [23,24].

There are several limitations to the present study. First and foremost are the limitations inherent to retrospective analyses. Although we have done multiple internal and external reviews of our consortium dataset, we excluded from this analysis patients for whom we could not obtain complete information, which could possibly create selection bias. In addition, the population in this study underwent RNU by multiple surgeons, indication and extension of LN dissection were not standardized, and the follow-up lacked uniformity. However, all surgeons operated at selected centres with significant experience in UC management, which might increase the external validity of the data, compared with the single-centre, single-surgeon setting. Similarly, whereas it may be preferable for a single pathologist specialized in genitourinary pathology to review each specimen, the multi-centric nature of the present study and the use of institutional pathological interpretation possibly make the results more relevant in the daily clinical setting. Nevertheless, all specimens were examined by dedicated genitourinary pathologists at selected centres. Another limitation is that there were few Hispanic and African-American patients, which prevented us from drawing conclusions on these racial groups. In addition we did not control for important factors such as patient comorbidity, socioeconomic status, marital status and other measures of social support, body mass index, and smoking status, which have been shown to be of interest in some reports [25–27].

In conclusion, there were major differences in the clinico-pathological characteristics of Caucasian and Japanese patients. However, RFS and CSS probabilities were not affected by ethnicity and race was not an independent predictor of either recurrence or cancer-related death, once adjusted for the effects of other clinical and pathological covariates. In terms of racial differences of biological behaviour, future research is warranted to take into account the components, including environmental and occupational exposures, lifestyle choices, socioeconomic, cultural and genetic factors.

TABLE 2 Univariable and multivariable Cox regression analyses of race for prediction of disease recurrence in 2163 patients treated with RNU and ipsilateral bladder-cuff excision for UTUC (554 recurrences)

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.01 (1–1.02)	0.001	1.01 (1.01–1.02)	0.017
Race	1.1 (0.9–1.4)	0.231	1.1 (0.9–1.4)	0.447
Gender	1.1 (0.9–1.4)	0.139	1.1 (0.9–1.3)	0.558
Type of RNU (open vs lap.)	0.8 (0.6–1.0)	0.048	0.9 (0.7–1.2)	0.437
Pathological stage:		<0.001		<0.001
– pTa/Tis	1, Reference	–	1, Reference	–
– pT1	1.6 (1.01–2.5)	0.043	1.3 (0.8–2.0)	0.309
– pT2	4.2 (2.9–6.3)	<0.001	3.0 (1.9–4.4)	<0.001
– pT3	9.2 (6.4–13.2)	<0.001	5.1 (3.4–7.7)	<0.001
– pT4	37.6 (24.9–56.7)	<0.001	14.7 (9.2–23.5)	<0.001
Grade	4.1 (3.2–5.3)	<0.001	1.8 (1.4–2.4)	<0.001
Lymphovascular invasion	3.6 (3.0–4.2)	<0.001	1.4 (1.2–1.8)	<0.001
Tumour architecture	3.8 (3.2–4.5)	<0.001	1.4 (1.1–1.7)	0.003
Tumour necrosis	2.2 (1.9–2.6)	<0.001	0.9 (0.7–1.1)	0.205
Concomitant CIS	1.6 (1.4–2.0)	<0.001	1.1 (0.9–1.4)	0.178
LN stage:		<0.001		<0.001
– N0	1, Reference	–	1, Reference	–
– Nx	0.9 (0.8–1.2)	0.954	1.3 (0.9–1.6)	0.054
– N+	4.6 (3.5–6.0)	<0.001	2.1 (1.6–2.8)	<0.001

Lap., laparoscopic.

TABLE 3 Univariable and multivariable Cox regression analyses of patients' race for prediction of cancer-specific mortality in 2163 patients treated with RNU and ipsilateral bladder-cuff excision for UTUC (461 cancer-specific deaths)

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Race	1.1 (0.8–1.3)	0.752	1.01 (0.8–1.3)	0.908
Gender	1.1 (0.9–1.3)	0.542	0.9 (0.7–1.1)	0.407
Type of RNU (open vs lap.)	0.6 (0.4–0.9)	0.004	0.6 (0.5–0.9)	0.012
Pathological stage:		<0.001		<0.001
– pTa/Tis	1, Reference	–	1, Reference	–
– pT1	1.5 (0.9–2.4)	0.145	1.2 (0.7–1.9)	0.570
– pT2	4.5 (2.9–7.1)	<0.001	3.2 (2.0–5.1)	<0.001
– pT3	10.1 (6.7–15.2)	<0.001	5.9 (3.8–9.2)	<0.001
– pT4	43.3 (27.4–68.4)	<0.001	17.4 (10.3–29.4)	<0.001
Grade	4.0 (3.0–5.2)	<0.001	1.8 (1.3–2.4)	<0.001
Lymphovascular invasion	3.9 (3.3–4.7)	<0.001	1.6 (1.3–2.0)	0.001
Tumour architecture	4.0 (3.3–4.8)	<0.001	1.3 (1.02–1.6)	0.029
Tumour necrosis	2.4 (1.9–2.9)	<0.001	0.9 (0.7–1.1)	0.380
Concomitant CIS	1.5 (1.2–1.8)	<0.001	1.0 (0.8–1.3)	0.766
LN stage:		<0.001		<0.001
– N0	1, Reference	–	1, Reference	–
– Nx	1.1 (0.8–1.4)	0.680	1.4 (1.1–1.9)	0.008
– N+	4.9 (3.6–6.6)	<0.001	2.1 (1.5–2.9)	<0.001

Lap, laparoscopic.



## CONFLICT OF INTEREST

None declared.

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**Abbreviations:** (UT)UC, (upper urinary tract) urothelial carcinoma; RNU, radical nephroureterectomy; RFS, recurrence-free survival; CSS, cancer-specific survival; CIS, carcinoma *in situ*; IQR, interquartile range; SE, standard error; LN, lymph node; HR, hazard ratio.