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Original article

Ethnic variation of the histological subtypes of renal cell carcinoma in Singapore

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Abstract

Introduction: The purpose of this study is to determine how the histological subtypes of renal cell carcinoma (RCC) vary among the heterogeneous Singaporean population and how this affects the survival rate.

Patients and methods: The data analyzed in this retrospective study of the histological subtypes of RCC cases treated in Singapore General Hospital over a ten year period (2001–2010) were obtained from the Cancer Registry of the hospital's department of urology. Statistical analysis was done using the Statistical Package Service Solution (SPSS) version 17.0 software. Chi Square and *z*-tests were used where appropriate; a p value <0.05 was considered significant.

Results: The records of 676 patients studied showed that 80.8% of the patients were Chinese, while Malays, Indians and other minor groups accounted for 6.5%, 4.6% and 8.1%, respectively. The mean age (SD) at presentation was 58.1 (12.1), 57.6 (10) and 55.1 (9.6) years for the Chinese, Indians and Malays, respectively. The commonest histological variant in each of the ethnic groups, irrespective of sex, was clear cell carcinoma which accounted for 79.7% of all the histological subtypes found in Chinese, for 70.5% in Malaysian and 77.4% in Indian patients. The sarcomatoid histological subtype was found in 4.3% of the studied population with a high prevalence in the Indian ethnicity (9.7%). The worst survival rate (33.3%) was recorded among Malays with the papillary cell subtype, and also in the Chinese population the highest mortality rate was found in cases with the papillary cell subtype (16.9%).

Conclusion: The commonest histological subtype of RCC in each of the studied ethnic groups in Singapore is clear cell carcinoma. However, most of the cancer deaths in Chinese (16.9%) and Malays (66.7%)

Abbreviations: RCC, renal cell carcinoma; Std, starndard.

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were associated with the papillary cell type, while in Indians the sarcomatoid component prevailed (9.7%). Thus, the usual prognostic trend for RCC subtypes cannot be applied to all Singaporean ethnicities, necessitating individualization of prognosis for each group.

Introduction

The incidence of renal cell carcinoma (RCC) varies across various geo-ethnic groups worldwide. RCC is the 13th most common malignancy worldwide, with approximately 271,000 new cases diagnosed in 2008 [1]. The highest incidence is found in Europe, North America, and Australia, whereas it is low in India, Japan, Africa, and China. In the United States, RCC accounts for 2–3% of all adult malignant neoplasms [1,2] and is the most lethal of all urologic cancers [2]. Incidence rates are 10–20% higher in African Americans for unknown reasons [2].

The Czech Republic has the highest age-standardised rate for RCC in Europe. This has been estimated to be 33.6 and 15.0 per 100,000/year for males and females, respectively [3]. Other European countries that have been documented to have high incidence rates include Lithuania, Latvia, Estonia, and Iceland, while the incidence is lowest in Romania, Cyprus, and Portugal [3]. The age-standardised rates for Singaporean males and females are 5.4 and 2.9 per 100,000/year [4], respectively. RCC typically occurs in the fifth to seventh decade of life and is more common in the Chinese population compared to Indians and Malays [4].

The histological variants of RCC differ in prognostic significance with the sarcomatoid variant signifying an especially poor prognosis [5,6] when present in any of the histological subtypes. These histological subtypes have also been shown to vary across different ethnic groups. Young African Americans with sickle cell traits have been found to rather have the medullary type of RCC [7,8]. Papillary RCC has also been shown to be commoner among the black compared to the white population in the United States [9]. In Malaysia, a neighboring country to Singapore, a ten-year review of the clinical characteristics of RCC revealed that the clear cell histological subtype was the commonest (75.1%) among the ethnic groups studied [10]. The sarcomatoid variant was also found to be commoner (2.7%) when compared with earlier studies in the region.

The aim of this study is to assess how the histological subtypes of RCC vary in each of the ethnic groups in Singapore, as these subtypes have been shown to contribute to the outcome of the disease.

Patients and methods

This is a retrospective study of the histological subtypes of RCC cases treated in Singapore General Hospital (SGH) over a ten-year period (2001–2010). The data and permission for the study were obtained from the Singhealth Centralized Institutional Review Board (CIRB, Ref: 2009/1053/D). The content of the data obtained included the ethnicity categorized as Chinese, Malays, Indians and others (Indonesians, Vietnamese and other minor groups). Other data collected included age, gender and the histological subtype categorized as clear cell, papillary, chromophobe, collecting duct and unclassified subtypes. The mean follow-up period and survival outcome were also recorded. Tumor staging was based on the widely accepted 2002 TNM classification. The data were analyzed using the Statistical Package Service Solution (SPSS) software version 17.0. Chi Square and *z*-tests were used where appropriate; a p value <0.05 was considered significant.

Results

The total number of patients diagnosed with RCC between 2001 and 2010 was 752. Out of these, 76 patients did not have any or had no complete histopathological report and were excluded from the study, thus leaving a total number of 676 patients. The Chinese accounted for 80.8% and the Malays for 6.5%, while the percentage of the Indians and other minor groups studied was 4.6% and 8.1%, respectively. The mean age (SD) at presentation was 58.1 (12.1), 57.6 (10) and 55.1 (9.6) years for the Chinese, Indians and Malays, respectively. The male to female ratio was 2:1 in the general population.

The results of the study also revealed that the commonest histological variant in each of the ethnic groups, irrespective of sex, was clear cell carcinoma. It accounted for 79.7% of all the histological subtypes found among the Chinese, for 70.5% in the Malays, for 77.4% in the Indians and for 70.9% in the other ethnicities studied (Table 1). This was followed by papillary carcinoma (11.9%) in the Chinese population and papillary carcinoma in conjunction with unclassified subtypes in the Indians (9.8% each). For the Malays and the other ethnic minorities in Singapore the unclassified histological subtype represented the second most common category (Table 1).

The sarcomatoid histological subtype was found in 29 patients (4.3%) with RCC, with the highest prevalence found in the Chinese ($n=20$; 68.9%). The majority of the sarcomatoid variants ($n=16$; 55.1%) was associated with the clear cell subtype (Table 2). All the studied ethnic groups mainly presented with stage-I disease which accounted for 77.4%, 63.6% and 59.2% of all cases in the Indians, Malays and Chinese, respectively. The second most predominant stage was stage II (18.5%) in the Chinese, stage III (18.2%) in the Malays and stage IV (12.9%) in the Indians. The mean follow-up period was 3 years, with a maximum duration of 10.3 and a median duration of 2.3 years. The overall mortality rate was highest (24%) in the Malays, while the mortality rates in the Indians and the Chinese accounted for 19.4% and 19.5%, respectively. Most of the deaths (68%) recorded among those with complete records (18.5%) were attributed to RCC. The cancer-specific death rate was 70% for the Malays, 64.1% for the Chinese and 33.3% for the Indians.

When cancer specific deaths within the ethnic groups were distributed according to the disease stage, more Chinese (45.4%) and

Table 1 Distribution of histological subtypes according to ethnicity.

Subtype	Chinese	Malays	Indians	Others
Clear cell	435 (79.7%)	31 (70.5%)	24 (77.4%)	39 (70.9%)
Papillary	65 (11.9%)	5 (11.4%)	3 (9.8%)	6 (10.9%)
Chromophobe	17 (3.1%)	1 (2.3%)	1 (3.2%)	2 (3.6%)
Collecting duct	1 (0.2%)	0	0	0
Unclassified	28 (5.1%)	7 (15.8%)	3 (9.8%)	8 (14.5%)
Total	546 (100%)	44 (100%)	31 (100%)	55 (100%)

Table 2 Cross tabulation of the histological subtypes with ethnicity and sarcomatoid component.

Histological subtype	Sarcomatoid component				
	Chinese	Malays	Indians	Others	Total
Clear cell	11	2	0	3	16
Papillary	1	0	0	0	1
Chromophobe	0	0	1	0	1
Collecting duct	0	0	0	0	0
Unclassified	8	0	2	1	11
Total	20	2	3	4	29

Indians (50%) were found to have died from stage IV disease, while most Malays (57.1%) died from stage III disease. Cross-tabulation of the histological subtype with cancer-specific death (Table 3) revealed that the highest cancer-specific death among the Chinese as well as the Malays was associated with the papillary subtype ($N=11$; 16.9% and $N=4$; 66.7%, respectively). The histological subtype associated with the highest percentage of cancer deaths among the Indians is the chromophobe subtype ($N=1$; 100%). The worst survival rate for renal cell carcinoma recorded in the Indians (0%) and Malays (33.3%) was due to the chromophobe and papillary cell subtypes, respectively. The worst survival rate in the Chinese was also found with the papillary subtype (83.1%) (Table 4).

Discussion

The prognosis of RCC has improved over the past few decades, partly due to a shift in the stage of presentation to the left as a result of radiologic screening and improvement in treatment modalities. Histological variants of RCC in conjunction with grade and stage are very crucial in the determination of the management and outcome of this disease [5,6]. Studies on the role of race in the distribution of the histological variants of RCC are scarce. The results of this study revealed that the mean age (years) at presentation for the Chinese (58.2) and Indians (57.6) was a little higher than that for the Malays (55.1 years). This is contrary to an earlier report on a similar population which showed that the Malays had a more advanced age at presentation compared to the Indians and Chinese [10]. This trend may be due to a disparity in the population size of each of the ethnic groups included in the studies in question; while the Malays constituted a high proportion of the population in the former study, the Chinese constituted the largest percentage in the current study.

The interpretation of survival data depending on the different RCC subtypes is controversial, but many studies suggest that chromophobe RCC has a significantly better prognosis than clear cell and papillary RCC, which have an intermediate prognosis [6,11]. Collecting duct carcinoma, reported in less than 1% of RCC, generally is

Table 3 Cross-tabulation of ethnicity with histological subtype and cancer specific death.

Ethnicity	Clear cell	Papillary	Chromophobe	Collecting duct	Unclassified
Chinese	53 (12.1%)	11 (16.9%)	1 (6.3%)	0	9 (9.8%)
Malays	2 (6.7%)	4 (66.7%)	0	0	4 (44.4%)
Indians	0	0	1 (100%)	0	1 (20%)
Others	1 (2.6%)	0	0	0	0

Table 4 Cross-tabulation of ethnicity with histological subtype and survival rate.

Ethnicity	Survival rate (%)				
	Clear cell	Papillary cell	Chromophobe	Collecting duct	Unclassified
Chinese	87.9	83.1	93.7	100	90.2
Indian	100.0	100.0	0.0	–	80.0
Malay	93.3	33.3	100.0	–	55.6
Others	97.4	100.0	100.0	–	100.0

an aggressive RCC type that tends to progress early with metastatic disease and is associated with a short survival time [12].

The results of our study show that the clear cell variant accounted for 78.3% of all the cases of RCC in the general population. This is in keeping with the 70–80% prevalence documented in an earlier study among the Western population by Störkel et al. [5] and also by Singam et al. (75.1%) in his ten-year review of the clinical characteristics of RCC among the Malaysian population [10].

The second and third predominant variants of RCC documented in the literature are the papillary (10–15%) and the chromophobe variants (1–5%) [7]. This trend was seen among the Chinese and the Indians. However, the unclassified subtypes were the second commonest in the Malays which is not in keeping with the said trend.

Sarcomatoid RCC, when present, is an uncommon but particularly aggressive component of RCC, accounting for 1– 5% of all renal malignant neoplasms [14–16]. It can occur in any of the histological subtypes of RCC [7] and its presence represents an ominous prognostic factor [17]. In this study, sarcomatoid histology was predominantly found in patients with clear cell carcinoma in all ethnic groups, which is in keeping with findings of other studies [13].

The sarcomatoid variant was found in 4.3% of the general population studied, which is higher than the value (2.7%) documented in a study by Singam et al. [10] involving a similar group. This may imply that the general Singaporean population with RCC is likely to have a worse outcome than their Malaysian counterparts, since the proportion of those with the sarcomatoid component amongst them is higher. Indians were found to have the highest percentage (9.7%) of the sarcomatoid variant when individual ethnicity was considered; this may be the reason why they presented with a more advanced stage of RCC (stage IV). However, the low number of Indians involved in this study precludes any significant association between them and this finding.

Cancer-specific deaths were found to be higher in Malays compared to Indians and Chinese, with more deaths occurring among Malays and Chinese with the papillary subtype and Indians with the chromophobe subtype. This finding related to the Malays and Chinese is contrary to that of a study in Americans where more deaths were recorded among patients with the clear cell and chromophobe subtype than with the papillary subtype [5]. The Chinese and the Malays are likely to survive less when the papillary variant is present, while the Indians survived less with the chromophobe variant (Table 4). These findings suggest that the expected trend is not applicable to all the ethnicities found in Singapore with regard to the prognosis based on subtypes. For example, the subtype usually considered favorable (chromophobe) was associated with an unfavorable outcome (higher mortality) in the Indian population. Also, Malays and Chinese with the papillary subtype are likely to have a bad outcome from RCC, hence necessitating closer surveillance and more rigorous intervention for this category of patients.

In conclusion, the commonest histological subtype of RCC in each of the studied ethnic groups in Singapore is the clear cell histological subtype. Taking into consideration the histological subtype, most cancer deaths in Chinese (16.9%) and Malays (66.7%) were associated with the papillary subtype, while the Indians had the highest sarcomatoid component (9.7%). Thus, the usual prognostic trend using RCC subtypes is not the same among all Singaporean ethnicities, thereby suggesting an individual prognosis for each group.

Competing interests

None.

Author's contributions

Ezenwa E.V. – interpreted the data and wrote the article. Tan Yeh Hong – performed some of the surgeries and supervised every stage of the write up.

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References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer 2010;15:2893–917.
[2] Chow WH, Devesa SS, Warren JL, Fraumeni Jr JF. Rising incidence of renal cell cancer in the United States. Journal of the American Medical Association 1999;281:1628–31.
[3] Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. European Journal of Cancer 2008;44:1345–89.
[4] Seow A, Koh WP, Chia KS, Shi LM, Lee HP, Shanmugaratnam K. Trends in cancer incidence in Singapore 1968–2002. Singapore Cancer Registry Report 2004;6:134–5.
[5] Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisms of outcome and prognostic features among histologic subtypes of renal cell carcinoma. American Journal of Surgical Pathology 2003;27(5):612–24.
[6] Amin MB, Tamboli P, Javidan J, Stricker H, de-Peralta Venturina M, Deshpande A, et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasm; an experience of 405 cases. American Journal of Surgical Pathology 2002;26(3):281–91.
[7] Störkel S, Ebie JN, Adlakha K, Amin M, Blute ML, Bostwick DG, et al. Classification of renal cell carcinoma: Workgroup no 1 Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997;80:987–9.
[8] Swartz MA, Karth J, Schneider DT, Rodriguez R, Beckwith JB, Perlman EJ. Renal medullary carcinoma: clinical, pathologic, immunohistochemical, and genetic analysis with pathogenetic implications. Urology 2002;60:1083–9.
[9] Sankin A, Cohen J, Wang H, Macchia RJ, Karanikolas N. Rate of renal cell carcinoma subtypes in different races international. British Journal of Urology 2001;37(1):29–34.
[10] Singam P, Ho C, Hong GE, Mohd A, Tamil AM, Cheok LB, et al. Clinical characteristics of renal cancer in Malaysia: a ten year review. Asian Pacific Journal of Cancer Prevention 2010;11:503–6.
[11] Beck SD, Patel MI, Snyder ME, Kattan MW, Motzer RJ, Reuter VE, et al. Effect of papillary and chromophobe cell on disease-free survival after nephrectomy for renal cell carcinoma. Annals of Surgical Oncology 2004;11:71–7.
[12] Srigley JR, Eble JN. Collecting duct carcinoma of kidney. Seminars in Diagnostic Pathology 1998;15:54–67.
[13] Gudbjartsson T, Hardarson S, Petursdottir V, Thoroddsen A, Magnusson J, Einarsson GV. Histological subtyping and nuclear grading of renal cell carcinoma and the implications for survival:

a retrospective nation-wide study of 629 patients. European Urology 2005;48(4):541–702.

[14] Cangiano T, Livo J, Naitoh J, Dorey F, Figlin R, Belldegrun A. Sarcomatoid renal cell carcinoma: biologic behavior, prognosis and response to combined surgical resection and immunotherapy. Journal of Clinical Oncology 1999;17:523–8.

[15] Delahunt B. Sarcomatoid renal cell carcinoma the final common dedifferentiation pathway of renal epithelial malignancies. Pathology 1999;31:185–90.

[16] Theil K, Schinelle R, Golimbi M, Waisman J. Prediction of survival in renal tubular adenocarcinoma. Laboratory Investigation 1985;52:67–70.

[17] Dall'Oglio MF, Antunes AA, Pompeo AC, Mosconi A, Leite KR, Srougi M. Prognostic relevance of the histological subtype of renal cell carcinoma. International Brazilian Journal of Urology 2008;34(1):3–8.