RESEARCH ARTICLE

High Occurrence of Non-Clear Cell Renal Cell Carcinoma in Oman

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Abstract

It is conventionally accepted that renal cell carcinoma (RCC) occurs in older patients and the clear cell type is the most common histology. However, ethnic variations exist and this study was carried out to determine the epidemiological pattern of RCC in Oman. Ninety RCC patients who presented to a tertiary care center in the Sultanate of Oman from 2010 to 2014 were studied. The main findings were that the median age of presentation was low, more patients presented with localized stage, and there was a higher incidence of non-clear (especially papillary) histology. Data from other Gulf countries and possible reasons for the different profile are discussed.

Keywords: Renal cell carcinoma - Oman - Gulf Cooperation Council Countries - papillary histology - ethnic variation

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Introduction

Renal cell carcinoma (RCC) arises from renal tubular epithelium and accounts 2% of all malignancies (13th commonest) worldwide. The occurrence of new cases of RCC across the world is 337,860, with an annual mortality of 143,406 (Ferlay et al., 2012). About 30% of RCC present with organ confined disease and another 30% relapse with metastatic disease after local treatment; thus about 40% of RCC cases eventually die of their disease (Ljungberg et al., 2011). A recent decline in mortality has been noted (Luke et al., 2011) partly due to early (incidental) detection with increasing use of imaging, and partly due to the availability of newer targeted therapies. The risk factors for RCC include increasing age, obesity, hypertension, diabetes mellitus (DM), exposure to certain chemicals (including cigarette smoke); few cases are attributable to inherited gene mutations (Moch, 2013).

The incidence of RCC in the Gulf Cooperation Council (GCC) countries (including Oman) is less than 2 per 100,000; slightly higher incidence is noted in Bahrain (Salim et al., 2009). RCC is a "fat cancer", due to its association with obesity and DM. The increasing incidence of obesity in the GCC countries (AL Nohair, 2014) and improvements in health care with more frequent imaging is expected to push up the incidence of this malignancy.

Three histological subtypes account for 85%–90% of all renal malignancies: clear cell RCC (75%–90% of tumours), papillary RCC (10%–15%) and chromophobe RCC (4%–5%) (Lipworth et al., 2006). Most of them have identifiable gene mutations, such as mutations of VHL gene in clear cell, and in FH or MET in papillary variant; translocation associated RCC have been identified more recently (Eble et al., 2004).

We did an institutional, retrospective study of RCC seen in the National Oncology Center of The Royal Hospital, Muscat in the Sultanate of Oman from 2010 to 2014 to identify epidemiological pattern specific to this GCC country.

Materials and Methods

After obtaining approval of the Ethical and Scientific Committee, patients were identified by searching computerised clinical records as well as detailed search of pathology reports and pharmacy data of the same years to ensure completeness. Data was entered into Excel sheet and analysed using SPSS (version 12)

Results

A total of 90 patients of RCC were seen in the Royal Hospital over a period from 2010 to 2014; 55 were male (65.5%). Their median age was 52 yrs (range 16–78 yrs). The right kidney was involved in 47 cases (52.2%); there were no cases of bilateral tumours but one involved horseshoe kidneys. Co-morbidities included hypertension (20 cases) and diabetes mellitus (9 cases). Two patients had a second primary malignancy (esophagus and colon) that presented synchronously.

Histology (Table 1) was available in 80 cases (10 were diagnosed radiologically; no intervention was offered due to poor condition).50 were of clear cell type (55.5%); non-clear were present in 32.2%. Fuhrmann's

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grade was recorded in 52 patients; 47 patients had either grade 2 and 3.

The majority of patients presented with localized disease (60 cases); of these, 32 were in Stage I (T1N0) and all were diagnosed incidentally while being imaged for unrelated complaints (Table 2). Eleven and seven cases presented in stage II (T2N0) and III respectively while 32 presented in stage IV (T4 or M1); the last group includes the 30 who were metastatic at presentation (M1). Staging information for eight patients (all localized and operated abroad were not available). Common sites of metastases of de novo metastatic disease were lung (60%), bone (50%) and liver (23.3%); less common were lymph nodes, soft tissue and brain (1 case). Multiple sites were seen in 43.3% of cases. A rare case of laryngeal metastasis was reported earlier from this centre (Mehdi et al., 2012).

All 60 cases presenting with localized disease were resected; of these 14 (25%) relapsed later at a median of 51 months (range 12 – 192 months). The pattern of metastatic relapse was slightly different, with bones (50%) predominating; lung (43%) and liver (21.4%) were the other common sites.

Fourteen of the 30 who presented with de novo metastatic disease also underwent radical nephrectomy. Two post-operative deaths were recorded (one localized and one with brain metastasis).

One patient was given post operative adjuvant radiation and another 20 were offered palliative radiation at various sites including bone and brain.

Adjuvant systemic therapy was not given to any patient with localized disease. Of those with metastatic disease (total 44 – 30 de novo and 14 relapse), only 23 were offered first line systemic therapy. Targeted therapy with sunitinib was the commonest first line treatment (11 cases); other first line treatment included sorafenib (4), pazopanib (1), temsirolimus (1) and chemotherapy. Interferon was given to 3 patients (one in combination with bevacizumab); none received interleukin. Mean duration of first line therapy with sunitinib was 11.9 months; duration of therapy with other agents was less than 5 months though one patient continues to be on sorafenib for 88 months. Only 7 patients were found eligible for second line therapy; 3 received third line and only one was given fourth line therapy (with gemcitabine).

The commonest reason for not giving systemic therapy to the 22 cases of metastatic disease was poor performance status (12/22); five patients refused treatment and two did not return for follow up. Three patients with limited relapse (larynx, bone and soft tissue) were treated with excision and local RT, and are alive and well. At present, 51 patients are alive and 35 have expired. Four have been lost to follow up.

Table 1. Histological Subtypes

Histology	Number	Percentage
Clear cell	50	56
Clear cell	20	22
Chromophobe	5	6
Oncocytoma	2	2
Collecting duct	1	1
Sarcamatoid	1	1
Trabecular	1	1
No histology	10	11
Total	90	100

Table 2. Stage Classification

STAGE	TNM	Number	Percentage
Stage I	T1N0M0	32	36
Stage II	T2N0M0	11	12
Stage III	T3N0M0	6	7
Stage III	T2N1M0	1	1
Stage IV	T4 Any N M0	2	1
Stage IV	Any T Any N M1	30	34
Unknown	TxNxM0	8	9
Total	90	100	

Discussion

The Sultanate of Oman is a member of the Gulf Cooperation Council countries. Renal cell cancer (RCC) occurs at relatively low incidence in GCC and other Arab countries (Ferlay et al., 2012; Salim et al., 2009), ranging from 2 to 4 (Table 3).

The Royal Hospital at Muscat is the major cancer treatment centre in Oman and is estimated to treat more than 80% of the cancers occurring in this country; hence

Table 3. Comparison of Incidence and Histology Data in Arab Countries

Country	Incidence Male	Incidence female	Histology percentage	Reference
Oman	2.13	2.06	Clear cell 56% Papillary 22%	Present
Saudi Arabia	2.77	1.84	Clear cell 77.7% Papillary 7%	Alkhateeb, 2015
Kuwait	2.62	1.48	Clear cell 32.6% Papillary 8.2%	Thotathil, 2005
Bahrain	2.66	2.53	No data	
Qatar	4.39	1.55	No data	
UAE	2.64	1.77	No data	
Yemen	0.8	0.44	No data	
Egypt	3.12	1.78	Clear cell 47% Papillary 20%	Ibrahim, 2012
Jordan	4.31	2.04	Clear cell 79.5% Papillary 11.35%	Khalil Ibrahim, 2013
Lebanon	4.83	1.77	Clear cell 59.1% Papillary 22.7%	Khafaja, 2015
Iraq	3.73	2.27	No data	
Syria	4.05	2.15	No data	
Algeria	1.85	0.6	No data	
Morocco	1.86	1.23	No data	
Libya	3.75	1.72	No data	
Tunisia	2.3	1.9	Clear cell 67% Papillary 18.7%	Ferchichi, 2012

the profile of cancers presenting here is a fair snapshot of those across the country. This study, however, suffers from all the limitations of a retrospective study. Although treatment is free for all Omani citizens and there is an excellent network of primary care centers and a strong referral system, it is possible that a referral bias may exist with elderly patients with metastatic disease and poor PS being recommended supportive care at home without reaching an oncology center. The excellence of the health system (Tandon et al., 2000) is indicated by the high percentage of localized disease in this series.

This study shows two interesting features worthy of comment – the relatively younger age of presentation and the increased occurrence of non-clear (especially papillary) variants of RCC. The median age of 52 is a decade younger than that reported from other countries but is consistent with other reports from developing countries with a higher proportion of younger population. Data from Gulf countries show a similar peak in age group 40-59 yrs (Saudi Arabia (data accessed from Saudi Arabian Cancer Registry), Kuwait (Thotathil et al., 2005)), as also Jordan (Ghalayini et al., 2003).A referral bias (as above) cannot be excluded. Oman has a higher incidence of consanguineous marriages (Rajab and Patton, 2000), and a higher incidence of heritable hematological diseases such as thalassemia and sickle cell anemia have been reported earlier, which could form the basis of a genetic etiology. However, none of the patients reported a family history of RCC, and other classical features of an inherited disorder are missing (such as bilateral tumours or other primary sites). It would be worthwhile to conduct genetic profiling of these tumours to detect mutations specific to this population.

The higher incidence of non-clear (especially papillary) RCC in our series could be related to either the younger age of the cohort, or ethnic mix of the population. Several series with predominance of younger patients have noted a higher incidence of non-clear RCC (Bruder et al., 2004; Rodriguez et al., 2002; Akhavan et al., 2015; Aziz et al., 2014), though this finding is not consistent - a large data set study showed that the incidence of papillary cancer actually increased with increasing age (Purdue et al., 2014). The median age of non-clear cell carcinomas in our cohort was lower than the clear cell subset (46.7 years versus 52.1 years).

Ethnic differences in the histology of RCC have been reported from countries with mixed populations such as USA(Sankin et al., 2011; Olshan et al., 2013) and Singapore (Ezenwa and Tan, 2014) , though not from Malaysia (Singam et al., 2010); data from other countries with heterogeneous population (Brazil (Nardi et al., 2010) and South Africa (Claassen et al., 2011)) have not been analysed based on ethnic background. Oman has a genetically admixed population with Caucasian, African and Asian ancestries (Albalushi et al., 2014). However, this possibility remains speculative.

Table 3 also lists the scanty data from other Arab countries. It is interesting to note that the relatively higher occurrence of papillary subtype has been noted from Lebanon as well (Khafaja et al., 2015).

Twenty five percent of cases treated as localized disease (14/60) relapsed with metastatic disease, which is currently incurable. There is an urgent need to have validated clinical or molecular criteria to predict patients at higher risk of relapse, and trials in adjuvant setting targeting these high risk groups to prevent relapse. At present, there are a plethora of risk models to predict recurrence, and some of these are being used in trials of adjuvant therapy such as ASSURE (with sunitinib or sorafenib), STAR (sunitinib), SORCE (sorafenib) and EVEREST (everolimus) trials for risk stratification (Clinicaltrials.gov). Previous trials using IL-2 and interferon in adjuvant setting have been negative. The results of the trials with the newer targeted agents are awaited (Pinto, 2014) but results of the ASSURE trial also does not show any advantage (Haas et al., 2016). The unique clinical profile of our patients as revealed in this study, presumably due to different underlying molecular mechanisms, suggest that results of such trials must be extrapolated with caution on our patients, and an effort undertaken to have our own studies at molecular and therapeutic levels.

It is interesting to note that none of the patients with metastatic disease were treated with the previous standard of care interleukin, and very few with interferon. This is partly due to lack of availability and partly due to the known toxicity of treatment. The availability of new targeted agents with have made a dramatic difference in the armamentarium but inability to use them in a significant percentage of patients due to poor performance status suggests that there is an unmet need for more "benign" drugs for this malignancy.

In conclusion, this retrospective study of renal cell carcinoma patients presenting at a comprehensive cancer centre in the Sultanate of Oman shows a different clinical profile with a younger age of presentation, more localized disease, and a higher occurrence of non-clear RCC. Studies at molecular level are indicated to shed light on these variations.

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