Detection, staging and clinical implications of renal cell carcinoma

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ABSTRACT

Objectives: To compare the epidemiologic, clinical, and pathologic characteristics of symptomatic and incidental renal cell carcinoma (RCC) in Jordan, with some emphasis on age distribution and its potential effect in defining groups of patients that may benefit from early detection programs. We compared our results with the published western figures.

Methods: Records of 119 patients with renal tumors diagnosed during the period January 1992 to December 2001 at Jordan University of Science and Technology, Irbid, Jordan were reviewed. Age, gender, discovery circumstances of the tumor, radiologic and biologic workup, treatment, tumor node metastasis classification, and histologic features of the tumor were analyzed.

Results: The mean patient age was 54, and the male to female ratio was 3.4:1. The annual frequency rate for RCC per 100,000 population was 1.2 for both sexes, while for men was 1.8 and for women was 0.5. Twenty-six percent of tumors were discovered accidentally. The mean age at the time of diagnosis was not influenced by the discovery circumstances. The incidental detection group had significantly small size of tumor (5.6 cm circumference (c.f) 8.1 cm), lower stage and lower histological grading. In the symptomatic group; women have significantly lower mean size of tumors than men (5.5cm c.f. 7.7cm; $p = 0.005$; t-test), while there is no significant difference among the incidental group. A radical nephrectomy was performed in 92% of the cases, and in 8% of the cases, conservative management was adopted.

Conclusion: The present study showed that the incidence rates of RCC in Jordan and other Middle East countries were less than most of the western countries. Malignant renal tumors in Jordan tend to affect people at a remarkably young age. This is mostly a reflection of the high proportion of young people in this country. This high portion of young people may explain the low incidence as kidney cancer is known to increase with age. Significant numbers of RCC were detected incidentally with lower pathological stage and grade. Subsequently these clinically and histologically less aggressive lesions lead to better survival and decreased recurrence. These data efforts should be directed to the development of a screening protocol to detect these lesions early, so that they may be prevented from progressing to the point when symptoms are apparent and prognosis becomes worse.

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Malignant tumors of the kidney account for more than 2% of cancer incidence and mortality in the United States of America (USA) with an estimated 31,200 new cases in 2000 causing approximately 11,900 deaths.[1] Recent clinical surveys have revealed that incidental detection of renal cell carcinoma (RCC) is rising, partly because of increased use of imaging procedures, such as ultrasonography, computerized tomography (CT) scanning, and magnetic resonance imaging (MRI)[2] This observation does not fully explain the rising incidence of RCC, because there has also been an increase in the diagnosis of advanced tumors as well as an increase in RCC mortality rates.[3] Epidemiology of RCC is still lacking in many developing countries. This study is aimed at the assessment of epidemiology of renal cancer in Jordan, which may be considered as a

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model for Middle East countries since the demographic, racial, and social features of these populations are comparable.

Methods. This multicenter study reviews 119 patients with the histological diagnosis of renal tumors whom were treated in the north of Jordan area during the period, January 1992 to December 2001 at Jordan University of Science and Technology. Data was collected from the medical records of 5 general hospitals and the single pathology center serving the area. We obtained data regarding age, gender, discovery circumstances of the tumor, radiologic and biologic workup, treatment, tumor node metastasis (TNM) classification and histologic features of the tumor. The discovery circumstances were defined as follows: Incidental tumors were tumors discovered during paraclinical workup for another cause not related to the kidney pathology. Symptomatic tumors were those revealed by urologic symptoms (pain, hematuria, or an abdominal mass) or by general symptoms (weight loss or fever) and synchronous or both, or prevalent metastasis. In the biologic profile, anemia was described as hemoglobulin (Hb) <10g/L and polycythemia as Hb >16g/L. The erythrocyte sedimentation rate was considered high when it passed 20 during the first hour. Oncocytomas, although they are benign tumors, were included in this study because the presurgical diagnosis workup did not allow us to distinguish them from adenocarcinoma. The adenocarcinomas were divided into tubulopapillary tumors, clear cell tumors, granular cell tumors, mixed tumors, and others. The TNM classification was adopted,[4] and the histologic grade was determined according to the Fuhrman classification.[5]

Results. The mean age of the patients with RCC was 53.8 (range, 7-80 years). The mean age at incidental discovery was 53.3 years (range, 7-80), and that of the symptomatic patients was 54 years (range, 35-75 years). The male-to-female ratio for RCC was 3.4: 1 (79 males, 23 females). Tumor discovery was incidental in 26 % (31) of the cases, and in 74% (88) of the cases the tumor

Table 1 - Kidney tumors revealed by clinical symptoms (N=88).

Symptoms	Frequency	(%)
Urologic symptoms	67	(76.1)
Hematuria	29	(32.9)
Loin pain	21	(23.9)
Loin mass	3	(3.4)
More than one primary	-	-
Symptom	14	(15.9)
General symptoms	13	(14.8)
Metastasis	3	(3.4)
Others	5	(5.7)

Table 2 - Tumor node metastasis classification and nuclear grading of incidental and suspected renal cell carcinoma.

Tumor characteristics	Incidental %	Suspected %
Stage		
pT 1	13.8	4.1
pT 2	65.5	50.7
pT 3a	13.8	27.4
pT 3b	6.9	17.8
Fuhrman nuclear grade		
1	17.2	16.4
2	62.1	39.7
3	13.8	32.9
4	6.9	11

pT - pathological stage

Table 3 - Various tumor cell types.

Tumor characteristics	Incidental %	Suspected %
Oncocytoma	13	10.9
Tubulopapillary tumors	16	13.4
Clear cell tumors	66	55.5
Granular cell tumors	3	2.5
Mixed cell tumors	8	6.7
Others	13	10.9
Total	**119**	**100**

Table 4 - Mean tumor size, according to discovery circumstances, adrenal, renal vein or IVC, lymph node involvement and visceral metastasis.

Renal carcinoma	Patient n	Mean tumor size	p value (t-test)
Discovery circumstances			0.000
Incidental	29	5.6	
Symptomatic	73	8.1	
Adrenal involvement			0.003
No	96	7.1	
Yes	6	10.4	
Renal vein/IVC involvement			0.000
No	86	6.6	
Yes	16	11.9	
Lymph node involvement			0.000
No	88	6.9	
Yes	14	11.0	
Visceral metastasis			0.005
No	97	7.1	
Yes	5	12.1	

IVC - inferior vena cava

Table 5 - Studies reporting detection of incidental renal cell carcinoma and survival.

Author, year, country	Study	Year	N	(%)	Remarks
Mevorach 1992, United States of America	Case series	1976-1987	235	(29)	Similar stage, no improved survival
Rodriguez-Rubio 1996, Spain	Case series	1979-1993	157	(35)	Lower stage, improved survival
Sweeney 1996, United Kingdom	Case series	1972-1992	189	(15)	Lower stage, improved survival
Gudbjartsson 1996, Iceland	Population	1971-1990	406	(15)	Lower stage, no survival benefit after correcting for stage
Jayson 1998, United States of America	Case series	1989-1993	131	(61)	Similar stage
Bretheau 1998, France	Population	1992-1994	1486	(40)	Smaller size
Siow 2000, Singapore	Population	1990-1998	165	(39)	Lower stage, improved survival

was revealed by clinical symptoms **(Table 1)**. Urologic symptoms were the most frequent features (76%) and hematuria was the most common presenting symptom (33%). In 80% of the cases, the incidental tumors were an echographic discovery. Bilateral tumors were observed in 2 cases (1.7%). Treatment consisted of a radical nephrectomy in 109 cases (91.6%) while nephron sparing surgery was carried out for 10 patients (8.4%). The transabdominal approach was the most frequently used (64%). An adrenal gland excision was concomitantly performed in 78% of the cases. It was spared mainly in small and lower pole tumors. In 17% of the cases the tumor was in the lower pole of the kidneys, while the remaining 83% were tumors of panrenal, mediorenal or superior polar situation. The biologic workup showed abnormality of hemoglobin in 31 cases (26%). In 23 cases, the patients had anemia, and in 8 cases the patients presented with polycythemia. The calcium and the creatinine rate were elevated in 4% and 13% of the cases. The TNM classifications for incidental and symptomatic adenocarcinomas of the kidney are presented in **Table 2.** In the incidentally, discovered adenocarcinoma, 14% were tumors 2.5 cm or less and 79% were intracapsular tumors (pathological stage (pT1 and pT2), compared with 4% and 55% in the suspected group. From a histological point of view, the various tumor cell types are presented in **Table 3**. Oncocytomas comprised 11% of the cases. The most frequently observed tumors were clear cell adenocarcinomas (55.5%). The mean size of all tumors was 7.1 ± 3.7 cm (range, 2.5-17 cm). The mean size of incidental RCC was 5.6 ± 2.5 cm as compared to 8.1 ± 4.1 cm for suspected RCC. This difference is statistically significant (p=0.000). Women have significantly lower mean size of tumors than men do (5.5 cm c.f. 7.7 cm; p=0.005; t-test), while the size showed no gender difference among the incidental group. Correlations of mean tumor size with the presence of clinical signs as well as with adrenal involvement, renal vein or inferior vena cava involvement or both, lymph node involvement, and the presence of visceral metastases were all highly significant **(Table 4).** Capsular invasion was noted in 32 cases (31%), 23 (72%) of whom had only perirenal fat involvement. Renal vein involvement was observed in 14 cases (13.7%) alone and in 2 cases (2%) was associated with inferior vena cava involvement (classified as pT3b, a total of 16 cases, corresponding to 15.7%). Lymph node involvement was observed in 14 cases (13.7%), and visceral metastasis was present in 5 cases (5%). The distribution of the patients with lymph node involvement according to the TNM classification shows it to be prominent in cases of perirenal fat or venous involvement. Adrenal gland involvement was observed in 6 patients (6%). It was observed in tumors of the upper pole in 3 cases and in panrenal tumors in the rest 3 cases. The mean tumor size was significantly larger than tumors without adrenal gland involvement.

Discussion. This study enabled us to centralize 119 patients from an area, which has 20% of the people of Jordan. Thus, the results of this study could be looked at as a pilot study investigating the clinico-pathological profile of RCC in Jordan. The ages in which this tumor is most frequently observed are in the 5th and 6th decades with the median age of 54 (range 7-80 years). The youngest patient with renal adenocarcinoma was a 7-year-old child who was diagnosed after being investigated for post-traumatic abdominal pain. Renal cell carcinoma is an uncommon tumor of childhood as it comprises only 2.3-6.6% of renal tumors in children[6,7] while Wilm's tumor constitutes 85-87%.[8,9] However, other cancers like breast cancer affect the patients at a remarkably young age in the Middle East.[10] Our figures are much lower than the mean ages in the previous publications from the Western countries. This is largely due to the fact that 50% of the Jordanian people are below the age of 16 years while less than 4% are above the age of 60 years (1998 census). The mean age at the

time of diagnosis is not influenced by the discovery circumstances in our study. In France, the tumor is most frequently observed in the 6th and 7th decades.[11] Also, the mean age of patients with incidental (61.9) versus symptomatic (62.3) tumors at diagnosis was similar. In Italy, the mean age in the incidental group rose steadily higher than in the symptomatic group.[12] This paradox may be partially explained by the fact that abdominal imaging is not truly being carried out for screening purposes but rather reflects the possibility that more radiological examinations are being performed in the elderly population in which other diseases more commonly develop.

Since 1950 in the United States of America (USA), there has been a 126% increase in the incidence of renal cell carcinoma accompanied by a 36.5% increase in annual mortality. In 1997 the incidence was 9.1/100000 population, while the mortality rate was 3.5/100000.[13] In the early 1970s approximately 10% of tumors were discovered incidentally compared with 61% of renal tumors in 1998.[13] However, the number of advanced cases, including those of regional extension and distant metastasis, also increased in all race and sex categories. In the USA, the highest incidence is in individuals in the 7th decades with a median age at diagnosis of 66 years and a median age at death of 70 years.[14] In relation to the world the USA is near the top in terms of incidence with the highest incidence in males in 1985 reported in Trieste, Italy and the lowest reported in Setif, Algeria.[14] Almost one-third of all new cases in the USA occurs in only 4 states, namely, California, New York, Florida and Texas, USA.[13] In the Netherlands, the annual incidence of this tumor is about 11 per 100,000. Men are twice as often afflicted as women are, most often in the 5th to 6th decade.[15]

The low incidence in Jordan is part of a generalized trend toward a lower incidence of kidney cancer in our region as indicated by reports coming from Egypt, Kuwait, Kingdom of Saudi Arabia, Libya and Iran.[16] We don't know if this is a result of different genetic susceptibility or environmental differences. This is supported by the fact that the incidence rates of renal cell carcinoma in Japan were approximately the same as among Japanese in Los Angeles, California, USA.[17] On the other hand, the incidence rates in the Hokkaido region in Japan were significantly higher than in other regions, among which there was no significant difference in incidence rates.[17] This could not be explained by any reason, but further epidemiological research is required. The 26% rate of accidentally discovered tumors in our series confirms the findings of other authors that ranged from 15-61% **(Table 5).**[18] Such a wide range of incidence in the literature could be related to differences in definition of incidental detection in various studies, as well as the referral pattern and health screening policies in different countries. Apparently, most of the major series included asymptomatic patients and patients with non-specific symptoms into the incidental detection group. Using similar criteria, the present series showed an incidence of 26%. The rate of accidental discovery has actually been constantly rising in the past 10 years. It reflects the extensive practice of abdominal ultrasonography, which proved to be the best screening method in our study (80%). While this is a retrospective series from a tertiary referral center, this institute is one of the few major hospitals serving the entire population. Significant portion of patients was treated here when compared with the data from the National Cancer Registry.[19] Thus, we believe that our results portray the national incidence of this cancer.

From a therapeutic point of view, radical nephrectomy by transabdominal approach has been the most frequent used procedure (61%). Lombotomy was the surgeons 2nd preference overall (30%). A conservative attitude has been proposed for 8.4% of patients; it was a surgical necessity in most of the cases. The adrenal gland was spared in 22% of the cases, especially with the small inferior polar tumors. This doesn't seem to be significantly associated with a poor outcome.[20]

Intracapsular tumors accounted for 61.8% of the population and 79.3% of the; incidentally, discovered tumors. Organ confined disease; for example TNM classification pT1 and pT2 was found in 79.3% of patients with incidental tumors, as compared with 54.8% of patients with suspected RCC. This difference is statistically significant ($P<0.025$, Chi square test). The incidental cancers had a significantly lower histological grading ($p<0.05$, Chi square test) **(Table 2)**. This pattern of distribution of the tumor staging and grading was approximately similar to that reported by other authors.[11,18,21] From a histological point of view, tumor distribution showed a predominance of clear cell adenocarcinomas (55.5%). The frequency of oncocytoma (11%) reflects the difficulty of presurgical diagnosis of these lesions; this results in abusive nephrectomy, which is not indicated for these benign tumors. However, CT scanning reveals features that favor a diagnosis of oncocytoma such as central scar and cartwheel aspect, and even though these features are not pathognomonic, the surgeon must keep in mind the possibility of an oncocytoma and choose a conservative surgical attitude and perform anatomopathologic analysis with fresh-frozen tissue during the operation. In our series, doing nephron-sparing surgery saved 40% of the kidneys with oncocytomas.

In our study, the mean tumor size was influenced by the discovery circumstances, similar to other series in the literature.[11,18,22] The incidentally, discovered tumors were smaller in size. In the symptomatic group; women have significantly lower mean size of tumors than men do (5.5 cm c.f. 7.7 cm; $p=0.005$; t-test), while there is no significant difference in the incidental group. However, in our series RCC is 3-4 times more frequent in men than women without significant difference in tumor staging a grading. The mean tumor size was significantly increased in the presence of poor

prognostic indicators (lymph node involvement, adrenal gland involvement, venous involvement and metastasis). The frequency of lymph node involvement was not easy to evaluate because of the small number of patients who underwent extensive lymphadenectomy. Nuclear grade, according to Fuhrman's classification, had a significantly lower histological grading in the incidental cancers ($p<0.05$). We noticed that it was correlated with the presence of poor prognostic indicators (perirenal fat involvement and lymph node involvement), thus emphasizing the interest of grade determination as reported by some authors.[22,23] To date, radical nephrectomy remains the mainstay of treatment for RCC, incidental or otherwise, in the presence of an anatomically and functionally normal contra-lateral kidney. However, with the favorable pathology and improved prognosis seen with incidental RCC, nephron sparing surgery may become the preferred treatment of choice.[24,25] Currently, we exercise strict selection for such procedures, namely, that the tumor is of early stage, small size, easily accessible and there is absence of multi-focal lesions.

This study has taught us a great deal about the clinico-pathologic features of adenocarcinomas of the kidney. We believe that our results may portray the national incidence of this cancer, since our institute is one of the few major hospitals serving the entire population. Also, our area has approximately one-fifth of the population of the country. In our opinion, we must extend this study in the future in order to have an exhaustive registry of all tumors of the kidney in Jordan in the course of a year. Significant numbers of RCC were detected incidentally with lower pathological stage and grade. Subsequently these clinically and histologically less aggressive lesions lead to better survival and decreased recurrence. These data efforts should be directed towards the development of a screening protocol to detect these lesions early, so that they may be prevented from progressing to the point when symptoms are apparent and prognosis becomes worse.

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