Chulalongkorn Medical Journal

Volume 43
Issue 5 *May 1999*

Article 4

5-1-1999

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Recommended Citation

Sookprasert, A.; Voravud, N.; and Prasopsanti, K. (1999) "Renal cell carcinoma at King ChulalongkornMemorial Hospital," *Chulalongkorn Medical Journal*: Vol. 43: Iss. 5, Article 4.
DOI: 10.58837/CHULA.CMJ.43.5.4
Available at: https://digital.car.chula.ac.th/clmjournal/vol43/iss5/4

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Renal cell carcinoma at King Chulalongkorn Memorial Hospital

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Sookprasert A, Voravud N, Prasopsanti K. Renal cell carcinoma at King Chulalongkorn Memorial Hospital. Chula Med J 1999 May; 43(5): 295-305

Background : *Renal cell carcinoma is not an uncommon disease in Thailand. Surgery is the treatment of choice in early stage disease. Even properly performed, some patients succumb from recurrence diseases. There is still no effective treatment for advanced and metastatic diseases. The basic demographic datas and survival in any stage of the diseases were collected and reported.*

Objective : *To review the clinical features, histology, treatment and survival of renal cell carcinoma patients in King Chulalongkorn Memorial Hospital*

Setting : *Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University.*

Subject : *Thirty-three renal cell carcinoma patients, from January 1993-December 1997*

Design : *Retrospective study*

Patients : *The records of 34 patients were reviewed. The median age was 57.4 years. There were 30 males and 4 females. The male to female ratio was 8:1. Most of the patients presented with advanced stages of the disease. Greater than 40 % presented with distant metastasis while only 11.1 % had stage 1 disease at initial presentation.*

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Method : *All basic demographic datas were calculated in proportion and percent. The survival rate was calculated using the Kaplan and Meire method.*

Results : *Four patients presented with stage I disease, no stage II disease was found. Six stage III disease and twenty patients presented with stage IV disease. Flank pain was the most common initial presentation followed by hematuria. Clear cell carcinoma was the most common histology. In distant metastatic group, bone and lung were the two most common sites of involvement. Surgery was performed to treat primary tumor at the kidney in nineteen patients and two metastatectomy were performed. Of the total nineteen patients with distant metastasis, only eight patients received treatment. The overall median survival of the patients was 12.85 months. The median survival for stage III and IV disease were 12.97 and 10.14 months respectively. Subgroup analysis was performed in stage IV disease, the median survival was 18.5 months in patients with metastatic disease whom received some from of treatments compared to only 1.25 months in patients with best supportive care.*

Conclusion : *The majority of renal cell carcinoma in Chulalongkorn manifested with metastatic disease. Treatment either metastatectomy or chemobiologic therapy was associated with better outcome compared to palliative care alone. The best treatment was metastatectomy.*

Key words : *Renal cell carcinoma, Clinical features, Treatment, Survival.*

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Received for publication. February 10, 1999.

เอื้อมแข สุขประเสริฐ, นรินทร์ วรวุฒิ, เกรียงศักดิ์ ประสพสันติ. ผู้ป่วยมะเร็งไตในโรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2542 พ.ค; 43(5): 295-305

วัตถุประสงค์ : *เพื่อศึกษาข้อมูลเกี่ยวกับระยะของโรค อาการและอาการแสดง การวินิจฉัย การรักษา และอัตราการรอดชีวิตในผู้ป่วยมะเร็งไตที่มารับการรักษาในโรงพยาบาล*

สถานที่ทำการศึกษา : *หน่วยมะเร็งวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

รูปแบบการวิจัย : *ศึกษาย้อนหลัง*

ผู้ป่วยที่ทำการศึกษา : *ผู้ป่วยมะเร็งไตจำนวน 34 ราย ตั้งแต่เดือนมกราคม 2536-ธันวาคม 2540 ผู้ป่วยชาย 30 ราย ผู้ป่วยหญิง 4 ราย อัตราส่วนชายต่อหญิงคือ 8 ต่อ 1 อายุเฉลี่ยคือ 57.4 ปี*

วิเคราะห์ทางสถิติ : *ข้อมูลพื้นฐานรายงานในรูปของสัดส่วนและร้อยละ อัตราการอยู่รอดคำนวณโดยวิธี Kaplan และ Meier*

ผลการศึกษา : *ระยะของโรคตั้งแต่เริ่มวินิจฉัย ผู้ป่วย 4 ราย เป็นระยะที่ I 6 รายเป็นระยะที่ III และส่วนใหญ่ของผู้ป่วยคือ 20 รายเป็นระยะลุกลามและแพร่กระจายไปยังอวัยวะอื่น อาการปวดเอวเป็นอาการที่นำผู้ป่วยมาพบแพทย์ที่พบได้บ่อยที่สุด รองลงมาคือปัสสาวะเป็นเลือด clear cell carcinoma เป็นลักษณะทางพยาธิวิทยาที่พบบ่อยที่สุด ในผู้ป่วยที่มาในระยะสุดท้ายพบว่ากระดูก และปอดเป็นอวัยวะที่มีการแพร่กระจายไปที่พบได้มากที่สุด ผู้ป่วย 19 รายได้รับการรักษาด้วยการผ่าตัดไตออก ผู้ป่วย 15 ราย ไม่ได้รับการผ่าตัด เนื่องจากมีการกระจายของโรคไปยังอวัยวะอื่นแล้วผู้ป่วย 2 รายได้รับการผ่าตัดของอวัยวะที่มีการกระจายของโรคไปเพื่อเป็นการรักษา และ ผู้ป่วย 2 รายนี้สามารถอยู่โดยปราศจากโรคได้เป็นเวลานานจนถึงปัจจุบัน ระยะการรอดชีวิตเฉลี่ยของผู้ป่วยทุกคนคือ 12.85 เดือน โดยจำแนกย่อยได้เป็น 12.97 เดือนและ 10.14 เดือน ในผู้ป่วยระยะที่ III และ IV ตามลำดับ ผู้ป่วยระยะที่ IV ที่ไม่ได้รับการรักษาจะมีระยะกึ่งกลางชีวิตเฉลี่ย 1.25 เดือน ในขณะที่ผู้ป่วยระยะที่ IV ที่ได้รับการรักษาอย่างใดอย่างหนึ่งมีระยะกึ่งกลางชีวิตเฉลี่ย 18.5 เดือน*

สรุปผลการวิจัย : *ผู้ป่วยมะเร็งไตที่มารับการรักษาที่ร.พ. จุฬาลงกรณ์โดยมากจะเป็นระยะที่มีการแพร่กระจายของโรคไปยังอวัยวะอื่นแล้ว ผู้ป่วยในระยะนี้ถ้าสามารถได้รับการรักษาอย่างใดอย่างหนึ่งไม่ว่าจะเป็นการตัดก้อนมะเร็งที่แพร่กระจายไปที่อวัยวะอื่นออก หรือการรักษาด้วยยาเคมีบำบัดร่วมกับยากระตุ้นภูมิคุ้มกัน จะทำให้มีระยะกึ่งกลางชีวิตที่ยาวนานกว่าการรักษาด้วยการประคับประคองอย่างเดียว และการรักษาที่ให้ระยะกึ่งกลางชีวิตที่ยาวนานที่สุดคือการผ่าตัด*

คำสำคัญ : *มะเร็งไต, อาการแสดง, การรักษา, ระยะกึ่งกลางชีวิต*

Renal cell carcinoma (RCC) is the most common renal malignancy. The manifestation of RCC is protean and is easily confused with other systemic disease.[1] This is especially true when the patient presents with advanced stages and metastatic diseases. Surgery is the most effective treatment to cure early stage disease.[2] However, when the patients are presented with metastatic disease, other treatment modalities such as chemotherapy and biological response modifiers (BRMs) may play a role in the management.[3] In this study, we report the clinical course and treatment out come of patients with RCC treated at King Chulalongkorn Memorial Hospital over the past five years.

Materials and Methods

Patient Population

Between January 1, 1993 and January 1, 1997, 40 adult patients over 15 years of age with RCC were treated at King Chulalongkorn Memorial Hospital. Data concerning demographics, clinical findings, laboratory studies, stage of disease, Histopathology, and treatment were retrospectively reviewed from the operative notes and pathological reports, Among the 40 patients, 6 were excluded from the study after pathology review; 3 had transitional cell carcinoma of the pelvis, and 3 adult had Wilm's tumor.

Definition of Terms Used in This Study

The pathological staging was defined according to the International TNM Classification of Renal/ Kidney Carcinoma (1982). Stage I tumors 7 cm or less in greatest diameter and limited to the kidneys , no lymph node involvement and no distant metastasis. Stage II tumors more than 7 cm in greatest diameter but confined to the kidneys and no regional lymph node involvement. Stage III - any tumor extending into major veins or invading adrenal glands or perinephric tissues but not beyond Gerota's fascia with or without single regional lymph node involvement; or tumors in stage I or stage II with single lymph node involvement. Stage IV -any tumor that invades Gerota's fascia or with lymph node metastasis of greater than one regional group or with any distant metastasis.

Local failure (LF) was defined as a relapse of disease within the renal fossa, or in the residual parenchyma. Regional failure (RF) was defined as a relapse within the para-aortic/para-caval lymph nodes,. Distant metastasis (DM) was defined as the occurrence of tumors in remote sites from the renal such as the brain, lungs, bones, liver or soft tissue as well as in lymph nodes in area remote from the regional sites.

Statistical Methods

The overall survival (OS), median survival and disease free survival rates were calculated from the date diagnosis according to each stage. Overall survival distributions were calculated by using the Kapan-Meirer method.

Result

Patient Characteristics

Patient characteristics are listed in Table 1. Median age was 57.4 years (range, 26.9 -93.8) and the male to female ratio was 7.5:1 Advanced stage III/V disease occurred in 72.3 % of the patients, with a predominance of clear cell carcinoma histology. Only

four patients (11.1 %) presented with stage 1 disease. No stage II disease was found in our study. Six patients presented with stage III disease (16.7 %). The majority of the patients (55.6 %) presented with stage IV disease, Unknown initial staging was found in four patients; two patients received initial surgery at other hospitals and were referred to King Chulalongkorn Memorial Hospital when their disease relapsed. In two other patients, the initial staging could not be performed because of missing operative notes and pathological reports. The presenting symptoms are shown in Table 1. Only 8.3 % of the patients presented with the classic triad of RCC, namely, hematuria, flank pain and palpable flank mass. The most common symptoms were flank pain, followed by hematuria, and weight loss, respectively. Asymptomatic patients whose renal cell carcinoma was found as an incidental finding comprised of only 5.6 % of the patients. Unilateral renal involvement was observed in 3.1 of 34 patients (86.1 %) and bilateral disease in 3 (8.3 %). Among the patients with bilateral involvement, there were no prior family histories of cancer.

Table 1. Patient characteristics.

Number of patients	34
Median age (range)	57.4 (26.9 - 93.8)
Male : Female	7.5 : 1
Stage (%)	
I	4 (11.8)
II	0 (0)
III	6 (17.6)
IV	20 (58.8)
Unknown	4 (11.8)
Histology (%)	
Clear cell carcinoma	13 (38.2)
Adenocarcinoma	5 (14.7)
Squamous cell carcinoma	5 (14.7)
Transitional cell carcinoma	4 (11.7)
Malignant mesenchymoma	4 (11.7)
Clear cell and sarcomatoid variant	2 (5.8)

Laboratory Investigation

Hematuria was the most common abnormal laboratory finding and found in 61.1 % of the patients. Anemia was the second most common finding, followed by elevated serum alkaline phosphatase. Half of the patients with elevated alkaline phosphatase did not have any liver or bony metastasis found by radioimaging studies. None of the patients had erythrocytosis.

Distant metastasis was found in the majority of the patients (52.7 %). Sixteen patients had distant metastasis at initial presentation and 3 developed distant metastasis. Eight patients with disease progression had single site metastasis with 3 patients developing lung metastasis, 3 bone, 1 soft tissue and 1 central nervous system (Table 3). Eleven patients had greater than one site for distant metastasis. The details of the sites of metastasis are shown in Table 4. The most common sites for distant metastasis in renal cell carcinoma were bone (52.6 %) followed by lungs (47.4 %), soft tissues (26.3 %) lymph nodes and the liver (21 %), respectively. Central nervous system metastasis were found in 2 patients. One patient had epidural cord compression and 1 patient had cerebral metastasis.

Table 2. Initial presenting symptoms of renal cell carcinoma.

Presenting symptoms	Number of patients	Percentage
Flank pain	18/34	50 %
Hematuria	15/34	41.7 %
Weight loss	14/34	38.9 %
Symptoms of Metastasis	13/34	37.1 %
Fever	7/34	19.4 %
Flank mass	7/34	19.4 %
Classic Triad	3/34	8.3 %
Incidental finding	2/34	5.6 %

Table 3. Patients with RCC and with distant metastasis.

Organ	Isolated metastasis (%)	Associated with other sites (%)	Total number of metastasis (%)
Bone	3/8 (37.5)	7/19 (36.9)	10/19 (52.6)
Lung	3/8 (37.5)	6/19 (31.9)	9/19 (47.4)
Soft tissue	1/8 (12.5)	4/19 (21)	5/19 (26.3)
Liver	-	4/19 (21)	4/19 (21)
CNS	1/8 (12.5)	1/19 (5.3)	2/19 (10.5)

Table 4. Number of sites of metastasis in RCC.

Organ	Number of sites	Percentage
Bone	10/30	32.3
Lung	9/31	29.0
Soft tissue	5/31	16.1
Liver	5/31	16.1
Central nervous system	2/31	6.5

Histology (Table 1)

Histologic diagnosis was performed with surgical resections or fine needle aspirations. Clear cell carcinoma was the most common histology diagnosed in our series. Renal vein invasion was detected in seven cases. The mean diameter of the primary renal tumor was 8.65 cm (range 1-20 cm).

Treatment

1. Treatment of primary tumor Surgery was performed in 19 patients. Two patients had metastatectomy in addition to the primary tumor resection. Resection of the primary tumor was not performed in fifteen cases because of the presence of distant metastasis at presentation. Among the surgical procedures performed, radical nephrectomy was done in nine patients, nephrectomy in nine other patients and one patient received only tumorectomy secondary to the very small size of the primary tumor of 1 cm.

2. Treatment of metastasis. Out of the total of nineteen patients with distant metastasis, only eight received treatment for distant metastasis. Metastatectomy was performed as the sole treatment in two patients, the other with lung metastasis and one patient with epidural cord compression. Laminectomy was performed in the patient and the final pathological diagnosis was clear cell carcinoma. In this patient, renal cell carcinoma was found later and a radical nephrectomy was done. This patient was still in complete clinical remission one year after diagnosis. Laminectomy plus radiotherapy was performed in one case with epidural metastasis and spinal cord compression. This patient was lost to follow-up after completion of treatment. Whole brain radiotherapy was performed in one case of cerebral metastasis as a palliative treatment. Four other patients received chemotherapy with 5-FU and interferon as a palliative treatment, and 2 patients died with progressive disease at 5.4 and 12.6 months after treatment. One patient had stable disease and lived at least 24 month s before being lost to follow-up. The last patient survived 6.03 months after the initiation of treatment with a duration of response of 4.5 months.

Relapse and Patterns of Failure

Out of nineteen patients with RCC, 4 developed recurrence diseases (1 local recurrence, 1 local plus distant metastasis, and 2 distant metastases). The median disease free survival (DFS) rate was 17.25 months (range, 3.8 - 36.47). The recurrences developed in one patient with stage III disease and one patient with stage IV. In the other two patients, the initial staging catagories were unknown because the patients had been treated in other institution and came to King Chulalongkorn Memorial Hospital due to recurrent diseases.

Survival and Cause of Death

Among 34 patients , 8 were lost to follow up, two were stage 1, one was stage III and five patients was stage IV diseased. Complete follow up data was available for 26 patients, nine patients were alive without disease, two patients were diseased and fifteen patients died. The details according to the final status and staging of the disease are shown in Table 5.

Table 5. Patient's status during last follow-up according to their stages of the RCC.

Status	Stage I	Stage III	Stage IV	Unknown
Alive without disease	1	4	3	1
Alive with disease	-	-	2	-
Death	1	1	13	1
Lost to follow up	2	1	3	1

The overall median survival rate of patients with RCC was 12.85 months (range 0.07 - 68.43 months). The median survival for stage III disease was 12.97 months and for stage IV 10.14 months. Five year survival rates for all stages of the disease were 35 %. Median survival was 18.5 months in patients with metastatic disease that received treatment., compared to only 1.25 months in patients without treatment. The most beneficial effects from treatment derived from metastatectomy that yielded a median survival of 37.9 months. A summary of survival by stages of disease and treatment is shown in Table 6. The survival curve for all stages of the disease is shown in figure 1. Until recently, most patients usually died from this disease. All patients that developed metastasis during the course died.

Table 6. Summary of the median survival determined by stage of the disease and treatment received.

Stage	Treatment	Number of patients	Median survival (month)
Stage I	Nephrectomy	4	- *
Stage II	-	0	-
Stage III	Nephrectomy	6	12.97
Stage IV			
- Total	-	21	10.14
	1. Metastatectomy	2	37.9
	2. Chemobiologic therapy	4	12.01
	3. No treatment	13	1.25

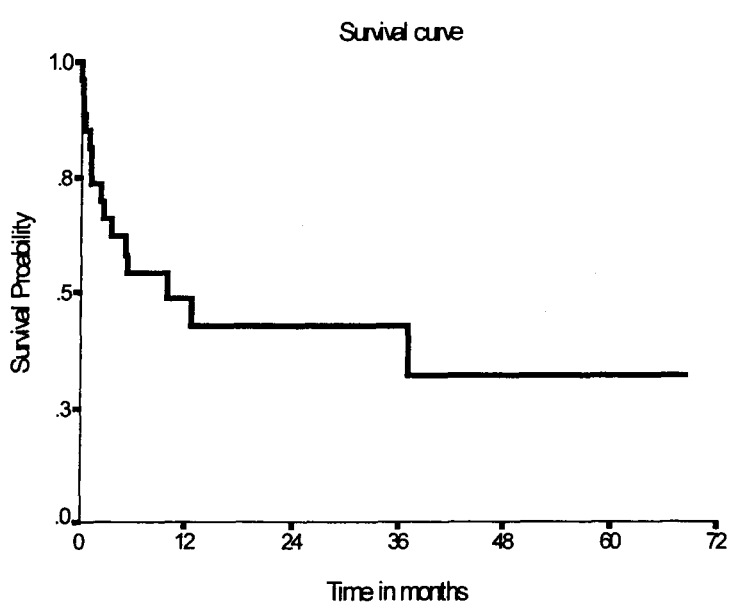

Figure 1. Survival curve of patients with renal cell carcinoma (N = 34)

Discussion

Thai RCC patients have a greater preponderance to be males than in Western populations, (7.5 :1 versus 1.5:1). More than half of the patients presented with metastatic disease. Only 11.1 % presented with stage 1 disease that was confined to the kidney. Common initial symptoms were flank pain, hematuria and weight loss. The symptoms and signs of the classic triad of RCC including fever, flank pain and palpable flank mass were found infrequently. The rate of incidental diagnosis was quite low and contrasted with other series.[4,5] Paraneoplatic syndromes such as polycythemia, elevated serum alkaline phosphatase and humeral hypercalcemia of malignancy were found infrequently. Among the paraneoplastic syndromes we found elevated serum alkaline phosphatase without definite liver or bone involvement. We did not find polycythemia and humeral hypercalcemia of malignancy. In addition, we did not observe the familial form of renal cell carcinoma even in patients who were young and had bilateral diseases.

There are some differences between our series and other series. At Chulalongkorn Hospital the most common site of distant metastasis was bone, followed by lung and soft tissue, lymph nodes and liver respectively. In Skinner's series,[6] the most common sites were pulmonary metastasis, soft tissue and bone.

Patterns of failure following surgical resection of RCC after treatment was reported by Rachel et al in 1994, [7] Among 172 patients who received definite surgical therapy, 36 patients relapsed, 6 developed local relapse and 30 developed distant metastasis. The rate of recurrence after treatment in that series was 21 %. the same proportion was found in our series (4 in 19) and 75 % of our patients failed at distant sites. Therefore, adjuvant systemic therapy after curative resection may be of value, especially in patients with adverse prognostic factors such as large tumor size, [2] advanced disease, lymph node involvement [8] and renal vein extension.[9]

Because of majority of our patients were stage IV disease, the overall median survival was rate only 10.14 months. The overall median survival rate for all patients was 1.85 months. Notably, the median survival of stage IV disease who received treatment were better than 18.5 and observation, 1.25 months, respectively. Although the major difference in the median survival rates between these two groups may be due to selection bias, only patients with good performance status and few sites of involvement were eligible for some forms of treatment. Metastatectomy in patients with single metastatic foci was the best form of treatment and achieved a median survival of 37.9 months.

Therefore, metastatectomy should be considered and offered to suitable patients with distant metastasis in such patients with single and resectable metastasis. However, limited numbers of patients can receive such treatment. In non-surgical candidates with a good performance status, chemobiologic therapy may be considered rather than offering only supportive care because the median survival of distant metastatic patients who received such treatment and responded to the treatment was better than those who did not.

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