Diagnosis, Treatment and Prognosis of Renal Cell Carcinoma

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Tsuchida, S., Sugawara, H., Harata, T., Yamaguchi, O. and Arai, S. Diagnosis, Treatment and Prognosis of Renal Cell Carcinoma. Tohoku J. exp. Med., 1974, 113 (4), 319-328 — Seventy patients admitted to the Tohoku University Hospital during the period from 1959 to 1973 with renal cell carcinoma were studied with regard to clinical and histologic features. Angiography, pyelography and scintigraphy were most contributory to diagnosis. The overall survival rate was 44% at 3 years, 39% at 5 years, and 35% at 10 years. Excluding those patients who exhibited metastasis at the beginning of treatment, the 3-year-survival rate was 78%, 5-year 69%, and 10-year 61%. Concerning clinical symptoms, prognosis was unfavorable for patients with a combination of fever and raised ESR. Although the pathologic staging of tumor growth correlated better with survival rate than the histologic grading of malignancy, both were important determinants in predicting prognosis of individual cases. ——

The incidence of renal cell carcinoma in a given population is relatively low. For instance, over a period of 13 years only 1.8% of all urological patients admitted to the Tohoku University Hospital proved to have this disease (Harata et al. 1973). Furthermore, when a patient finally visited the clinic his status was often so advanced that the operation could no longer be carried out, thereby making a thorough statistical analysis of the problem virtually impossible. This rather widespread dilemma has in turn led to the wide variety of opinions concerning diagnosis, treatment and prognosis offered by leading experts. This study is a statistical compilation of renal cell carcinoma cases treated over a 14-year-period at the Tohoku University Hospital.

MATERIALS

Between 1959 and 1973, 84 patients with renal cell carcinoma were admitted to the Hospital. Fourteen cases underwent no operation of any kind because their status was far advanced. Other 9 had extensive metastasis so that only an exploratory biopsy was

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possible on the primary tumor. The remaining 61 patients underwent radical nephrectomy. A complete follow-up study was done on patients in the latter two groups. The survival rate was calculated using the method of Ederer et al. (1961).

**Results**

**Clinical observations**

Males outnumbered females by 4.6:1. In 22 cases, a combination of gross hematuria, pain and an abnormal mass — the so-called “classic triad” — was noted. In 25 cases, there was a combination of hematuria and pain. Hematuria and abnormal mass were presented in 36 cases and there were 40 patients with only hematuria. One patient had secondary polycythemia on admission (hematocrit >50%, hemoglobin >15.5 g/100 ml) but anemia (hematocrit <33%, or hemoglobin <10 g/100 ml) was a commoner finding noted in 10 cases. Two male patients showed varicocele on the left side.

**Diagnosis**

Three diagnostic approaches; radiologic examination, scintiscanning and exfoliative cytology were utilized.

*Radiologic findings.* The plain abdominal film may show an abnormal profile of the kidney or, less commonly, generalized unilateral enlargement of the kidney. These abnormalities were discovered in 39 cases, 5 of which showed calcification figures, too. Intravenous urography and retrograde pyelography showed abnormalities in 68 patients. In 18 cases pyelograms could not be obtained by intravenous urography although retrograde pyelography was successful in 12 of these 18 cases. The pyelographic findings included deformed elongation of the renal pelvis and calyces in 41 cases, partial defects of the pelvis and/or calyces in 32, hydronephrosis in 7, and abnormal ureteral displacement in 4.

Angiography was applied to 58 cases. Using percutaneous femoral artery catheterization the selective renal arteriography was performed in 38 cases, the aortography in 4, and the translumbar aortography in 16. Abnormal findings were obtained in 57 cases. Pooling signs were observed in 48 patients, and displaced or divergent intrarenal arteries in 36.

*Scintigraphy.* Thirty-three patients were subjected to this examination. In 13 cases there were no signs of isotope uptake in the entire kidney. In the remaining 19 cases, a cold area was detected. From these results, renal scintigraphy was considered to have been useful in the diagnosis of renal cell carcinoma in 32 cases.

*Exfoliative cytology.* Papapanicolaou examination which is widely used in gynecology for detection of tumor cells, was performed on 35 patients. Of these 9 showed positive results.

**Metastases**

Thirty out of the total 70 cases showed solitary or multiple metastases: 23 to the lung, 5 to the bone, 2 to the lymph node, 1 to the mesenterium, 1 to the liver
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and 1 case to the cerebrum. In the group showing lung metastasis there was 1 patient upon whom segmental resection of the lung was performed. He died 5 years later. In the case of cerebral metastasis the focus was removed from the cerebrum. The patient has remained well for 6 months.

Treatment

Radical nephrectomy was performed on 61 of the 70 patients. Lumbar nephrectomy was carried out in 38 cases, thoracoabdominal nephrectomy in 5, and transperitoneal nephrectomy in 18.

The weights of the removed kidneys were as follows; less than 200 g in 9 cases, 200-500 g in 33 cases, 500 g-1 kg in 7 cases, and heavier than 1 kg in 4 cases. The average weight was 623 g.

Chemotherapy was performed on 40 patients. In 39 cases 5-fluorouracil was given 250 mg bi-weekly totaling 3.5 g and Chromomycin A3 3 mg bi-weekly totaling 21 mg. In 1 exceptional case intra-arterial continuous infusion was performed for 10 days before the operation. The patient died 7 months later.

Prognosis

Of the patients who underwent surgery, 59% survived for 1 year after the operation, 44% lived at least for 3 years, 39% 5 years, and 35% more than 10 years.

Clinical symptoms

Pyrexia. The cases were divided into 2 groups for comparison, the first 45 cases showed a slight fever lower than 37.5°C or a normal temperature, and the second 25 cases exhibited a fever higher than 37.5°C. The survival rate of the first group was 68% at 1 year, 60% at 3 years, 52% at 5 years; while that of the second group was 44% at 1 year, 27% at 3 years, 27% at 5 years (Fig. 1).

Erythrocyte sedimentation rate (ESR). The cases were again divided into two groups; the first group showed an ESR level of less than 30 mm/hr (38 cases) and the other greater than 30 mm/hr (42 cases). The survival rate for those with the lower ESR was 84% at 1 year, 76% at 3 years and 70% at 5 years; while for the raised ESR group 23% at 3 years, 20% at 5 years (Fig. 2).

In order to compare the survival rates among the patients with and without clinical symptoms, a test of independence was made using the paired $\chi^2$ test. The results obtained from a comparison in the 3- and 5-year survival rates showed a poor prognosis for the patients with pyrexia and/or a raised ESR ($p<0.01$ at 3 years, $p<0.02$ at 5 years).

Chemotherapy

Of 38 patients without metastasis, 24 underwent both nephrectomy and chemotherapy, whereas 14 underwent only nephrectomy. Their prognoses are shown in Fig. 3. There was no difference in the survival rates of the two groups, which made it difficult to draw any definite conclusion concerning effectiveness of chemotherapy.
Pathologic staging

The scheme of pathologic staging proposed by Robson et al. (1968) was employed for evaluating the results of treatment. In this method of evaluation, patients were divided according to four stages of development which were based upon specific pathologic involvement.

Pathologic Stage I. Tumor confined to the kidney; perinephric fat, renal vein and regional nodes are negative (13 patients).

Pathologic Stage II. Tumor involving the perinephric fat but confined within Gerota's fascia; renal vein and regional nodes are negative (20 patients).

Pathologic Stage III. Tumor involvement of renal vein and/or regional nodes, with or without vena cava or perinephric fat involvement (7 patients).
Pathologic Stage IV. Distant metastases secondary to renal cell carcinoma present on admission, or histologic involvement by tumor of contiguous visceral structures (30 patients).

Fig. 4 shows the correlation between the pathologic stages and the survival rates. Definite statistical differences in the 3- and 5-year survival rates between Stage II and III were proved ($p<0.02$). Definite differences were also proved between Stages I-II group and III-IV group ($p<0.01$). No significant difference could be observed between Stage I and II or between III and IV. The results from these comparisons indicate that the patients of Stage III and IV have markedly lower survival rates than those of I and II.
Histologic classification

The histologic appearance of renal cell carcinoma varies from case to case in terms of size, shape and staining characteristics of the tumor cells. An attempt has been made to classify the tumors based on these differences in nuclear and cytoplasmic structures. Since it was impossible to obtain sufficient tumor specimens from 8 patients who underwent an exploratory biopsy, 62 of the 70 patients were classified. For the classification of nuclei the method of Skinner et al. (1971) was used, and the tumors were grouped according to the lowest degree of differentiation.

Grade 1. Nuclei are indistinguishable from those of normal tubular cells.

Grade 2. Nuclei are often pyknotic, and slightly irregular in shape but only slightly enlarged and without abnormal nucleoli. Since the differences between Grades 1 and 2 are often difficult to distinguish, they are here regarded as one group (26 cases).

Grade 3. Nuclei are moderately enlarged, irregular and pleomorphic, often with large nucleoli, but there are no bizarre forms (29 cases).

Grade 4. Bizarre, giant nuclei are numerous (7 cases).

The relation between nuclear grade and survival rate of the total 62 patients is shown in Fig. 5. Among the patients included in Grades 1–2, the survival rate was 75% at 1 year, 58% at 3 years and 58% at 5 years, but among those in Grade 3 58% at 1 year, 47% at 3 years and 37% at 5 years. In statistical comparison for the 3-year survival rate between Grades 1–2 group and Grade 3 group the difference was not clear, whereas for the 5-year survival rate there was a significant difference between the two groups ($p<0.02$). The differences between Grade 3 and 4 with regard to the 3- and 5-year survival rates were also significant (each $p<0.001$).

Of 37 patients without metastasis the survival rate for Grades 1 and 2 was 92% at 1 year and remained constant thereafter (Fig. 6). For the Grade 3 patients, the survival rate was 78% at 1 year, 63% at 3 years and 50% at 5 years.

![Fig. 5. Nuclear grade and survival rate of total 62 patients.](image)
The survival rates for those with metastases are shown in Fig. 7. In Grades 1 and 2 the survival rate was 22% at 3 years, while the survival rate of those in Grade 3 was very low. All Grade 4 patients died within 1 year.

Based on the grading method of Claes (1963), tumors were histologically classified depending on cell types. Since most of tumors showed a mixed cell picture, i.e., cells of different types occurring in the same tumor, the grouping was arranged according to the lowest degree of differentiation.

*Grade I.* Tumors consisting only of highly differentiated clear cells (15 cases).

*Grade II.* Tumors with intermediary cells as their least differentiated component (35 cases).
Grade III. Tumors with plasmic cells as their least differentiated cell type (12 cases).

The survival rate of the total 62 patients is shown in Fig. 8. Among the patients in Grade I, the survival rate was 92% at 1 year, 73% at 3 years and 73% at 5 years; in Grade II, 59% at 1 year, 51% at 3 years and 38% at 5 years; and in Grade III, 33% at 1 year and 17% at 3 years. Differences between Grades I and II in the 3- and 5-year survival rates were significant ($p<0.02$, $p<0.001$). The difference in the 3-year survival rate was also significant between Grades II and
Fig. 10. Cell type and survival rate (with metastasis).

R III (p <0.05). However, there was no clear difference between Grades II and III in the 5-year survival rate. As shown in Fig. 9, for patients without metastasis, the survival rate of Grade I remained constant at 100% over a 10-year-period, while those of Grade II and III were considerably low. For patients with metastasis, the differences in survival rate among these three grades were not clear at least for the first 2 years. However, only patients in Grade I lived more than 5 years (Fig. 10). Therefore, both nuclear and cytoplasmic gradings although limited in value, correlated to a considerable degree with the ultimate prognosis.

DISCUSSION

The observation of the 70 patients involved in this study was carried out in terms of three points; clinical symptoms, pathologic staging and the grading of histologic patterns.

In addition to local symptoms which form the classic triad, i.e. pain, hematuria and palpable tumor, other unspecific clinical features, such as pyrexia and high erythrocyte sedimentation rate (ESR) were also found in a number of cases. Since the pyrexia may be attributed to the absorption of necrotic material from the tumor or the formation of pyrogenic substances in the tumor, as suggested by Böttiger (1960), Claes (1963), as well as by others, the survival rate and the incidence of pyrexia seem to be related directly. Several authors have also pointed out that high ESR value is found in patients with renal cell carcinoma. According to Claes (1963), raised ESR appeared most often in patients with tumors containing plasmic cells, and indicated a poor prognosis. The results of this study also showed a definite relationship between incidence of pyrexia and/or raised ESR and unfavorable prognosis.

A number of writers have dealt with instances where a tumor has extended
beyond the renal capsule. Their conclusion was that, regardless of the treatment, such cases showed very poor prognosis and were usually terminal. In instances where the tumor invasion reached the renal vein and vena cava, prognosis was always poor. None of our patients who exhibited these conditions survived more than 3 years.

While virtually all investigators agree that pathologic staging is important in prognosis there is much controversy as to the importance of histologic grading. As Skinner et al. (1971) described, histologic grading is notoriously difficult to perform reproducibly and depends largely on personal experience and understanding of the categorical criteria. In this study we have tried to simplify the grading by utilizing the nuclear morphology proposed by Skinner et al. (1971) and the cytoplasmic classification of Claes (1963). The results of this approach were gratifying. To a considerable degree prognosis correlated with both histologic grading and pathologic staging and both served as important determinants in the clinical course. The chance of survival for patients with renal cell carcinoma of a low grade histologic classification was larger than that for patients of a high grade. Even in Stage IV with metastasis, the patients of Grades 1 and 2 tended to have a much lower mortality rate.

Therefore, it is the conclusion of this study that any patient showing solitary metastasis should undergo nephrectomy, and in cases where the nuclear morphology of the renal cells is normal and the tumor consists only of pure clear cells, further aggressive treatment of the metastasis seems justified, and longer survival for the patient can be expected.

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References