Radiol Oncol 2007; 41(2): 64-71. *doi:10.2478/v10019-007-0012-y*

Kidney cancer

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Background. *The purpose of this paper is to present the epidemiology, diagnostic workup and treatment of renal cell carcinoma (RCC) with an emphasis on the Slovenian epidemiological data. RCC represents 2% of all cancers and is the third most common genitourinary tract tumour. It most frequently occurs among people of ages, between 50 and 60 years. Male patients are more prone to it than female. A number of environmental, occupational and genetic factors have been found to be associated with the development of RCC. Patients often have nonspecific symptoms and this is the reason why for half of them the disease is already metastatic when diagnosed. The most common sites of metastases are lungs (75%), followed by soft tissues (36%), bones (20%), liver (18%), skin (8%) and central nerve system (8%). In the evaluation of RCC multiple diagnostic procedures are needed with obligatory image diagnostics.*

Conclusions. *Radical nephrectomy is still the mainstream treatment of localized disease. Nephron sparing techniques have been used in cases, where radical operation would result in an anephric patient. Efficient adjuvant therapy has not been discovered yet. Until recently interpherone and interleukin were the only known effective treatments for metastatic disease, but now new and more efficient biologic agents are being discovered. The most important prognostic factor for survival is stage at the beginning of treatment. The 5-year survival rate is 95% for patients with stage I disease, 88% for stage II, 59% for stage III and 20% for stage IV.*

Key words: carcinoma, renal cell – epidemiology – diagnosis – therapy; nephrectomy; survival analysis

Epidemiology

General notes

Renal cell carcinoma RCC (e.g. hypernephroma, Grawitz's tumour) accounts for approximately 2% of all cancers. It is the third most common genitourinary cancer. The other two are prostatic and bladder cancer.[1] Over the past 65 years its incidence has been constantly growing with an annual rate of 2-4%.[2,3,4] The reason for this rise is unknown.[3] This type of cancer is more common among people of age between fifty and seventy years. Male patients are more prone to it than female patients.[2] The ratio male to female patients is 1.5 : 1.[3,4] People in urban environments a have higher incidence of RCC than those in rural.[4]

Received 3 May 2007
Accepted 18 May 2007

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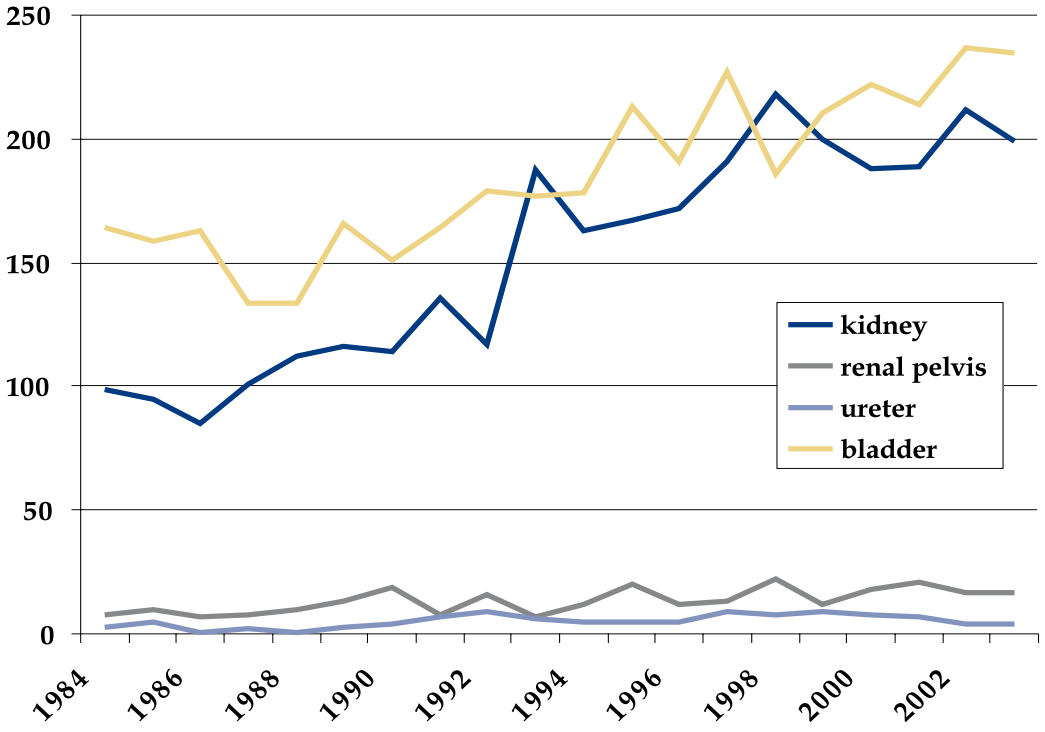

Figure 1. Newly diagnosed urinary tract tumors by site (1984-2003).

Slovenian epidemiological data

Data from the Cancer registry of Slovenia show that in the past twenty years the number of kidney cancers has been constantly rising as has the number of bladder cancers, while the number of newly diagnosed tumours of renal pelvis and urether remained approximately the same during this period (Figure 1).[5]

In the year 2003 there were 9997 newly diagnosed cancers in Slovenia (5026 of them among men and 4971 among women). In the same year the number of new cases of renal cancer was 193 (121 male patients and 72 female). Incidence for 2003 was 12,4 for males and 0,7 for females. Figure 2 shows the number of new renal cancers by gender.[5]

Renal cancer is the tenth most common cancer among Slovenian males and accounts for 2.4% of all male cancers. Others, in order by incidence, are: lung cancer, colorectal cancer, prostate cancer, head and neck cancer, melanoma, bladder and pancreatic cancer. Kidney cancer is not among the ten most frequent cancers in females, which are: breast cancer, cancer of the skin, colorectal cancer, cancer of the uterus, lung cancer, cervical cancer, stomach cancer, ovarian cancer, melanoma and non Hodgkin lymphoma.[5]

The average age at diagnosis is 55 to 60 years and the ratio of the male to female patients is 1 : 1.5,[5] which is the same as the general average reported in literature.[3,4]

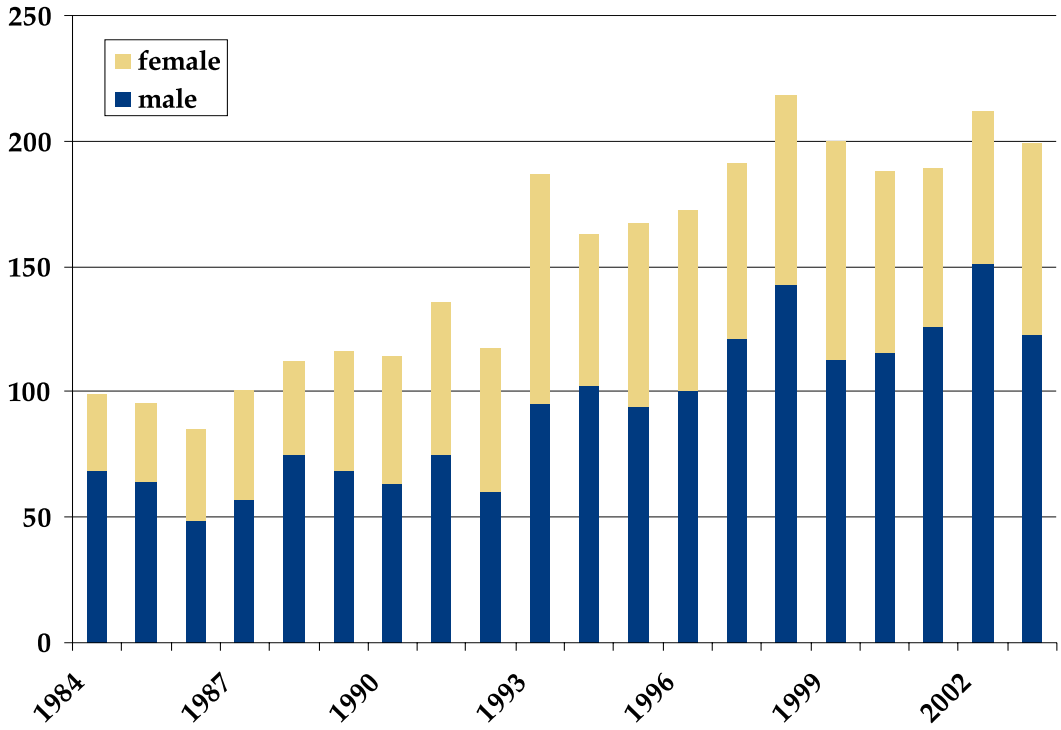

Figure 2. Number of newly diagnosed kidney cancers by gender (1984-2003).

Risk factors

A number of risk factors have been associated with RCC.[1] One of the most important is tobacco use. It is estimated that 30% of RCC in men and 24% in women are associated with smoking.[4] Exposure to some environmental factors can also lead to the development of RCC. These factors are exposure to cadmium, thorium dioxide, asbestos and petroleum products. People in certain professions are more at risk (e.g. leather tanners, shoe workers and asbestos workers). Other risk factors are hypertension, obesity, and long term use of analgesics, particularly those containing phenacetin.[1,2]

A special group of patients are those with end stage renal disease. These patients have a 100-fold greater incidence of RCC which is associated with development of acquired polycystic disease and the hyperplasia of the epithelium in these cysts.[4]

The relation between these factors and the development of RCC is weak, so that primary prevention seems to be quite ineffective. An effective screening system has not been developed yet, because of the relatively low incidence of RCC and the lack of simple diagnostic procedures.[2]

RCC occurs in sporadic and hereditary form. The most studied form of hereditary RCC occurs as a part of von Hippel-Lindau syndrome (VHL). VHL syndrome is a hereditary cancer syndrome caused by a mutation of the VHL gene. Affected individuals are at risk of developing tu-

mours in a number of organs including the kidney.[3,4] As many as 28-45% people with von Hippel-Lindau disease develop RCC.[1] In hereditary syndromes, people are affected at a younger age and tumours tend to be bilateral. More renal cancer occurs among people with autosomal dominant polycystic kidney disease and with tuberous sclerosis.[4]

Natural history

RCC may spread by local infiltration trough the renal capsule to involve the perinephric fat and Gerota's fascia or may grow directly into the renal vein (21% of cases) or vena cava (4% of cases). Lymph node metastases are most often found in the renal hilar, paraaortic and paracaval nodes.[1]

At the time of diagnosis, the disease is localized in 45% of patients, locally advanced in 25% of patients and metastatic in 30% of patients.[1,4] About half of patients with RCC develop metastases some time in the course of the disease. The most common site of metastases are the lungs (75%), followed by soft tissues (36%), bones (20%) liver (18%), skin (8%) and CNS (8%).[1]

Spontaneous regression of the tumour has been reported. The reason is probably immunogenic. The same phenomenon was observed with metastases after nephrectomy. The enthusiasm vanished when the review of literature showed that less than 1% of the patients experience it. This is the reason why nephrectomy is not recommended for this purpose any more.[1,4]

Pathologic classification

RCC is a tumour of the renal cells which develops from the proximal renal tubular epithelium.[4] The most common histological diagnosis is clear cell carcinoma which represents 85% of tumours.[3,4] Others are: papillary carcinoma (10%), chromofobic carcinoma (5%), carcinoma of Belliniy's duct (<1%) and the extremely rare carcinoma of medullary cells.[2,3]

Presentation

For almost half of patients the disease is advanced at the time of diagnosis. Most of them have some nonspecific symptoms like fatigue, weakness, nausea, night sweating and fever.[2,3] The classical triad which consists of flank mass, haematuria and pain in the lumbal area is rare, present only in the 1-5% of patients. It is a sign of advanced disease.[2,3] The most frequent symptom is either gross or microscopic haematuria.[1]

In some cases a large tumour growth has been reported. Such tumours can grow to the retroperitoneum without causing any symptoms.[4]

Lately more and more RCC are being discovered incidentally, while patients have some form of radiological diagnostic procedure. These tumours have a better prognosis because of the lower stage at detection.[1-4]

Less frequently patients present with signs or symptoms resulting from a metastatic disease, like bone pain and pulmonary symptoms.[3]

One of the most common signs is anemia due to haematuria or haemolysis. It has been observed in 30-88% of patients with RCC. Other signs are polycitemia, nonmetastatic hepatic dysfunction and acquired dysfibrinogenemia.[4]

RCC can also cause paraneoplastic symptoms. A lot of substances have been detected at an elevated concentration in patients with RCC: parathyroide like hormones, erythropoietin, rennin, gonadotropins, placental lactogen, prolactin, enteroglucagon, insulinlike hormones, adrenocorticotropic hormone and prostaglandins.[1]

Diagnostic workup

Image diagnostics is a part of the initial workup. Beside ultrasound examination, the mostly recommended are CT (with and without the contrast) or MRI of the abdomen and pelvis. CT is a very good method for the assessment of the lymph node status. The use of CT contrast has improved its sensitivity in detecting very small tumours. MRI is preferred to CT in cases where involvement of the inferior vena cava is suspected or instead of the CT when there are contraindications to the administration of the contrast material. When there is suspicion of the involvement of the inferior vena cava, an US with colour flow Doppler should be performed to determine the position of the tumour thrombus and to help the surgeon with the surgery planning.[3,4] US has replaced the previously used venacavography. Sometimes other studies are needed to asses the tumour, like intravenous pyelogram, renal arteriogram and cyst puncture with fluid cytology.[1]

For the optimal staging and planning of the surgery multiple diagnostic procedures are recommended.[4]

Imaging of the chest, either CT or radiography should be performed for assessment of the stage of disease.[3] When a patient complains of bone pain or has an elevated serum alkaline phosphatase, the suggested test is a bone scan which is not performed routinely otherwise. The same holds for the CT or MRI of the brain, which is to be performed if brain metastases are suspected. PET is not considered as a routine diagnostic procedure.[3]

Treatment

Treatment of localized disease

Surgical treatment is considered the only effective treatment for the localized disease. The preferred operation is a radical nephrectomy which consists of removal of the kidney, perirenal fat, regional lymph nodes and ipsilateral adrenal gland. The removal of the regional lymph nodes is not a therapeutic procedure, but is being performed for staging purposes. Patients, who have metastases at their lymph nodes, tend to sub sequentially relapse with a distant metastases despite lymphadenectomy.[3,6]

Nephron sparing surgery (NSS) was originally considered only when radical operation would result in a patient requiring dialysis, such situations are:[3]

– RCC in a solitary kidney,
– Bilateral synchronous RCC,
– RCC in one kidney and inadequate functioning of the other.

Recently NSS gained a role in the treatment of small tumours (less than 7 cm in diameter) with equivalent results to the radical nephrectomy. Not all tumours are appropriate for NSS, but only those in the upper or lower pole and in the peripheral location.[3]

After surgical treatment 20-30% of patients experience a relapse, most commonly in the lungs. The median time to relapse is 1-2 years after surgery. Time to relapse is associated with the length of survival after the relapse.[3]

Adjuvant systemic treatment proved not to be effective and the same holds for adjuvant radiation therapy. Patients, to whom adjuvant radiation therapy has been administered, did not have a better survival or locoregional disease control compared to the non-irradiated patients despite characteristics which in other cancers require adjuvant radiotherapy. These are: incomplete tumour resection or metastatic lymph nodes found at the operation. This leads to the conclusion that after the nephrectomy observation of the patients is the only reasonable option.[3]

Treatment of advanced disease

Advanced disease (stage IV) is incurable and the intent of therapeutic proceedings is to prolong life, to reduce patient's symptoms and to improve the quality of life.[3]

Patients with resectable RCC and a solitary resectable metastasis are candidates for nephrectomy and metastasectomy. This holds for patients with synchronous discovery of NCC and metastatic site and also for the patients who develop metastases after neprhrectomy. Sites of metastases which are amenable for such management are bone, brain and lung. Most patients treated with metastasectomy experience a relapse at some time. However, some long disease free intervals have been detected.[3]

Some patients with metastatic disease benefit from cytoreductive surgery before the start of chemotherapy. These are patients with lung metastasis only, patients with a good performance status and those with good prognostic features.[3]

Kidney cancer is one of the few cancers in which systemic chemotherapy and hormonal therapy do not have a substantial benefit. The reason for this seems to be a big expression of the p glycoprotein. This is a protein in the membrane of the renal tubules and renal cancer. The function of this protein is to expel toxic lypofilic substances from the cell, and only those chemotherapeutics that are not the substrate for this glycoprotein, have some effect.[2]

Until recently the only effective systemic treatment was with interferone-α or IL-2. In both of these drugs the response rate is 30%, the median survival is 13 and 12 months respectively. These drugs have substantial undesirably side effects, which can be acute or chronic.[2]

Recently the FDA (Food and drug administration) approved 2 kinase inhibitors sunitinib and sorafenib for the treatment of metastatic RCC. Escudier *et al*. presented the results of a phase III study with sorafenib. Patients who progressed on the immunotherapy were randomized into two groups, those who received sorafenib and placebo. Progression free survival was 24 versus 12 weeks. Some degree of response was observed in 78% of the patients. Good response rates were also observed with the administration of sunitinib. Motzer *et al*. reported a 40% partial response rate, when sunitinib was administered as a second line treatment after patients progressed on the cytokine therapy. In another study patient were randomized to receive either a sunitinib or IFN-α as a first line therapy for methastatic disease. The median progression free survival was 47.3 in the sunitinib group and 24,9 weeks in the IFN group and the objective response rates were 35,7% and 8,8%.[3]

Other patients not suitable for the systemic therapy require a good palliative care which should include good pain management, and some of the procedures like radiation of painful methastatic sites or palliative nephrectomy in the cases of severe haematuria.[3]

Survival and prognostic factors

Survival of patients differs according to the initial stage of the disease which is the most important prognostic factor.[2] Patients who have tumours confined to the kidney, have much better prognosis than those with locally advanced or methastatic disease at the time of diagnosis. Table 1 presents 5-years survival rates in different stages of the disease.[1,4]

Metastatic disease is incurable and the duration of survival depends on the number and site of metastases.[2] Patients who have bone and CNS metastases, have a shorter survival time than patients with other metastatic sites. Other factors that influence (shorten) the survival are:

Table 1. 5-year survival of patients with RCC according to stage of the disease

Trial	Total No. of patients	Stage I	Stage II	Stage III	Stage IV
		5-years survival rate			
Robson	88	66	64	42	11
Skinner	309	65	47	51	8
Waters	130	51	59	12	0
Boxer	not known	56	100	50	8
McNichols	506	67	51	34	13
Cherrie	not known	not known	not known	50	0
Selli	115	93	63	80	13
Bassil	not known	91-100	not known	not known	18
Golimbu	326	88	67	40	2
Javidan	381	95	80	59	20
Dinney	314	73	68	51	20
Guinan	337	100	96	59	13
Kinouchi	350	96	95	70	24
Tsui	643	91	74	67	32

– bad patient performance status
– high degree of weight loss
– short disease free interval from the beginning of the treatment to the manifestation of metastases and
– some laboratory findings like high LDH values or low haemoglobin level.[2,4]

Another prognostic factor is the grade of the tumour. As expected tumours of the lower grade have a better prognosis.[2,3]

Incidentally found tumours have a generally better prognosis as they are being discovered at a lower stage. Five year survival rate of these patients is close to 100%.[1]

Conclusions

Survival statistics for RCC have not changed for the last 25 years. This is due to the fact that an effective adjuvant therapy for the locoregional disease has not been discovered yet, and that until recently there were only few possibilities of an effective systemic treatment for metastatic disease.[1] With the progression in diagnostics, surgery, new radiotherapy techniques and the discovery of the new biological therapies which are more effective and less toxic, major changes of the therapeutic results are expected. In spite of this, RCC still remains a big challenge for future research.

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