New clinical features in renal cell carcinoma
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In 1883 Gravitz published the first description of a kidney tumor, which he termed a hypernephroma. Much later the more appropriate name renal cell carcinoma (RCC) was introduced. At the moment RCC accounts for 2-3% of all adult cancers. Between 1989, the year of the first report of the Netherlands cancer registry, and 1992 the total number of patients with RCC in the Netherlands increased from 1287 to 1438. For males the incidence increased from 11.6 to 12.5 per 100,000 and for females from 6.3 to 6.6 per 100,000.

The pre-operative diagnostic work-up in patients with a clinical suspicion of RCC has changed, especially during the last decade due to the introduction of ultrasound, CT and MRI. Also the surgical therapy improved from a simple nephrectomy to a radical transabdominal or thoracoabdominal nephrectomy with regional or extended lymph node dissection. Even patients with caval tumor thrombus involvement up to the right atrium can be managed often successfully with extensive surgery. Nephron-sparing surgery, entailing complete local resection of a renal tumor while the largest possible amount of normal functioning parenchyma in the involved kidney remains in situ and vital, is an accepted treatment for RCC when preservation of functioning renal parenchyma is mandatory. For less demanding indications its applicability is under study.

Much research has continuously been focussed on patients with metastatic RCC. At present immunotherapy is an option, but because of the rather low overall response rates (up to 20%), the short duration of response and the side effects, the optimal combination of drugs and the right dose and route of administration is not yet established.

Adjuvant therapy for patients with RCC is under investigation. Adjuvant means that after surgery no macroscopic tumor is left behind with no signs of metastatic disease. A problem for this kind of therapy is the patient selection, which patient may benefit from this kind of treatment. Therefore research to develop more precise prognostic parameters is necessary, being aware that the two parameters in use (tumor stage and grade) are not reliable enough to predict the clinical course.

Also in the field of the pathological investigation of RCC changes have occurred. The WHO classification of renal tumors, based on macroscopic, histological and ultrastructural features, proposes a division into adenomas, carcinomas and other tumors. This classification provides little insight into the clinical behaviour. At present the genetic etiology of cancer is generally accepted. It is caused by mutations in the genetic make-up of the cells. These mutations can be hereditary or acquired during life. A classification based on these genomic changes would be more informative about oncogenesis and clinical behaviour.

Thoenes et al. started with a different approach leading to a classification based on the assumption that the various subtypes of RCC are derived from different cells of origin.
from the different parts of the nephron. Five basic cell types are distinguished: clear cell and chromophilic cell, both derived from the proximal tubule; chromophobic and oncocytic cell, both derived from the cortical collecting duct; and Bellini duct cell, derived from the medullary collecting duct. Three growth patterns, which can be deduced from the tubule, are distinguished: compact, tubulopapillary and cystic. Certain chromosomal aberrations or combination of aberrations correlate with the histological subtyping of RCC. Based on the prognostic potential of the above mentioned cell types and growth patterns, Störkel et al. devised a prognostic score combined with the three usual parameters: Staging according to Robson, tumor grade and the patients age.

In Chapter 1 a current overview is given about epidemiology, etiology and clinical course of RCC. Clinical and pathological diagnosis and staging are discussed as well as the different treatment options. The impact of prognostic factors on outcome is presented.

There is a steady increase in the incidence of RCC. In technologically more advanced countries, with more liberal use of ultrasound and computerized tomography, the increase in incidental RCC is probably responsible for the rising incidence. It is unclear whether the increase in incidental RCC results from an actual increase in the prevalence of the disease or simply from the enhanced detection of subclinical cancer.

In Chapter 2 the recent literature on incidental RCC is studied. Combining the various studies the percentage of incidental RCC rose during the last decades from 10% to 50%. The relative percentage of incidental RCC in Japan is almost 60%. When adjusted for the pathological tumor stage and grade at presentation, the prognosis of incidental RCC is not better than that of symptomatic RCC. From the literature it is evident that incidental RCC has a smaller tumor size and lower stage than symptomatic tumors. Because in incidental RCC the tumor stage at presentation is lower, the overall 5-years survival rate is better. Screening for RCC, because of a better prognosis for incidental RCC, is at the moment with the available techniques not realistic. The most important drawback is the cost associated with screening the population with ultrasound. Certain subgroups with an increased risk for RCC, like von Hippel-Lindau disease, acquired renal cystic disease and renal transplant patients with native kidneys in situ, are candidates for an early detection program. We found in the northern part of the Netherlands an increase in incidental RCC. Between 1977-1987 and 1987-1994 the incidence rose from 33% to 49% with ultrasound as the principal mode of detection. Although the stage at presentation between incidental and symptomatic tumors did not statistically significantly differ, the disease free survival was better in the incidental RCC group (p=0.0159).

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for staging patients with RCC. In patients with an elevated serum alkaline phosphatase a bone scan is advised.

In Chapter 3 the role of duplex Doppler ultrasound (US) in staging patients with RCC is studied by comparing the accuracy and reliability of duplex Doppler US and computerized tomography (CT). Sixty-six patients were evaluated pre-operatively with duplex Doppler US and CT. The results were compared with the surgical and histopathological findings. The tumor stage (pT) was determined correctly with duplex Doppler US and CT in 56 and 50 cases respectively. In 4 patients with nodal disease duplex Doppler US was correct in 2 patients, 1 was false positive. With CT 3 patients nodes were staged correctly and 3 were false positive. Of the 14 patients with vascular tumor thrombi 13 were staged correctly with duplex Doppler US and 12 with CT scan. False positive vascular tumor invasion was seen only with CT. We concluded that duplex Doppler US is at least as accurate as CT scan in the staging of RCC. Also in patients with renal or caval thrombi duplex Doppler US is accurate in establishing the diagnosis and in the determination of the extent of the thrombus.

The value of bone scans and serum alkaline phosphatase (serum AP) in staging patients with RCC was evaluated in 107 patients. In 8 patients (7.5%) the bone scan was true positive for bone metastases. Of these 8 patients only 3 had an elevated serum AP. Thirteen patients had a false positive bone scan. An elevated serum AP had no positive predictive value because 90% (28/31) of the patients with an elevated serum AP had a negative bone scan. We concluded that a routine bone scan for staging patients with RCC without skeletal pain is not efficient, even not when serum AP is elevated. Serum AP is not a specific marker for bone metastases in patients with RCC.

In Chapter 4 the prognostic value of a new proliferation marker KI-67 in RCC is evaluated and related to cytogenetic aberrations in these tumors. A total of 49 patients with clear cell RCC and cytogenetic analysis of the tumor were studied. Apart from tumor stage and grade, the KI-index correlated significantly with disease-free survival. A higher KI-67 index correlated with a worse prognosis. There was no correlation between the KI-67 index and the presence of numerical or structural chromosomal aberrations. We found the KI-67 index of prognostic significance in patients with clear cell RCC.

Not only proliferation markers have been investigated in RCC, also cytogenetic aberrations may be of prognostic significance in RCC, although data are rare in the recent literature. In Chapter 5 we present the study of the prognostic significance of cytogenetic aberrations. A total of 101 consecutive patients, all with histological proven clear cell RCC,
were studied. Forty-eight patients came from the Department of Urology, Groningen University Hospital, and 53 patients from the Department of Urology, Johannes Gutenberg University, in Mainz.

The effect of tumor grade, TNM stage, number of clonal numerical and structural aberrations, the specific types of chromosomal aberrations, age and country (the Netherlands or Germany) on patient survival was evaluated by a Cox regression model and visualized using Kaplan-Meier curves. Next to tumor grade and stage, the presence of (partial) monosomy 10 or trisomy 16 had a significant poorer prognostic value. A correlation between structural aberrations and prognosis could not be found. Cytogenetic analysis of RCC is valuable because of its prognostic significance when (partial) monosomy 10 or trisomy 16 is present.

Two sisters affected with RCC is a rare finding, and may indicate a hereditary pattern or the presence of other predisposing factors.

In Chapter 6 we describe two sisters presenting with clear cell RCC. Examination for von Hippel-Lindau (VHL) related features and tuberous sclerosis (M. Bourneville) turned out to be negative. Both patients had a normal constitutional karyotype. Cytogenetic analysis of the tumor tissue of both patients showed a translocation involving chromosomes 3 and 5, resulting in loss of 3p sequences and gain of part of 5q. The 5q breakpoints were similar, but the breakpoints at 3p seemed to differ. Allelic imbalance analysis supported these observations. Microsatellite analysis revealed that both sisters inherited different chromosome 3 parental alleles. For chromosome 5 three different haplotypes could be deduced, but the chromosome 5 alleles overrepresented in the different tumor samples were from different parental origin.

So the development of the two RCCs in these two sisters can not be explained by inheritance of other gene defects at chromosome 3p or 5q. Although the chances that two sisters develop sporadic RCC are very low in the presented cases it is probably coincidental or related to another genetic predisposition.

Idiopathic regression of metastasis is one of the features of the unpredictable behaviour of RCC. It can be anticipated in only a very small percentage of cases, mostly "metastatic" lung lesions who disappear after nephrectomy.

In Chapter 7 we report a unique case of a patient with pulmonary lesions and a tumor thrombus in the inferior vena cava with spontaneous regression of the lung lesions and necrosis of the thrombus before any therapy was instituted.

This thesis has made it clear that certain clinical aspects of RCC do change. The value