Introduction

Being the third most frequently occurring urological malignancy, 3 percent of malignant tumours in adults develop in the kidney. The overwhelming majority, 80-90 percent of kidney tumours is comprised by cancer developing from the epithelial cells of the kidney tubules. This kind of tumour which used to be called hypernephroma and currently referred to by the collective term "renal cell carcinoma" (RCC) is the most widely known and frequently occurring malignant renal tumour.

Its incidence is continuously increasing and nearly at the same pace increases its mortality. Renal tumours are the most lethal type of urological tumours. The likelihood of death caused by renal cancer is 40 percent. The expected five-year tumour-free survival rate at the early stage of the disease is 50-90 percent, while in the case of metastasizing tumours is 0-13 percent. 25-40 percent of the cases are symptomless and diagnosed by chance, however, in nearly 30 percent of the cases close or remote propagation can be detected on the first time the patient presents. The male /female ratio is 3.1/1.5, the mean age being 70 years, however nowadays more and more young patients get affected.

RCC develops from the epithelial cells of the kidney tubules. For the histological classification of tumours the "Mainz" system described by Thoenes and the "Heidelberg" histological classification based on genetics are used most widely, which are characterized by clear-cut histological and genetic chromosomal features (74, 75, 80).

The immunogenity of kidney tumours is proven, it is capable of MHC presentation by itself, without APC, which means that it "offers itself" for the immune system. The presence of the presentation, its extent and the ratio of the elements of cellular immune response can be investigated by immunohistochemical methods.

Only radical nephrectomy provides acceptable chances for healing. In selected cases, provided the size of the tumour does not exceed 40 mm, organ-sparing surgery can be performed, although its oncological value is still unproven. In case nephrectomy is only a palliative measure or the tumour could not fully have been eradicated, prior to or following local recidives and prior to the resection of lung metastases supplementary treatments are recommended.

These include mono- or combined therapies of biological response modification. Rarely, in selected cases irradiation may also be considered in combination with other supportive therapies in accordance with the stage of the tumour.

In my research and curative work a most important purpose of my efforts was to elaborate a uniform and accurate diagnostic and therapeutic protocol for patients operated on for kidney tumours and receiving biological response modifying therapy at the Department of Urology of the University Medical School in the Medical and Health Sciences Centre of the University of Pécs.

The present research was aimed at the accurate assessment of the histological picture of patients with progressive metastasizing renal tumours, as well as at the application of biological response modifying therapy. At the same time I also studied the immunogenity and immunopathology of renal tumours, the clinical aspects of various possible therapies and the relations between biochemotherapy and immune response. The investigations concerning the therapy of progressing and already metastasizing renal tumours were focused on five issues:

1. the accurate assessment of histological pictures in renal tumour tissue
2. immune response in RCC tissue
3. the value of the findings of tumour immunological investigations in immune- and biochemotherapy
4. the mutant pVHL protein as a potential target protein
5. biological response modifying therapy of progressive renal tumours

The present thesis contains the findings of this research.

1. Objectives:

1. 1. The accurate assessment of the histological picture in renal tumour tissue

Question 1: To what extent is accurate histological classification a novelty in terms of clinical outcome?

1. 1. 1. My aim of establishing the Pécs Renal Tumour Team in 1992 was to process the molecular biological and immunological aspects of all the renal tumour cases between 1985-2004.

1. 1. 2. I wished to use the histological classification introduced earlier by Mostofi and also to assess the histological picture based on Thoenes (Mainz classification).

1. 1. 3. Furthermore, reconsidering the defects and faults of the Mainz classification by Thoenes, to be the first in Hungary, to switch to the application of the Heidelberg system based on genetic histological classification.

1. 1. 4. To use this brand new classification retrospectively in cases previously classified by Mostofi and Toenes. To carry out this classification in the histological material of nearly all our tumour patients.

1. 1. 5. To prepare a comparative study of this new and the earlier type of classifications.

1. 1. 6. To prove the objective advantages of the clinical application of a new classification, in the future, based on clinical follow-up carried out in close cooperation with the Heidelberg team.

1. 1. 7. To find genetic parameters, which can be used for distinguishing renal oncocytoma from chromophobe RCC.

1. 2. Immune response in RCC tissue

Question 1. 2. Is there such a marker in the tissues of patients having undergone surgery for renal tumour, which indicates immunological defense against the tumour, and how does the immunological recognition of the tumour in the patient work out?

1. 2. 1. While investigating into the immune response my aim was to approach the behavior of the renal tumour and the operation of the defense mechanisms participating in the tumour immunity at the molecular pathological level.

1. 2. 2. To investigate the histological markers in the immune response in renal cell carcinomas.

1. 2. 3. To assess the marginal and intratumoural MHC expression and the presence of CD4, CD8 and CD57 lymphocyte subgroups.

1. 2. 4. To study the phenotype (T, B, Mo) of tissue-infiltrating lymphocytes and the extent of necrosis.

1. 2. 5. To determine the values of HLA-class I and HLA-class II expressions in kidney tumour tissues.

1. 2. 6. To show the major histocompatibility complex (MHC I and II) genes in criostate sections.

1. 2. 8. To classify and statistically assess the findings in accordance with the clinical status and the degree of differentiation.

1.3. The value of the finding of the tumour immunological examinations in immune- and biochemotherapy

Question 1. 3. Is it possible to utilize the findings of immunological investigations in the treatment of patients?

1. 3. 1. The tumour immunological investigations by means of the clinical follow-up of the patients were intended to study the prognostic/predictive value of the histological classification, classical pathological, clinicopathological parameters (grade, stage, metastasis) and immunological parameters in the case of immune therapy (IFN – VBL) as opposed to BronchoWaxom / Decaris -B / D.

1. 3. 2. To statistically evaluate the relationship between the histological picture and clinical malignancy.

1. 3. 3. To investigate the correlation of prognostic data (met., std., grd., TIL, TIC) in accordance with the clinical status.

1. 3. 4. To compare the indicators originating from the prognostic data (WHO status, std., grd., TIL, TIC)in metastasizing and non-metastasizing cases.

1. 3. 5. To find a parameter prognostically applicable in daily clinical routine, which may prove predictive in the case of biological response therapy.

1. 4. The mutant pVHL protein as a potential target protein

Question 1. 4. Can pVHL (antigen) play a role in developing clinically effective tumour immunity?

1. 4. 1. My investigations targeting at pVHL protein were intended to find out about the von Hippel Lindau protein expression and its immunological importance of the conventional clear cell subtype of RCC.

1. 4. 2. To investigate into the immunogenity of VHL protein in paraneoplastic nephropathies associated with RCC.

1. 4. 3. To compare the simultaneous presence of tumour antigen expression (pVHL), antigen presentation (MHC I-II) and effector mechanisms (tumour-infiltrating lymphocytes and immune complexes).

1. 4. 4. To determine the specificity and sensitivity of the immunehistochemical method and to carry out a comparison with histologically classified renal tumour sub-classes.

1. 5. Biological response modifying treatment of progressive tumours.

Question 1. 5. Investigations performed to find out about the efficacy, the extent of side-effects and tolerability, and also to decide whether the risk of the therapy used in out-patients was higher than that could have been in in-patients?

1. 5. 1. Relying on the biological response modifying therapies of progressive renal tumours I wished to gain experience in the immune- and immunochemotherapies of progressive renal tumours.
1. 5. 2. I wished to investigate into the efficacy and safety of Intron-A - as opposed to - Intron-A + Vinblastin in a multicentric randomized prospective study.
1. 5. 3. I wished to study the toxicity and tolerability of biological response modifying therapies.
1. 5. 4. I wished to find out if the out-patient treatment presents a risk for the patients and if yes, how high it is.

2. Hypothesis:

2. 1. The accurate assessment of the histological picture in renal tumour tissue
2. 1. 1. The cytomorphological classification by Thoenes, which is capable of identifying various types of tumours originating from individual parts of the kidney is more transparent than the "Mostofi" histological classification.

2. 1. 2. The Heidelberg histological classification based on genetic considerations is the most applicable histomorhological classification in the case of histological processing renal tumours.

2. 1. 3. The applicability of various histological classifications has an influence on the prognosis.

2. 1. 4. In the case of renal tumours the categories used earlier can be re-classified and their values be calculated from the aspect of prognosis.
2. 1. 5. From the prognostic point of view there is a statistically detectable positive correlation between the accurate determination of the clinical status and the accurate histological classification.

2. 1. 6. Earlier the assessment of the oncocytomas was not correct in each case, in some cases it was regarded as an entity with a worth prognosis.

2. 1. 7. At the same time some cases classified as versions of clear cell renal tumours appeared in prognostically more advantageous classes.

2. 1. 8. The phenotype classification based on the Heidelberg system can be reproduced on the basis of reclassified cases.

2. 1. 9. Rare renal tumour types can be more accurately identified by means of the Heidelberg system.

2. 1. 10. The assessment of the dignity of the papillary tumours and the molecular progression of non-papillary RCC is safe when relying on the chromosomal differences.

2. 1. 11. The genetic alterations lying in the basis of the Heidelberg system, as opposed to the morphological variety developing in the course of tumour progression, remain constant.

2. 1. 12. In the course of the histological differentiation between chromophobe RCC and RO certain specific alterations may be of help.

2. 2. The accurate assessment of the histological picture in renal tumour tissue

2. 2. 1. In the overwhelming majority of renal tumours a highly expressed immune activity can be observed, which can be a decisive factor in the response capability of the immune therapy.

2. 2. 2. In renal tumour tissues in criostate sections antigens belonging to HLA -class I-II and the major histocompatibility complex (MHC I and II) detailed immunological assessment can be revealed using the indirect immunoperoxidase method.

2. 2. 3. The presence of the cellular antitumour immune response, its phenotype and the antigen presentation can be determined.

2. 2. 4. The presence of immune deposits and antigen presentation has a prognostic value.

2. 2. 5. As a result of the exogenous administration of cytokines (IFNα, γ, IL2) used for the immune therapy of RCC, in addition to the enhancement of NHC-class I-II expression, NK activity, T-cell differentiation and growth, "co-stimulation" and CTL activity stimulation takes place.

2. 2. 6. The presence of cellular immune elements determines the efficacy of cytokine stimulation.

2. 3. The value of the findings of tumour immunological investigations in immune- and biochemotherapy

2. 3. 1 The clinical prognosis of oncocytomas genetically entirely distinct from renal tumours is better than it was thought previously.

2. 3. 2. The sarcomatose histological subtypes of renal tumours can be regarded as indicators of unfavorable prognosis.

2. 3. 3. From the prognostic point of view the presence of the metastases (TIL, TIC) is a primary determining factor, which shows statistical correlation with the local clinical status (T) and the degree of differentiation of the tumour (G), and also with the immunological parameters (TILL, TIC).

2. 3. 4. The presence of tumour immunity parameters TIL and TIC has a predictive value in patients undergoing IFN + Vinblastin therapy and in BronchoWaxom / Decaris immune modulated patients.

2. 4. Mutant pVHL protein as potential target protein

2. 4. 1. Some of the tumours originating from the epithelial cells of the kidney VHL (von Hippel Lindau gene) can be characterized by mutant expression.

2. 4. 2. The mutant pVHL protein can be a potential target protein.

2. 4. 3. The efficacy of the specific immune therapy depends on the expression of human leucocyte antigens (HLA-I and most importantly HLA-DR), and on the presence of TIL and TIC (tumor infiltrating lymphocytes and tumour immune complexes).

2. 4. 4. The pVHL protein in clear cell conventional RCC (CCRCC) occurs in combination with HLA-expression and TIL and TIC immune phenomena

2. 4. 5. Using the immunohistochemical method the response capability in some types of CCRCC can be predicted.

2. 5. The biological response modifying therapy of progressive renal tumours

2. 5. 1. For the patients the interferon Vinblastin combination therapy is the only opportunity in cases when no other successful intervention is possible.

2. 5. 2. In the cases of renal tumours classified as Robson III.-IV. The use of immune response modifiers can result in remission in 20-30% of the cases.

2. 5. 3. A combined administration of cytokines and cytostatics improves the remission rate and the simultaneous use of the two drugs does not impose a greater burden on the patient.

2. 5. 4. The therapies are tolerable for the patient and the out-patient therapy does not include a higher risk than the same intervention under institutional conditions.

3. Materials and method

3. 1. The application of the cytomorphological "Mainz classification" by Thoenes in the histological classification of renal cell carcinomas.

3. 1. 1. Histological classification according to the cytomorphological categorization by Thoenes was performed in 137 renal tumours randomly selected from the cases that underwent surgery between 1994-1996.

3. 1. 2. In addition to the histological character (clear, chromophil, chromophobe, “Bellini duct“, oncocytoma, pleomorph, mixed form) I also studied the form of growth (compact, tubulopapillary, cystic or mixed), the differentiation of the cells comprising the tumour and their relation as compared to the clinical stage of the patient.

3. 2. Reclassification (thesis I.)

3. 2. 1. In adult renal cell carcinomas three benign and four malignant entities can be identified using the Heidelberg Classification System, which have characteristic karyotype differences, histologically different appearances and they prognostically also mark different groups (45, 46).

3. 2. 2. The reclassification of 335 tumours removed from patients operated on between 1988-1997 by my collegues and by myself was performed on hematoxilin-eozin painted sections.

3. 2. 3. Of these cases 144 were also included in later immunological studies.

3. 3. The differentiation between oncocytoma and chromophobe cellular RCC (thesis I)

3. 3. 1. In 48 nephrectomy cases the tumorous and the adjacent intact kidney tissue sample was assessed in native tissue samples.

3. 3. 2. The occurrence of polymorphic microsatelite markers was studied in 27 oncocytoma and 21 chromophobe RCC tissue samples. Our observations focused on the genetic alterations, which are usually assessed in the case of renal tumours.

3. 3. 3. Localization and sequence analyses were performed using the MapView method taken from NCBI data base (http: www. ncbi.nlm.nih.gov./MapView).

3. 4. An expressed tumour infiltrating lymphocyte invasion can be observed in renal cell tumour tissues, whose phenotype varies (thesis II)

3. 4. 1. The phenotype and location of tumour infiltrating lympocytes in our material were analysed in detail.

3. 4. 2. The histological classification of 42 tumours removed between 1991-1994 was performed using the usual histological and immunehistochemical methods.

3. 4. 3. T lymphocyte infiltration, the location and activity of helper (CD4) and cytotoxic (CD8) lymphocytes were investigated.

3. 4. 4. The intratumoural location and activity of "natural killer" (NK) cells were investigated.

3. 5. The expression, location and activity of the major histocompatibility complex proteins (MHC I and II) functioning independently in renal tumour tissues and developed by the tumour tissues can be determined in renal tumour tissues (thesis III.)

3. 5. 1. The expression and location of the major histocompatibility complex protein (MHC I and II) were determined in renal tumour tissues.

3. 5. 2. Tissue samples were taken from the margin between tumour and intact tissue of kidneys removed in the course of 456 cases of tumour nephrectomy performed between 1994-1997. All the tumours included in this study were classified as a conventional subtype of RCC (13).

3. 5. 3. The indirect immunoperoxidase method was used in the case of 62 randomly selected samples to determine HLA class I-II, the major histocompatibility complex antigens (MHC I and II) in criostate sections.

3. 5. 4. CD4, CD8, CD 57 positive lymphocytes were detected using the indirect immunoperoxidase system. B - lymphocytes (CD45RB), memory T lymphocytes (UHCL-1) and monocytes (MAC 387) were determined by monoclonal antibodies using the usual 3-step ABC method.

3. 6. The investigation of prognostic immunehistochemical markers in renal tumours treated with immune therapy (thesis IV.)

3. 6. 1. The MHC-dependent "killer" cells, i.e. cytotoxic T-lymphocytes (CTL) and CD57 positive “natural killer” (NK) cells can preserve their immunogenity against the original tumour cells for several years after the removal of the primary tumour (11).

3. 6. 2. The investigation of native tumour tissue and samples obtained from the tumorous-intact margin in its vicinity was performed in the case of 132 randomly selected patients operated on renal cell cancers.

3. 6. 3. Polyclonal anti-human IgG, IgA, IgM and complementer (C1q, C3) antibodies were investigated with direct fluorescent isothiacyanate (FITC) technique on criostate sections by acetone fixation.

3. 6. 4. The VHL protein was detected with secondary biopolimer reagent by using the immunoperoxidase method. The ABC- immunoperoxidase method was used to detects the tumour infiltrating lympocytes (UCHL - 1), the MHC-I beta-chain (β_2 - microglobulin) and the HLA-DR δ-chain (MHC-II).

3. 6. 5. The specificity and sensitivity of the immunohistochemical method was assessed, the comparison of the results with the histologically categorized renal tumour classes was performed and the specificity and sensitivity of the methods were defined.

3. 7. The investigation of the efficacy and safety of Intron-A vs. Intron-A -Vinblastin treatment, a two dimensional, randomized, multicentric study (thesis V.)

3. 7. 1. Using interferon alpha 2 in monotherapy and/or combined with Vinblastin could result in a higher remission rate than any other previous forms of treatment. The observation of tolerability and efficacy of immune and biochemotherapy started at the beginning of the 1990s in this country was performed by a multicentric two dimensional randomized study with the participation of 12 centers. 112 of the 124 patients included in this study could be assessed (90.3%). 56/51 patients were treated with IFN-α monotherapy, while 68/61 patients with IFN-α +VBL biochemotherapy.

3. 7. 3. The randomized selection and the inclusion of the patients were performed according to strict criteria. The complete and partial remission rate was used to assess success, while tolerability and safety were assessed by registering the side-effects of toxicity indicators in accordance with WHO criteria.

3. 7. 4. Findings obtained in the two dimensional study were compared and the statistical relations of the incidence of side-effects in the two-dimensions were investigated.

4. Conclusions

4. 1. 1. We were the first to perform massive histological reclassification of kidney tumour tissue, determining its value essential in the prognosis.

4. 1. 2. Our investigations proved that there is a statistically assessable positive correlation between the accurate correct determination of the clinical status and the accurate histological classification.

4. 1. 3. Our study provided evidence that in 70% of the cases oncocytoma was regarded as an entity with a lot more unfavorable prognosis.

4. 1. 4. Cases categorized as a version of clear cell renal tumour, several times were classified into the more favorable chromophobe class.

4. 1. 5. Based on the reclassified cases we found that the phenotype classification based on the Heidelberg Classification System can be reproduced and more than 94% of the tumours can be classified into the group characterized by appropriate genetic and biological features.

4. 1. 6. Rare types of kidney tumours can be more accurately identified with the Heidelberg Classification System, which also provides an opportunity for clarifying disputable cases, where the histological recognition of the tumour is indispensable for the prognosis.

4. 1. 7. The assessment of the dignity of the papillary tumours and non-papillary RCC molecular progression is safe when chromosome differentiation is analysed. The genetic alterations lying in the basis of the Heidelberg Classification System as opposed to the morphological variety observed in the progression of the tumours, remain constant.

4. 1. 8. The histological differentiation between the chromophobe RCC and RO has led to false results several times. We found evidence that with the detection of certain genetic changes the chromophobe RCC tumour cells can safely be differentiated from RO.

4. 1. 9. We were the first to publish the observation that the complexity of the exchange of alleles of chromosomes 1, 2, 6, 10, 13, 17 and 21 is characteristic of chromophobe RCC only.

4. 2. 1. We were the first to perform detailed immunological survey of the renal tumour tissue in Hungary to show HLA class I-II and major histocompatibility complex (MHC I and II) antigens on criostate sections (6-7 μm), using the indirect immunoperoxidase method.

4. 2. 2. We were also the first to investigate the phenotype and the presence of the elements of the antitumour cellular immune response in the individual tissue samples, and

also the antigen presentation in relation to the clinical status, the histological typology (Grade) and the extent of necrosis.

4. 2. 3. Our study gave evidence that the antitumour immune response in kidney tumour tissues is extremely strong. The co-expression of MHC-II could be observed in almost each study material, which suggests that cellular kidney tumours are capable of presenting the antigen, however the process for some reason is analysed, i.e. it either cannot start or gets blocked while in progress.

4. 2. 4. It is only the MHC presentation that seems to have prognostic value.

4. 2. 5. Our investigations suggest that the occurrence of CD4-8-57 cells in RCC tissues is around 30%.This ratio was found to be even lower when MHC expression and the simultaneous presence of the cells were investigated (23, 18, 14%). The objective of the exogenous administration of cytokines (IFNα, γ, IL2) used for the treatment for the immunotherapy of RCC includes enhancement of MHC class I-II expression and the stimulation of NK activities T-cell differentiation and growth, "co-stimulation", and CTL activity. Remission rate of no higher than 30% could be achieved by all the biological response modifying treatment schemes used so far.

4. 2. 6. We think that the lack of cellular immune elements may provide an explanation why a higher ratio of response cannot be achieved by cytokine stimulation. Further investigations were necessary for me to find out to what extent all this can be regarded as a prognostic factor and in what form it can be used in designing and implementing the therapy.

4. 3. 1. The investigations of the correlations of the histological and immunological findings suggested that the clinical prognosis of oncocytomas genetically entirely distinct from renal carcinomas is excellent..

4. 3. 2. The sarcomatose subtypes of renal tumours proved to be extremely bad prognostic factors in the same comparison.

4. 3. 3. Very close correlation was found between the presence of metastases and the clinical outcome.

4. 3. 4. Several times correlations between tumour grade/ stage and clinical outcome and immune parameters and prognostic values proved to be negligible.

4. 3. 5. The primary determining factor in the prognosis was found to be the presence of metastases, which shows only weak correlation with the local clinical status (T) and the extent of tumour differentiation (G). No correlation whatsoever exists between that and the immunological parameters (TIL, TIC).

4. 3. 6. No predicted value could be associated tumour immunity parameters TIL and TIC in the case of patients receiving IFN + Vinblastin treatment, while in BronchoWaxom / Decaris immune modulated patients TIL proved to be negative, while TIC a positive prognostic factor.

4. 3. 7. B / D-therapy stimulates humoral immune reactions, brings about TIC positivity and at the same time blocks T-1 cellular "helper" type of T activation, while in the alpha - interferon therapy (IFN-α), due to its direct tumour killing effect, neither TIL nor TIC alteration can be observed.

4. 4. 1. Of the tumours originating from the epithelial cells of the kidney the conventional subtype of the clear cell type (CCRCC) can be characterized by the mutant expression of VHL (von Hippel Lindau gene).

4. 4. 2. Mutant pVHL protein as a potentially target protein (antigen) may play a part in the development of a clinically effective tumour immunity.

4. 4. 3. A further prerequisite of the efficacy of specific immune therapy is the presence of human leucocyte antigen expression (HLA-I and most importantly HLA-DR) and TIL and TIC (tumor infiltrating lymphocytes and tumour immune complexes).

4. 4. 4. Our investigation suggest that simultaneously with HLA expression TIL and TIC immune phenomena the pVHL protein can be determined with high specificity in the so called "immunogenic" clear cell conventional renal cell carcinomas (CCRCC). Our immunohistochemical findings may provide explanation for the clinical immunotherapeutic response capability of patients with CCRCC, on the other hand they may offer help prior to starting the immunotherapy - by way of an immunohistochemical analysis of the resection of the removed kidney tumour - with the selection of the potentially well responding patients.

4. 5. 1. Remission rate achieved by monotherapy is 19%, it is worth considering while in the combined group the remission rate is only 23%, which is lower than the data in the literature.

4. 5. 2. Vinblastin should be used in the form of bolus injection.

4. 5. 3. The best results could be achieved in the case of lung metastases.

4. 5. 4. The most frequent side-effect was an influenza like syndrome, the gravest rate being G3.

4. 5. 5. No significant difference in toxicity could be found in either branch of the two dimensional study.

4. 5. 6. No disadvantages of the out-patient treatment mode could be identified.

4. 5. 7. IL-2, IFN α-2, 5-FU treatment is recommended for low-risk patients in good general state.

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