New diagnostic and prognostic examinations of malignant tumors of urinary bladder

Ph.D. theses

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Introduction

Urinary bladder carcinoma is rather frequent not only in Hungary but also in all over the world. Moreover, bladder carcinoma is the second leading malignant tumor in urology. In the case of early recognition of the disease, we can achieve acceptable life quality with curative methods. One of the most important issues in cancer research are early diagnostic methods and developing the diagnostic procedures. Likewise these issues, the prognostic assessment, the prediction of life expectancy and other therapeutic possibilities are frequently chosen research topics as well.

Just like in all cases, it is inevitably important when the bladder tumor is recognized. Besides time factor, the categorization of bladder tumors shares high importance. We can set up two categories: non-muscular invasive and muscular invasive; moreover, these could be divided into subcategories. The two main categories are so different from one another especially in behavior, prognostic factors, life expectancy and metastases that we can talk about two different entities. In addition, the survival times in the two groups are outstandingly different (95% vs. 50%). This shows us their behavior as well.

Although most of the urothel-cell carcinomas could be categorized in one of the two groups, there are some of them sharing both features: for instance, non-muscular invasive tumors with pT1, G3 and Tis. This validates the fact that these kinds of tumors are the most difficult to be handled fittingly. Now the most important task would be to define which tumor is going to appear and progress in the future. Namely, this would be very useful for planning therapy and the follow-up of patients.

Although recent researches have been carried out to describe the molecular changes in tumorous urethel-cells, there is not a clear explanation for the changing of normal epithelial cells. It would be very ideal to calculate the short as well as long term possibilities of progression and recidivism on the basis of clinical and pathological data. Molecular marker examinations have been used during the clinical researches, however, they are not really used in everyday practice. We cannot define the proper biological behavior of these tumors yet. The research of bladder tumor is therefore primarily aimed to diagnose them as early stage as possible and to differentiate the stages of the bladder tumor progression.

Aims of the thesis

The investigations of our work group who deals with bladder tumors pointed at the two basic targets. First, we applied the diagnosing methods of bladder tumors (such as tumor markers, genetic examinations in our clinical practice), moreover, we had the results compared with the international examinations. Secondly, our task aimed at mapping associations in fine tissue structures of bladder tumors, life expectancy and progression. Due to the fact that these are totally different groups, we would like to present the data separately - the clinical diagnostic and prognostic examinations:

1. *The examination of tissue polypeptide antigene concentration in patients with bladder carcinoma*

The polypeptide antigene concentration was examined in belignant tumors with both the dissimilar differentiated tissues and the stages as well as in patients being healthy. Moreover, our examinations have also carried out in people having not malignant bladder tumors.

We would have liked to find answers to the question if serum tissue polypeptide antigene could be used as a marker or not, furthermore, we intended to present if this polypeptide antigene serum could anticipate the muscular invasive progression of the disease.

2. *The detection of bladder cancer via urine analysis by fluorescent in situ hybridization (FISH) method*

We have carried out several examinations with fluorescent in situ hybridization method which is especially designed for the detection of bladder tumor. With this new technology we aimed at evaluating the appropriate specificity and sensitivity and refining the methodology of the medical control in order that we could achieve better results, moreover, realizing if invasive cystoscopy could be brought about with FISH techniques.

3. *Microsatellite investigations in patients with bladder tumor*

We had the goal to validate the diagnosis of bladder cancer with the analysis of microsatellites in human urine. In general, we planned to elaborate a methodology with increasing the specificity and sensitivity of examining methods. Moreover, we carried out experiments to prove that much better results could be achieved with the utilization of the supernatant of the urine instead of the precipitate. It was also important that we should take the tumor category (non-muscular invasive or muscular invasive) into consideration when regarding the detection limit results of the microsatellite analyzing methods.

4. Occurrence of the inverted papilloma in the bladder

We treated the patients who were diagnosed with inverted papiplloma at the Urology Clinics of Semmelweis University with prospecitve monitoring and with the help of these therapies we aimed to get answer for the query of the prevalence concerning the malignity and recrudescence of the disease. In addition, we also wanted to respond the question that how tense had to be the follow-up of the patients.

5. Investigations of the expression of E-cadherine in bladder carcinoma

The strength of expression of E-cadherine which is one of the most important molecule in cell adhesion were examined in histology segments of the patients with bladder tumor. We would have liked to present the correlation among the expression of E-cadherine and the stage or the degree of differentiation of tumor, the number of recidives as well as the survival. Namely, we were on determining if the investigations of the expression of E-cadherine could be utilized for clinical prognosis regarding the aspects of the outcome of the disease.

6. *Investigations of the fluctuations in the expression of Claudine in the bladder cancer*

We had opened up the composition of the expression patterns and the extent of the expression in urotheliums of normal bladder, in harness of inflamed bladder and in different stages of bladder cancer with dissimilar tumor stages. During these examinations we wanted to make for the mapping of the distribution of claudine expression in human urothelium. Furthermore, with revealing these data we wanted to get closer to the understanding of the role of cell connection structures such as claudine in the formation and progression of bladder carcinoma. As for our investigations, we payed particular attention to the non-muscular

invasive bladder tumors with high risk (pT1G3) as this group of tumors composes the clinical borderline between radical cystectomy and TUR surgery. However, the expected characterization of claudine expression in recidival and non-recidival tumors could help with setting up prognoses of the pTG3 group of tumors more precisely in the future research.

Methods

In order to attain our goals, we carried out three clinical diagnostic tests and three prognostic assays as well. The patients participating in our survey were treated and operated at the Urology Clinics of Semmelweis University between 1st January 1996 and 31st December 2006. They had malignant bladder carcinoma and as for controlling group members, patients were healthy or had other benignant urological illnesses. The investigations of pathologic histology and immunohistochemistry have been carried out in the Institute of Pathology II at Semmelweis University and the molecular experiments were made both in the Pathological and Experimental Cancer Research Institute I and at the Molecular Pathology Laboratory of Institute of Pathology II.

Diagnostic investigations of bladder cancer

No. 1. Clinical diagnostic examinations: Measuring the tisssue antigene polypeptide concentrations in patients with bladder carcinoma

At the Urological Clinics of Semmelweis University we examined the levels of serum tissiue antigene polypeptide (TPA) in case of 39 patients with bladder cancer between March and October in 1998. For these assays, we got the materials in trasurethalis resection or radical cystectiomia. Determining of the TPA was carried out from plasma before the surgery with the usage of immunoluminometric method by BYK Sangtec. According to the factory standards, the upper limit of the range of reference in case of these experiments was 65 U/l. There were two controlling groups consisting of healthy and patients with benignant urological diseases.

No. 2. Clinical diagnostic examinations: Detection of the bladder tumor from urine with fluorescent in situ hybridization method

The urine probes of 43 patients with histologically verified urothel cells were verificated with the help of 6 samples of patients with inflammations, 2 with hyperplasia and 2 with benignant lesions (papilloma) as for controlling. The method of the FISH check was the following: we measured the first and the second urine of the patients per a day as a probe with the reagents of UroVysion (Vysis-Abbott, Downers Grove, IL). The sample considered to be positive if there were no specific signal for 9p21 locus in at least 12 cells or at least two have been multiplied from the peri-centrometric regions of chromosomes 3, 7 or 17 (CEP3, CEP7, CEP17) in at least 4 cells which namely equals with 3 or more signals.

No. 3. Clinical diagnostic examinations: Examinations of losing an allele of microsatellites

Regarding our examinations of microsatellites, 44 blood, urine and tumorous tissue samples were utilized which were from patients operated at the Urological Clinics of Semmelweis University. To have controlling samples as well, we collected blood and urine probes from 16 healthy (normal controlling) and from 20 patients with non-tumorous urological diseases (urological controlling). The urine samples were separated into the supernatant and the precipitate. Concerning the DNS isolation of the disposed samples with High Pure PCR Template Preparation Kit (Roche, Indianapolis, MN, USA), we amplified 12 microsatellite region in PCR reactions which could have been found in 6 different chromosomes. Our results corresponded well with the data from the relating literature.

Prognostic tests of the bladder carcinoma

No.1. Prognostic test: Prospective follow-up examinations of patients who were operated with the reason of vesical inverted papilloma

In the Urological Clinics of Semmelweis University we operated twelve patients because of inverted papilloma between 1st January 1998 and 28th February 2005. As for the follow-up of the patients, we carried out urine analysis in every three months, ventral ultrasound inspection as well as bladder examination with speculum. Although, two years after the surgery we made probes only once a year. Summing up the period of the follow-up treatments, the average was 52,1 months (4-84 months).

No.2. Prognostic tests: The investigation of the expression of E-cadherine in bladder carcinoma

The intensity of the expression of E-cadherine was examined in case of 50 patients who had over with their first transurethral resection (TUR) with primer bladder cancer in the Urological Clinics of Semmelweis University between 1st January 1996 and 1st February 1997. In addition, we made hematoxilin-eosin coloring and immunohistochemical reactions with monoclonal antibody against anti-human-E-cadherine on sections from samples in paraffin oil and fixated with formalin. In tumors, we determined its stage and grade. As a result, in 2004, after the follow-up of the patients for eight years, we analyzed the survival and the chance of following recidives as a function of the expression of E-cadherine.

No. 3. Prognostic tests: The investigation of the expression of Claudine in bladder carcinoma

We examined and compared the expressions of the peptide claudine-1, -2, -3, -4, -5, -7, -10 and mRNS in samples from 48 patients operated with bladder cancer and with 8 non-tumorous diseases, altogether from 56 samples. We categorized the probes into groups of normal, inflamed, TaG1, T1G1, T1G2, T1G3 and T2G3. Moreover, we subdivided group T1G3 into two parts according to the emerge of the recidive. The proteine expression was determined with the method of immonohistochemistry: with monoclonal anti-mouse claudine-2,-4,-5 and polyclonal anti-rabbit antibodies. Furthermore, the expression of mRNS was determined in real-time quantitative RT-PCR with the usage of SYBR Green Green PCR Master Mix (AB4309155, Foster City, USA).

Results

No. 1. Clinical diagnostical examinations: Measuring the tisssue antigene polypeptide concentrations in patients with bladder carcinoma

Concerning the TPA values in patients with bladder tumors, we found them to be high in various ratios in different stages. In addition, we discovered the highest values in the muscular invasive (T2-T4) tumorous cases and the average value was 177,6 U/l (53,9-736,2), moreover, the range of reference has been exceeded by the 73% of all cases. Under the circumstances of non-muscular invasive bladder cancers (Ta, T1) 55% and 58% of all values were over-ranged. Therefore, we could not point out positive correlation between the stage of stages of tumors and the level of serum TPA. For the controlling group of patients, the average TPA value found to be 47,6 U/l (45,8-58,0), while it was 54,2 U/l (36,4-78,2) in the

group of benignant tumorous diseases. In the special case of that two patients in whom the histological investigations resulted in papilloma, the level of serum TPA was above the upper level of the reference range.

No. 2. Clinical diagnostic examinations: Detection of the bladder tumor from urine with fluorescent in situ hybridization method

As for the detection with fluorescent in situ hybridization method in urine samples, we compared the chromosomal deviations which could be characteristic for tumorous cells with the histological diagnosis had been valued after the transurethralis biopsy. We considered the specificity as 100% and the sensitivity as 87%. 34 cases were found to be positive with the reagent UroVysion and all these cases has been validated as bladder tumor. Other 16 probes gave negative results. In case of these 16 patients, 5 was regarded as tumor by the further histological process and all of them was non-muscular invasive with pTa stage, furthermore, 3 had the size of exactly or lower than 5 mm. Among the 34 positive cases the two ones in the stage of T1 and other two in T2 with intermediate transitional cell carcinoma, the main genetic lesion was the loss of 9p21 (rate of 12%). As for the remaining 30 occurrence (rate of 88%) including the 3 FISH positive case with Ta stage as well, 3/7/17 multiplications were found. Albeit, to the accumulation of chromosomes 3/7/17 the multiplication of 9p21 also joined and in 7 special cases the multiplication of 3/7/17 was parallel with the deletion of 9p21 in the same cells.

No. 3. Clinical diagnostic examinations: Examinations of losing an allele of microsatellites

Regarding our examinations of microsatellites, 44 samples from patients with bladder cancer were analyzed. As for the 93% of every 3 samples per patient (tumor, urine precipitate, urine supernatant), minimum one difference were experienced. In one hand, the allele losing (LOH) was detectable in 85% of the examined tumor samples with the application of 12 markers of microsatellites. On the other hand, the urine analysis consisted of two separated analytic parts: one was the precipitate analysis which contains cells as well and the other part was analytics of the supernatant with solubility DNS and without any cells. No wonder their sensibility was different: in the supernatant it was 86% (38/44) and in the precipitate 68% (27/40). In addition, the evaluation were also done according to the stages of bladder cancer whereas there is a more significant difference between the sensitivity of the two urine fraction in case of non-muscular invasive tumors (pTa-T1): supernatant 84% (21/25), precipitate 67%

14/21). Our summing up the validated allele losing in the course of the examinations, 9p21 was the locus which was deletioned the most often (46%) followed by 9q32 (34%) and 5q15 (34%).

No.1. Prognostical test: Prospective, follow-up examinations of patients who were operated with the reason of vesical inverted papilloma

Following up the patients, we could not detect the renewal of inverted papilloma or its metastasis except of a 64-year-old man who has macroscopical blood in his urine 13 months after the surgery. However, the elimination of his right-side kidney was appeared in his case-history owing to cirrhosis in kidney caused by chronic pyelonephritis in renal stone. Finally, the carcinoma was confirmed at the distal end of the stump of the urether and we removed the stump of the urether with opened operation. In spite of we were founding non-muscular invasive pT1 G2 transitiocelluralis carcinoma, the patient has been clear of symptoms and recidives for seven years after surgery. For the urine test, ventral ultrasound inspection as well as cytoscopia are used for the other eleven patients and anyway, there were no suspicion of the renewal or malignity of inverted papilloma.

No.2. Prognostic tests: The investigation of the expression of E-cadherine in bladder carcinoma

40 patients attended the urological check regularly. As for the expression of E-cadherine, it was not detected (-) in 13/40 (32%), maintained (+ or ++) in 25/30 (63%) cases and it was doubtful in the other cases. If the intensity of the reaction was the same as the intensity of the standard urothel, it was (++) and when it was maintained but weaker than the standard, it marked as (+). Unfortunately we could not find significant correlation between the strength of the expression of E-cadherine and the level of differentiation or tha stage of tumors.

Even the decrease of the expression showed any correlation with the sexes (in case of male 30, female 34). Moreover, we investigated the development of subsequent recidives in 40 cases and experienced that in 11 (25%) it has really formed, however, even with the utilization of contingency analysis we find no correlation with strength of the E-cadherine expression. Altogether 18 people were exited in the following eight years of the first TUR, furthermore, 13 of them in five years. In 72% (13/18) of the template of the tumors the

expression was maintained (+ or ++) and decreased expression was found only in 27% (5/18). The average rate of survival was not in correlation with the expression of E-cadherine, either.

No. 3. Prognostic tests: The investigation of the expression of Claudine in bladder carcinoma

In comparison with the normal and inflamed bladder, we found decreased claudine protein expression at the different stages of bladder cancer (pTaG1A→pT2G3). In details, the claudine-1 protein expression increases from stage pTaG1 to pT1G2 and it begins to decrease in stage pT2. As for comparison, the claudine-1 protein expression is significantly lower at the group of recidiving pT1G3 than the non-recidive pT1G3. Surprisingly, there was more decreased claudine-4 expression that we found at the other tumor stages than in pTaG1 tumors and at the group of pT1G3 the expression of claudine-4 was higher than in group pT1G2. Bringing the claudine-4 protein expression into comparison, in the recidiving pT1G3 group it was on higher level than in the non-recidiving pT1G3. In tumors of group pT2G3, we found extremely more decreased claudien-4 expression than in both non-recidiving pT1G3 and recidiving pT1G3. Namely, this decrease was more expressed in the recidiving group. For expression of claudine-7, we found decreasing tendency in parallel with the grade and stage (TaG1→T1G3) but after the appearance of the invasion (pT2) the increasing was discovered in relation to the group pT1G3. Moreover, in tumors of pT2G3 the expression of this protein rose significantly opposite to the pT1G3 and non-recidiving pT1G3. On the contrary, we discovered no significant difference between the recidiving and non-recidiving group of pT1G3.

The results of the examinations of RNS expression

During our experiments, we found no significant difference between the claudine mRNS expression of normal and inflamed vesical tissue. Although we experienced arisen claudine-1 mRNS expression in the pTaG1 stage of bladder carcinoma as we compared it with the normal epithelium. The expression of this protein decreases gradually from stage pTaG1 to pT2 as we reported. Our comparison of the recidiving pT1G3 tumors with the non-recidiving came to the conclusion that they showed higher claudine-1 mRNS expression. As for the claudine-4 mRNS expression, in relation with normal epithelium, significantly higher expression could be detected in pT1G1 or in tumors with more advanced stage. Similarly to the protein expression, the expression of claudine-4 mRNS increases in parallel with the decrease of differentiation (G1→G3) and then begins to decrease as the invasion (pT2) takes place. From another respect, the claudine-7 mRNS expression increased significantly in

certain tumor stages opposite to the case of normal epithelium, moreover, this expression shows decreasing tendency with the increase of the grade or stage of tumors from the beginning of pTaG1. Opposite to the protein expression, the claudine-7 mRNS expression increases in the recidiving pT1G3 group while in the non-recidving it does not. Eventually, as it was not detected in case of recidiving group pT1G3 we detected decreased claudine-7 mRNS expression in pT2G3.

Consequences

- The value of serum tissue polypeptide antigene (TPA) was significantly higher in muscular invasive tumors than in non muscular invasive cases. Unfortunately, no correlation could be detected between the grade of differentiation and the serum TPA. As for conclusions, the solely utilization tumor marker TPA is not suffice for diagnostics of bladder carcinomas and for following them..
- Our developments to detected bladder cancer from urine with UroVysion test based on the method of fluorescent in situ hybridization (FISH) resulted a non-invasive methodology with high sensitivity (87%) and with awesome specificity (100%). On the lab checks we experienced pseudo-negative result in only the case of non muscular invasive stage pTa. To reduce the errors due to the alternate quality of urine, the UroVysion check has to be done both with the first urine per day and with the second which is a consequence of the forced fluid intake. Moreover, that must be the reason of the fact that invaluable cases decreased. Despite the method having excellent results, the price and the work demand block the spread of it.
- The allele losing from urine samples is similarly a sensitive and non-invasive method for diagnosing bladder carcinoma. As for the supernatant of the urine, the investigations on DNS without cells are much more sensitive than the probe on the precipitation of the urine. However, these methods have prominent diagnostic results, they cannot permanently take the cystoscopy out from usage.
- In addition, the inverted papilloma is a benign lesion, there are, however, no literature existing with analyzing bigger amount of patients which are in favor of this statement. According to both literature and our results, we suggest patients to be followed up in compliance with pTa G1 bladder carcinomas.

- We investigated the role of the cell-adhesive molecule E-cadherine in the carcinogenity of bladder cancer, moreover, we could not detect any correlation among its expression, the grade or clinical stage of tumors, the sex of the patients, the life expectancy and the renewal of cancer. As different work groups came to entirely different conclusions concerning the topic, more further investigations are frequently needed with analyzing more data of patients in order to get opinion.
- No significant difference could be detected between the inflamed and normal vesical epithelium in the claudine expression. However, compared with the stages pT1G2-G3, the mRNS expression of claudine-1, -4 and -7 decreases in parallel with the progression while the mRNS expression of claudine-2, -3 and -10 increases. Furthermore, the mRNS expression of claudine-1, -4 and -7 decreases when the invasion (pT2) occurs. As for the targeted therapies, claudine-4 seems to be the most promising. From the claudines' point of view, the stage of pT1G3 seems to be a stage between tumors pT1G2 and pT2G3. In recidival cases of the stage pT1G3, the protein expression of claudine-1, -4 and -7 is hihger thus it really could help with making the correct therapeutic decisions in case of this inestimable group of carcinoma. Regarding the further investigations, we are planning to do more experiments to clarify the role of claudines in carcinogenesis.

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