New diagnostic methods of urological tumors

Doctoral (Ph.D.) Theses

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Introduction

The incidence of urothelial carcinoma worldwide increases, being the second most frequent urological tumor. It occurs most frequently in the urinary bladder.

Early recognition is very important for appropriate treatment, more favorable clinical course and better quality of life of the patient.

The recognition of the presence of an UCC is based on clinical examination for haematuria. The diagnosis of UCC is usually based on histological diagnosis

after transurethral resection (TUR).

At present there is no known non-invasive method that could prove the existence of UCC better than cystoscopy, which has a 90-95% sensitivity.

The histological grade of UCC is basically low or high grade. There is important difference between the two groups: low grade lesions are non-invasive for a long time, and the overall survival is longer than 120 months, while high grade lesions tend to be invasive, and when invasive, the overall survival is only about 33 months.

Although low grade lesions might recur, only 10-20 % shows histological or clinical progression . At present, no known method is available, which could show, which of the histologically similar tumors will behave in such a way, showing a need for more aggressive treatment.

Investigations focused on this problem in the past decade were numerous, with conflicting results. Their use is more promising if performed in combination concerning prognostic significance. The results might be also conflicting for the fact, that histological grading and staging of UCC is rather subjective, with relatively high inter- and even intra-observer variability. The examinations of prognostic markers are based on histological diagnosis, so the results based on false histological diagnosis are false as well.

Az E-cadherin a Ca-dependent cell.-adhesion marker, that is responsible for homotypic intercellular connections. It can be found ont he cellular surface, being the member of. zonula adherens. Some authors consider the low expression of E-cadherin of poor tumor-differentiation and early progression.

Epithelial cells protect the species from the external world, or separate tissues.

In the urothelial canal it hampers the back-diffusion of toxic agents.

The epithelial intercellular connections can be different, the most tight junctions are the so-called zonula occludens type ; „tight junctions".

There are also connections of the so-called zonula adherens type, or hemidesmosomes, or so called gap junctions. These play role in the inter-cellular communication. The base of tight junctions are proteins having transmembrane domain (occludin, claudin, junctional adhaesio proteins, tricellulin).

Their structure dinamically changes according to the actual needs of the cells.

Transmembrane or cortical proteins are present – among these there are transcription factors, or tumorsupressor proteins as well.

The skeleton of tight junctions are the so called claudins. They were first described in 1998. At present we know about 27 subtypes. Certain subtypes are organ or tissue-specific. The main difference among claudins is in the two inner loops of the four transmembrane regions.

They play role in tissue development, differentiation and ion-transport.

The most variable part is the C-terminal extracellular loop, extracellular proteins get connection via this region. As certain microorganisms (Helicobacter pylori, Clostridium perfringens) use this loops as receptors, these loops might be the *entrance* for target-specific therapy.

Since different claudin proteins can be shown in tumors of different tissue origin, they are in the focus of numerous investigations.

Aims

Our investigations focused on certain urothelial tumors (benign and malignant) to see, whether there is a difference in the pattern and expression of different cell-junction proteins. We investigated, whether there is any specific difference that that could help in the diagnosis of difficult cases, or help in the estimation of prognosis.

1. Examination of possible association of E-cadherin expression with grade-stage, or prognostics with immunhistochemical methods

We examined the E-cadherin expression with immunhistochemical methods, whether there is any association between E-cadherin expression pattern, and UCC grade, stage, tumor recurrence, clinical progression – overall survival

2. Examination of claudin expression in low and high grade UCC-s.

We examined Claudin-1,-2,-3,-4,-5,-7,-10 proteins and their messenger RNA and Ki 67 proliferation marker expression in low ill. high grade UCC-s, focused on the question, whether

A: is there any difference in expression,.

B.: in case there is , does it bear any prognostic significance.

3. Comparison of the expression of claudins, cytokeratins and Ki67 in non-malignant, and low grade UCC-s

We compared the Claudin -1,-2,-4,-7, cytokeratin 5/6, cytokeratin 20, and. Ki67 protein-expression in urothelial papillomas, inverted papillomas, in grade I (PUNLMP) and grade II (low grade) UCC-s focused on routine diagnostical wiew, and from the wiewpoint of possible estimation of recurrance.

Materials and methods

1. Examination of E-cadherin expression in UCC-s

We examined E-cadherin expression on 40 tissue samples of primary UCC, taken by TUR from patients of the Urological Clinic of Semmelweis University between the 1st of Jamuary 1996. 1st of February 1997. We reclassified the tumors according to grade and stage. We examinde cases that fit to the previously described grade and stage. Grading – at that time – was based on WHO classification of urothelial carcinomas 1973.

We examined E-cadherin expression on 3 mm thick slides taken from appropriate blocks of the cases, with immunohistochemical reaction against E-cadherin antibody.

Semiquantitativ methods were used for evaluation of the strength of the reactions. The results were matched with clinical course (tumour recurrence, progression, etc.). Since our results were basically different from those stated in the medical literature, we repeated our investigations in 2012, on new selected UCC cases. These UCC cases were low and high grade tumors, (GrI-III), with or without invasion (TA-T2).

2. Examination of claudin expression in low and high grade UCC-s.

We examined 103 samples, 86 taken from UCC-s, and 17 non-tumorous controls taken from patients who never had UCC earlier.

We compared the claudin expression in the low and high grade tumors and non-tumorous bladder samples.

We evaluated the immunohistochemical results on conventional slides semiquantitaively and photometriy. We also examined claudin mRNS with reverse transcription. Statistical analysis was based on Statistiva V8.0 (Statsoft Inc., Tulsa, OK, USA) program. Comparison of the expression results were performed by non-parametric ANOVA test (Kruskal-Wallis). Kaplan-Meier method was used for evaluation of overall tmor-free survival. Survival curves were compared by Log-Rank test.

Spearman- correlation test was used to evaluate the results gained by semiquantitative and quantitative analysis. Difference was considered of results showing $P<0.05$.

3. Examination of non-malignant and low grade, non- invasive UCC-s

Claudin-1,-2,-4,-7 protein expression pattern was examined in 80 urothelial tumors resected by TUR, and in 5 non-tumorous bladder tissue. 15 of these were inverted urothelial papillomas (IP), 20 urothelial papillomas (UP), 20 grade I. (PUNLMP), and 20 Grade II. (low grade) UCC-s. Non-tumorous controls were taken from patients who never had UCC earlier.

Immunhistochemical examinations were performed in usual immuno-slides and on slides taken from tissue microarray blocks. Analysis was performed with semiquantitative methods and (4 independent pathologists) and morphometry. Results were examined in the focus of overall survival and the lengths of disease-free overall survival. Statistical analysis was according to described in point 2, concerning examinations of „low/ high grade UCC-s.

Results

1. Examination of E-cadherin protein expression

In 13of 40 cases (33%) E-cadherin reaction was negative. 25 cases (63%) showed +, or ++ positivity. Positivity was equal to normal urothelium or sligthly weeker. No significant association was detected with either grade or stage. Repeated E-cadherin results on another UCC group (low and high grade invasive and non-invasive cases), all cases showed + or ++ positivity, even in cases that showed well and poorly differentiated areas in the same sample (being the same strength in positivity in the same sample). Our previous statement – even though based on immunohistochemical reactions showing completely opposite results- can be sustained.

No association was found neither with the strength of the reaction and overall survival. The repeated E-cadherin reactions were performed on cases of new patients, so no disease and overall survival was possible to examine.

2. Examination of claudin expression in low and high grade UCC-s.

We found membrane positivity in the basal cell layer of the urothelium in the non-tumorous samples. On the contrary, Claudin-4 and Claudin -7 showed membrane positivity in the upper cell layers, that showed diminishing strength towards the mintermediair layers. In some cases Claudin 7 showed strong positivity through the full thickness of the epithelium. Claudin-3, and -5 reactions showed weak positivity in the superficial layers. Claudin-5 – showed positivity mainly in endothelial cells, similar to the results of other working groups. No positivity was observed with Claudin-10 in any of the cases. Ki67 proliferation marker showed occasional positivity.

Those samples that were taken from urocystitis showed significantly higher Claudin-2, and -7 pozitivity than samples taken from non-inflammatory mucosa. Positivity was shown in umbrella cellsa as well, as opposed to other samples.

Claudin-1, -2, -4 and -7 positivity was observed in most tumor-cases. Claudin-3, or -5 reactions showed positivity in some, mostly highly differentiated tumors. Claudin-10 reactions - similar to normal and inflamed urothelium were negative.

UCC-s showed similarly strong reactions at the same locations as was observed in normal urothelium with Claudin-1, -2 and -7.

Claudin-4 positivity was observed in the whole thickness of the epithelium.

Tumor cases showed lowered Claudin-1 expression, and enhanced Claudin-2, -4, and -7 positivity on both protein and messenger RNA level as opposed to inflammatory control samples. Ki67 proliferation marker showed also stronger positivity on protein-level.

We compared the results of low and high grade samples: low grade ill. high grade tumor cases showed the same statistical results when muscle invaseve cases were not counted. High grade tumors showed enhanced Claudin-4 expression, such as Ki67 positivity. Moreover, Claudin-1 expression showed lowered expression on protein level as well. Semiquantitative examination showed similar results in the two groups. In the low grade tumour-group no death occured until the termination of the investigations in 4-120 months'. In the high grade tumor-group, 1/3 of the tumours died of their UCC. 17 of the 19 patients had T2, 2 had T1 stage disease. 64 patients could be followed: 27 of them had low grade, and 37 had high grade tumor. Recurrence occured in 13 (48%) of the low gade, and 7 (18%) of the high grade patients. Recurrence-free survival in the low grade tumor group was 38 months', while in the group of high grade tumor-patients was longer - 47 months'. Those samples that showed higher Claudin-7 expression than the other cases, (over the median curves), showed shorter disease-free survival. None of the low grade tumors showed stage progression during the examination-period, while 3 of the high grade group showed higher stage on recurrence. 2 of these 3 cases died of the disease.

Survival rates show significantly worse data in the high grade group as opposed to low grade groups, similarly to data described in the international literature.

It is also clear, that the overall survival data are much better in patients treated with cystectomy than those treated with other methods (48 contra 14 months').

It was not possible to perform multivariant analysis since no death occured in the low grade group, while 19 deaths' were registrated in the high grade group.

3. Examination of non-malignant and low grade, non- invasive UCC-s

All claudins examined showed the same pattern as described in previous articles. Since on H&E stained slides the crowded and compressed papillae of an inverted papilloma might be difficult to evaluate, the location of Claudin 1 and or Claudin 4 might help in the proper examination – not to misdiagnose a papilloma as a malignant urothelial tumor. As it was described earlier, Claudin-1 is located in the cells of the basal layer, while Claudin-4 is expressed in the more superfitial layers. Claudin-7 shows equal location to Claudin-4, although much weaker.

Claudin-2 positivity is granular, located in the basal cell layer, although in some inverted papillomas umbrella cells showed positivity as well. Weak positivity of the umbrella cells was also seen with Claudin-3.

Significant difference was seen only with Claudin-1: it's expression was much stronger in inverted papillomas than in any other tumors of the urothelium. This was observed with semiquantitative analysis and morphometryas well.

Claudin-1, and 2 was weaker in low grade UCC compared to other urothelial neoplasms. No significant alteration was seen with Claudin-4, nor with Claudin-7. It is well known from literature-data, that cells of the basal cell layers show positivity with CK/5-6, while CK20 positivity is seen only in the umbrella cell layer in normal urothelium. Our cases showed elevated CK20 positivity in only low grade (Gr. II) UCC-s. These tumors showed enhanced Ki67 positivity as well. This observation was seen with both semiquantitative analysis, and morphometry. Difference in CK/5-6 expression was not significant in the examined tumor groups.

The average follow-up period of our patients was 60 months (3-126), (follow up was possible in 73 cases- 20 low grade UCC, 20 PUNLMP, 15 inverted papilloma, and 18 urothelial papilloma. One death occured for other reason than UCC. All but two cases were primary tumors. Recurrence occured in 10 low grade UCC-s and in 6 PUNLMP cases. Average recurrence-free survival was 21 months' (4-60). No recurrence was registered among the inverted papilloma, and papilloma cases. Patients wis papilloma

and inverted papilloma received no postoperative treatment. No significant correlation could be shown in patients with malignant tumor getting different therapy, concerning the presence of recurrent tumor, but those patients who got immediate chemo-instillation after TUR of their tumor showed longer disease-free survival; 22 contra 16 months. Kaplan-Meier-analysis showed, that cases that showed lower Claudin-1 expression showed shorter recurrence-free survival, while higher expression of Claudin-4 was associated with short recurrence-free survival.Expression of further proteins showed no association with clinical course.

NEW STATEMENTS

1. As opposed to findings shown in the literature, there is no association between E-cadherin expression and UCC grade, stage and clinical course.

2. Although the expression of Claudin-4, Claudin-7, and Ki67 seems to be statistically significantly different in low and high grade UCC-s (in low grade UCC-s Ki67, and Claudin-4 expression is lower, Claudin-7 is higher than in high grade UCC-s, the difference is not significant with light-microscope, and it's significance in daily routin is questionable.

3. In low grade UCC cases, if Claudin-4 expression is elevated, shorter recurrence-freee period can be estimated with appropriate statistycal analysis, it's real relevance has to be investigated in larger cohort-studies.

4. In cases, where the posiiblity of the presence of an IP is raised, examination of Claudin-1 expression might help to make definitive diagnosis.

5. Localisation of Claudin-4 might help in the diagnosis of urothelial papilloma

List of publications

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(IF: 6,691)

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