Comparison of the molecular and the clinical prognostic factors of prostate cancer

Ph.D. thesis

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INTRODUCTION

Prostate cancer (PC) is the most common cancer in men. Despite the evolution the diagnostic and therapeutic methods with special regard to the reduction of cardiovascular-related death and to the increase of average age it proves to be the second most common cancer related cause of death. Genetical and environmental factors both did exist in connection with the development of PC. According the to international epidemical researches, the migrants, who come from areas where PC isn't so common, and enter countries where there is a much bigger chance for PC, consequently, they suffer from these illnesses much fewer. In families where we can find a person with PC the other male family members might also tend to catch this kind of illness, so sums up it briefly, the PC contains a genetical component.

The therapeutic possibilities and the prognosis depend on the stadium of PC. As the progression of the PC is very slow in stadium T1-2 N0 and M0, comes the question, do we even have to cure it? It is questionable, that incidental or low status PC with which method or aggressively has to be cured? Are we entitled to let the patient suffer from the side effects of the aggressive treatment if owing to our current knowledge they were completely symptom-free for 10 years. We cannot predict the biological activity of the PC in different stadiums. The biological aggressiveness (viz. local progression and distant metastasis) depends on the age of the patient, on the size of the tumor and on the characteristic of the tumor grade (Gleason score).

Prognostic factors of PC in clinical use

Although, for laical patients the massage of the PC is vital, but in the urological practice the prognosis is the most significant. The natural history of PC varies from indolent disease that might not cause symptoms during a patient's life to a highly aggressive cancer the metastases quickly and causes untimely death. The well timed curative treatment could save the patient's life, but many PCs are

harmless and perhaps would better be left undetected. The side effects of over-treatment, like incontinence and erectile disfunction after radical prostatectomy, are well-known. Prognostic using of the most frequent used diagnostic tool, the prostate specific antigene (PSA) is a 30% diagnostic value for harmless PC (which doesn't influence the life expectancy), furthermore almost the 25% of the patients have invisible, but occult metastases. So, it is with crucial importance to separate the PCs with low risk factor, which progress during years and which progress much faster. The proposed active surveillance protocol use the PSA, rectal examination (RE) and prostate biopsy triad to follow the progression. During a 2-year follow-up period with this protocol we can determine the 25% of patients whom worse prognosis can be expected than we hoped based on the biopsy. Therefore it is important to find a prognostic factor which can be separate the PCs with more aggressive behavior as the require also a more aggressive treatment.

The microscopical grade of PC determines not only the local status of the cancer but also the existence of the lymph nodes and bone-metastases, and it shows the efficiency of the therapies and the overall survival of PC. In order to determine the grade, the most common method is to determine the Gleason score. The Gleason score can show with an exceptional accuracy the biological behavior and the possibility of bone-metastases, although, the single use of the Gleason score is not sufficient to predict the prognosis of PC. The stadium of the cancer is also a significant prognostic factor. In clinical use the methods for the determination of the stadium means the RE, PSA, characteristics of histology of the prostate biopsy and the radiological examinations. Nevertheless, as these examinations are inappropriate for answering the microscopical questions, in most cases it can be used only with limitation. The pathological stadium can be determined with the help of the removed prostatic tissue and if it was available the characteristics of the seminal vesicles and lymph nodes, can be used for the same thing. In order to decrease the disadvantages and to use advantages the factors upwards are involved in nomograms, to create a more effective prognosis in clinical use with their combined use.

Molecular prognostic factor of PC

Most of the bio-molecular markers which were examined for the prognosis of PC are the regulators of lots of cellular mechanisms (for example: cell-cycle, cell-death, apoptosis, signal-transduction, cell-adhesion and angiogenesis). Besides these markers a lot of genes and proteins were examined as the signal of PC's prognosis and as possible therapeutic tools. The most significant researches of these are the studies, which deal with tumor-specific proteins, hormonal-receptors, cytokines, oncogenes and tumor-suppressor genes.

OBJECTIVES

Our studies which deal with prognostic factors of PC are from two different studies with two different groups of patients. In our first study we examined the correlation between molecular prognostic factors and PCs with different clinical prognosis based on the Gleason score. In our second research we studied the previously examined and the other prognostic factors in prostate cancers which progress from androgen-sensitive (AS) to castration-resistant (CR). The two examined groups showed remarkable differences, therefore in the different paragraphs (i.e. Aim, Methods and Results) we will introduce the studies completely differently.

I. Our goal was to find a factor, which is able to show the different prognosis of each PCs, which has different aggressiveness correlated with the Gleason score. During these researches we hoped to find the answer for the following questions:

1. Does the Gleason score also correlate with PC's prognosis?

2. Is there any difference in the expression of the androgen receptor (AR) in the different aggressiveness and prognostic groups?

3. Is the expression of p21, p27, p63 different in the diverse Gleason score groups?

With our previous questions we were searching for the answer, that instead of the subjective and hardly reproductive Gleason score are we able to find another markers with prognostic value? Is the AR suitable for these kind of markers?

II. If we compare the AS versus CR PC histological material, the question is, whether we can find other prognostic factors based on earlier studies. Accordingly the clinical practice we believed that the development of the CR form equal to the sign of progression.

1. During the first research the AR expression didn't show any differences. Will be any difference present in AR expression with development of CR-form?

2. The p27 expression was found different to the other group in the first study. Is there any connection between the p27 expression and the progression coded by androgen-resistance?

3. Does the change of the expression of ß-catenin, HIF-1 alfa, MCM-2, MGMT, Ki67 and geminin correlate with the progression, so with the transformation to CR?

Until nowadays a lot of models were examined, where we could observe the progression of PC to CR form. These researches were mostly based on cell-cultures, xenograft models, transgenic animals and the results often proved to be contradiction. In our research we studied human PC tissues analyzed immuno-histochemically with the similar number of samples like in the earlier studies in the literature and a few markers were examined firstly by us.

METHODS

The PSA-level shows the efficiency of the antitumoral treatment, defined by the American Society for Therapeutic Radiology and Oncology's guideline. In our studies the pathological examinations were done by a single pathologist, who used the new, ISUP-modified classification for the grading of PC samples.

The study subjects underwent transurethral resection of the prostate cancer because of urinary obstruction, radical prostatectomy because of PC and prostate biopsy because of suspicion of PC. The adenocarcinoma diagnosis was made based on the histopathological analysis of the removed tissue.

In the first study we examined 13 Caucasian patients with low and 13 with highly malignant PCs. We separated the patients by the difference of the PCs determined by the Gleason score.   Biopsies of patients suffering from prostate adenocarcinoma of low (3+3, 3+4) and high (4+5, 5+5) Gleason scores. They were immunostained for positive regulators of cell cycle control (p21(waf1/cip1) and p27 (kip1)), and essential markers of normal prostate gland ontogeny (p63) and growth (androgen receptor) to find differentially expressed markers of malignant progression. Serum prostate specific antigen levels were also monitored at the time of biopsy and following anti-androgen therapy. We investigated the expression pf p21, p27, p63 and AR proteins in relation to different prognostic levels in low and high Gleason score prostate cancers.

In our second study, prostate adenocarcinoma samples from 18 chemically or surgically castrated Caucasian patients were included in this study. Nine of them were diagnosed with androgen-sensitive PC, and 9 of them were diagnosed with castration-resistant PC, depending on the PSA responses to anti-androgen therapy. We thought the developing castration-resistant form with a worse prognosis, according to the clinical practice. We investigated androgen-sensitive and castration-resistant prostate cancer samples to evaluate the expression levels of AR, p21, p27, p16, ß-catenin, HIF-1, MCM-2, geminin, MGMT and Ki67. The study subjects

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underwent transurethral resection of the PC because of urinary obstruction in the group of castration-resistant form.

RESULTS

In our first study, in the group of 13 males described by the low Gleason-score (3+3, 3+4) moderately and high PSA-levels referred to the diagnosis. Their average age was 70.38 (60-80). 12 patients (92%) were AR positive. With regard to the p21 and p63 the tumors were negative just like in the group with high Gleason-score. Although, the p27 was positive in all patients of the group.

In the group with high Gleason-score (4+5, 5+5) before the biopsy we found extremely high PSA-value, which reduced during the treatment except one case. The histological examination justified adenocarcinoma in every case. Their average age was 71.08 (61-81). The PC cells were AR positive except one case. The patient who was AR negative died 3 months after the biopsy. Every sample was p63 negative. We could observe p21 positivity only in the adenocarcinoma which produces the mucin. The positivity of p63 did exist in the normal or in the hyperplastic prostate cells, even in the peritumoral area. We could observe p27 positivity in 7 cases (54%).

In the second study 9 patients' cancers were AS and other 9 patients' cancers were CR. The average age 73.22 (66-84) vs. 73.22 (65-84) was the same in the CR and in the AS groups. The average Gleason-score wasn't different (8 ± 2 vs. 8.85 ± 0.89, t-test, p=0.18) in the 2 groups, either. However, the PSA-levels showed significant difference in the AS and in the CR groups (in order: 5.33 ± 13.1 vs. 87.31 ± 120.72, t-test, p=0.03) accordingly to the definition of castration-resistant PC.

The statistical investigation showed that MCM-2 and AR expressed a significantly higher level in CR PCs than in the AS PCs (Mann-Whitney U-test, U=56 vs. 63.5, z=1.9 vs. 2.03, p=0.05 vs. 0.04). The expression of geminin was also higher in the AS group, but not significantly (Mann Whitney U-test, U=58.5, z=1.58, p=0.11). Nevertheless, we discovered lower MGMT levels in the CR pros-

tate cancer than in the AS (Mann Whitney U-test, U=63.6, z=2.03, p=0.04). The immunohistochemistry of the 6 other proteins that we examined (Ki67, p27, p21, p16, ß-catenin, HIF-1- alpha) didn't show any difference in the two examined groups.

DISCUSSION

Despite the therapy which at first seemed to be effective the PC during its treatment showed progression. In the clinical part of our study accordingly to the daily practice, we estimated the high Gleason-score and the increase of the PSA as the sign of the progression. In the part of the immunohistochemical studies we classified the castration-resistant cancers in the group where the tumors with progressive pattern.

We couldn't observe any activity of p63 in the samples of the first study which was the same as the previously in the literature. In our first study the reaction of the **nuclear p21 wasn't perceptible**, either, only in the adenocarcinoma which produce mucin. **In the determinant majority of the examined samples** (with one exception in the two examined groups) **we could observe AR positivity**.

We could detect a difference in the activity of the nuclear p27 between the PCs with lower (not so aggressive) and the ones with higher Gleason-score with disregard to the protein (p21 and p63) which is unable to express. There wasn't any difference between the two groups with regard of the expression of AR. P27(kip1) protein, however, was detected in all low Gleason score prostate cancers, but it was found in only 7/13 (54%) high score cases. **The reduction of the expression of p27 is the marker of the progression**.

Prostate specific antigen levels, either pre- or post-treatment, did not show strict correlation with the p27 (kip1) results.

One of the most frequent characteristics in the CR PC is the over-expression of the androgen-receptor. In more studies we can read about the methylation of the AR promoter with a 8-39% chance to occur in samples of the PC. The methylating agents are the part of the carcinogenesis, but the MGMT protein (which repairs the DNA) removes the methyl groups.

The methylation of the AR promoter was more significant in the CR form than in the AS form. The methylation of MGMT can be detected in a wide range (0-76%). Several studies showed that the mutation of genes (for example: MGMT) plays a

crucial role in the progression of the PC. Until nowadays only one research investigated the methylating status of AS and CR. Accordingly with this study, MGMT is a potential marker of the PC with more aggressive. Contrariwise, during our study **we found a lower MGMT expression in CR PC than in AS PC**. Our datas strengthens the facts that the **expression of AR is higher in the CR PC than in AS PC.** According to the results of the first study, the expression of AR is independent from the Gleason score.

In PC the MCM-2 and geminin levels are high, but only the MCM-2 was held to be the independent factor of the survival. The results were controversial with the geminin. Other studies examined the MCM-2 expression in relation to the prostatic tissue and to the PC. They found that the independent predictive factor of cancer-free survival after radical prostatectomy is the expression of MCM-2. Nevertheless, this expression wasn't influenced by the accidental preventive anti-androgen treatment. Exactly like in the literature, according to our datas the **expression of MCM-2 was also significantly higher in case of CR PC than in AS PC**. The geminin-level was also higher in case of CR, contrary to the controversial results of a few previous studies.

The p27(Kip1) and the Ki67 are useful markers of cell-proliferation and of the damage of DNA. P27(Kip1) regulates down, whereas the Ki67 regulates up in the PC. The connection is well-known between the expression of these proteins and the grade and the stadium of the tumor. According to the results of our second research, **the occurrence of p27 didn't show a remarkable difference between the AS and CR cancers**. In connection with the occurrence of **Ki67** our results are similar, as the others', who **didn't found appropriate markers for predict to the prognosis**.

A previous study found that cytoplasmic expression of p16 is the independent prediction of the efficiency of the anti-androgen therapy in AS PC, but not in case of CR PC. The lower level of p16 expression shows significantly the chance of distant metastasis. The expression of p21 predicts the transformation

from AS to CR in untreated PC and it is the negative predictor of survival of patients is treated by anti-androgen.

According to our immunohistochemical results **nor the expression of p16, neither the expression of p21 changes in CR PC compared to the AS PC**.

The mutation of ß-catenin is a common characteristic of the PC. The ß-catenin is the cofactor of AR and the stimulator of the AR-signal way. Earlier studies showed that the ß-catenin plays an important role in the progression of PC. The AR and the ß-catenin levels might be the indicators of the progression of AS to CR cells. The meta-analysis of 5 studies and 500 patients showed the level of ß-catenin and the cancer's grade is inversely proportional and it is undetectable in aggressive form of PC and in bone-metastases. Our study **didn't find a significant difference in the expression of the ß-catenin between the AS and CR PC**.

The activation of ß-catenin signal results the expression of HIF-1-alpha which increase the potential of invasion of cancer cells. HIF-1-alpha also defends from apoptotic stress in PC cells. The HIF-1-alpha correlate with more aggressive metastatical phenotype of PC. In our study we **didn't find a significant difference in the expression of HIF-1-alpha in AS versus in CR PC**. In our opinion the increased HIF-1-alpha expression doesn't influence the transformation from AS to CR PC.

The understanding of this cellular mechanism means the possibility of an anticancer-therapy. A good example for it is the study which deal with the inactivation of the MGMT (which has higher expression in CR PC according to our study) with pseudo-substrate inactivator lomeguatrib which showed reassuring results.

CONCLUSIONS

We examined 26 samples of prostate cancer, both with 13 low (3+3, 3+4) and with 13 high (4+5, 5+5) Gleason score, the expression of the p21, p27, p63, and AR. Our goal was to find the marker which is able to differentiate the PCs which at first were thought to be with different prognosis, based on the Gleason score. According to our histochemical results the expression of p21 and p23 didn't exist in the samples. Our facts correspond with previous literature datas, so the **p63 didn't exist in PC**. In addition, the **p21 is unable to show the difference between the different kinds of PCs with different aggressiveness**. We could observe a lower expression of p27 in the PCs with higher Gleason score. According to the result of our research when we examined the PC groups with different aggressiveness based on the Gleason score, **there wasn't any difference in the expression of the AR**. From p21, p27, p63 and AR only p27 proved to be appropriate to show the difference between the PCs with different malignancy which was different even by the time of the diagnosis. Briefly, by the time the **malignancy increased the expression of p27 decreased**.

We examined expressions of 10 proteins in 9 androgen-sensitive and 9 castration-resistant samples. Some of this proteins were included in the previous study and which might have played a role in oncogenesis and in the progression of PC. According to our histochemical results, tree examined proteins (**minichromosome maintenance-2, metilguanin-DNS methytransferase and AR) did exist significantly more times in CR PC** than in AS PC, whereas the expressions of 7 other examined proteins (ß-catenin, p27, p21, p16, Ki67, hypoxia- inducible factor-1 alpha and geminin) didn't show significant difference in the two groups. In our opinion the **minichromosome maintenance-2, the metilguanin-DNS methyltransferase and the androgen-receptor are the indicators of being castration- resistant: the expression of MCM-2 and AR are directly, whereas the expression of MGMT is inversely proportional to the progression.**

When we compared the two researches, we concluded that during the **progression of different aggressiveness PCs based on the Gleason score, the different p27 and not different AR expression definitely changed and the difference of the presence of the p27 disappears in the comparision of AS and CR**. At the same time, **in the CR samples we can observe the increase of the expression of AR**, **the increase of the expression of MCM-2 and the decrease of the expression of MGMT**.

The results of our study suggest that with **the help of the Gleason score, as an only factor, it is unable to judge the prognosis**.

Nowadays, we can find a huge amount of studies which are about the changes of protein expression in PC. Nevertheless, these researches compared only the healthy and the malignant prostatic issues. Our goal was to compare the expression of the earlier examined and new proteins in PC characterized by low and high Gleason score and androgen-sensitive versus castrate-resistant. It is vital to define the function of these proteins both in prostatic oncogenesis and in the transformation from AS to CR. If the selection of PCs with worse prognosis was going to be more effective and the transformation of PC to CR will become more understandable, we could hope fewer over-treatment and could find more effective therapeutic possibilities. The better understanding of the pathological progression regulated by these markers, have the potential to serve not only as prognostic factors but may be targets for new therapeutic strategies.

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