SERUM PSA LEVEL AND GLEASON SCORES OF NEEDLE BIOPSY SPECIMENS PREDICT THE POSTOPERATIVE PATHOLOGIC GRADE OF PROSTATE CANCER

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ABSTRACT

Objective: To investigate the correlation between postoperative pathological grade of prostate cancer (PC) and preoperative serum PSA as well as grade of biopsy specimens.

Methods: The serum PSA and preoperative and postoperative Gleason scores of PC were retrospectively analyzed in 75 patients. Correlation between serum PSA and postoperative Gleason score was evaluated, and the Gleason score before surgery was compared with that after surgery with Wilcoxon signed rank test.

Results: The PSA before operation was 4~230 ng/mL (mean: 33.5 ng/mL) and the Gleason score of biopsy specimen was 2~9 (mean: 4.4). The Gleason score of specimens following radical prostatectomy was 2~10 (mean: 4.8). Preoperative serum PSA was positively correlated with postoperative Gleason score ($r_s=0.279$, $P=0.015$). Gleason score of biopsy specimens was significantly lower than that after radical prostatectomy ($P=0.011$).

Conclusions: High PSA level is associated with high Gleason score of specimens after radical prostatectomy. Pre-operative pathological examination of biopsy specimens may under-grade the PC. Re-biopsy is recommended to avoid underestimation of PC if necessary.

Key words: Prostate specific antigen, prostate cancer, gleason score, needle biopsy, radical prostatectomy.

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Introduction

In daily clinical practice, Gleason score (GS) discordance is often found between pathological examinations in pre-operative needle biopsy (NB) and after radical prostatectomy (RP), which hinders the determination of therapeutic strategies. In order to develop an effective way to accurately predict tumor grade, we analyzed the correlation among preoperative serum PSA and Gleason scores of preoperative NB specimens and those after radical prostatectomy in 75 patients with prostate cancer (PC) who underwent laparoscopic radical prostatectomy in our department from May 2005 to May 2009.

Patients and methods

A total of 75 patients with a mean age of 68 years (range: 49-77 year) were recruited into this study. Among them, 59 patients suffered from lower urinary tract obstruction symptoms including worsened dysuria, nocturia and frequent micturition, and 16 had painless gross hematuria, abnormal digital rectal examination or increasing PSA level. Radiotherapy and hormonal therapy were not found in these patients. Blood was collected in the morning for the PSA measurement before biopsy, which was not performed in the period of urinary retention, catheterization, digital rectal examination and in the presence of other factors affecting PSA levels. Reagents for PSA measurement were purchased from Sweden CanAg Company.

Transrectal prostate biopsy was performed with BK1846 ultrasound probe (Denmark) and 18-gauge needle (BIP GmbH, Türkenfeld, Germany). Conventionally, biopsy was performed at 6 sites in bilateral peripheral region of the prostate.
with 3 sites in each side and 2 sites in the transition zone with one in each side. In addition, biopsy was also done at 1~2 sites of the hypoechoic area if present. Biopsy specimens were immediately fixed in 4% formaldehyde. Four paraffin-embedded sections were obtained from each biopsy specimen, among which, one was used for Hematoxylin and Eosin Staining (HE staining) and 3 for Alpha-methylacyl-CoA racemase (P504S), high molecular weight cytokeratin (34βE12) and P63 triple cocktail staining, respectively. Specimens collected during the radical prostatectomy included the whole prostate and seminal vesicle and were also fixed in 4% formaldehyde. Tissues were cross-sectionally cut and the suspected lesions were visually identified and collected; paraffin-embedding, sectioning, HE staining and immunohistochemistry for P504S, 34βE12 and P63, were performed.

An experienced pathologist, according to the criteria for Gleason scoring developed in the International Society of Urological Pathology Consensus Conference (2005), evaluated pre-operative specimens and those collected in surgery with Gleason score system(1). PC of score 2~5 was defined as well-differentiated cancer, that of score 6~7 as moderately differentiated cancer, and that of score 8~10 as poorly differentiated cancer. Preoperative TNM staging was also performed in these patients. T1c PC was found in 8 patients, T2 PC in 62 and T3 PC in 5.

SPSS 11.0 statistical software program was applied for statistical analysis. The correlation between serum PSA level and Gleason score before and after surgery was analyzed with rank correlation analysis. Paired rank sum test was used for comparisons between Gleason scores before and after surgery. Comparisons of qualitative data were done with χ² test.

Results

The mean preoperative PSA level was 33.5 ng/mL (range: 4~230 ng/mL) and mean Gleason score before surgery was 4.4 (range: 2~9). Preoperative PSA level was positively correlated with pre-operative Gleason score (rs = 0.253, P=0.029, P<0.05). The mean Gleason score of specimens collected in the surgery was 4.8 (range: 2~10). Post-operative Gleason score was significantly higher than that before surgery (Z=-2.55, P=0.011, P<0.05).

Preoperative serum PSA levels and Gleason scores are shown in Table 1. Among patients with preoperative PSA>20 ng/mL, the proportion of patients with post-operative Gleason score >7 was significantly higher than that in those with preoperative PSA ≤ 20 ng/mL (χ²=9.507, P=0.002, P<0.05). Preoperative PSA level was positively correlated with Gleason score after surgery (rs=0.279, P=0.015, P<0.05).

Gleason scores before and after surgery are shown in Table 2. The proportion of specimens with Gleason score of 2~6 before surgery turning to be post-operative 7~10 was about 15.5% (9/58).

Postoperative TNM stage: T1c PC was found in 2 patients, T2 PC in 65, T3 PC in 8, and 3 were diagnosed with T3 PC and pelvic lymph node metastasis. The proportion of patients with prostate capsular invasion (>T2) was 31.25% (5/16) in patients with post-operative Gleason score of 8~10 and 5.08% (3/59) in those with Gleason score of 2~7 showing significant difference (χ²=6.506, P=0.011, P<0.05).

Discussion

Currently, there are three histological grading systems for PC, including the Gleason grading system, Mostofi grading system and MD Anderson...
Hospital classification system. Gleason grading system is the most frequently used one in the Department of Urology and has been found to be superior to other grading systems\(^{(2)}\). The higher Gleason score usually means high malignance, and poorer differentiation and prognosis. Studies have demonstrated that PC with Gleason score of ranging from 8 to 10 was possibly the non-hormone-dependent one and had a high possibility for metastasis\(^{(3)}\). Gleason grading system is significantly related to the biological behaviors and prognosis of PC. Therefore, Gleason score has become an important index to determine the therapeutic strategies for PC. In the United States, when the PC has no involvement of capsule (absence of lymphatic metastasis), radical prostatectomy, rather than watchful waiting, is recommended for patients with Gleason score of \(>7\) who are physically suited for surgery and have a life expectancy \(>10\) years. Gleason score, capsular invasion, blood PSA, pathological stage, and aneuploidy are good markers for the progression in organ confined disease\(^{(4)}\). Since 1990s, the United States cancer association has recommended in the PC guideline that Gleason grade, serum PSA level and tumor stage are the most important indicators in determining the therapeutic strategies. Among them, Gleason score is regarded as not only a good predictor of disease progression, but a favorable factor in determining the therapeutic efficacy of radical prostatectomy\(^{(5,6,7)}\). Therefore, correctly predicting the Gleason score of PC is critical for to determine reasonable clinical treatments.

However, in the transrectal prostate needle biopsy, only a small amount of tissues is collected. Thus, it may bias the Gleason scoring and sometimes lead to a false negative diagnosis. Some reports have shown that biopsy Gleason score is frequently lower than the Gleason score after surgery\(^{(8,9,10,11)}\). Under-grading of carcinoma in needle biopsy now has become a common problem, occurring in 42% of all reviewed cases\(^{(12)}\). Our results indicated that the Gleason score of biopsy specimen was also lower than that after surgery.

The main contributing factors may be as follows:

- In the Gleason score system, the borderline between two adjacent levels is vague.

- PC is heterogeneous and multicentric. Thus, the lesioned tissues might be not collected in the biopsy. A less differentiated pattern may not have been sampled in the biopsy\(^{(10)}\). Even the same cancer focus may have different grades pattern, which causes the underestimation of PC grade. In the postoperative pathological examination, the whole prostate was collected and the lesioned tissues were collected for examination, which significantly increases the accuracy.

- Tumor malignancy, including invasion and proliferation of cancer cells, is dependent on the levels of differentiation. With the cancer development, the compositions of cancers will change. Proportion of poorly differentiated carcinoma might have already increased by the time patients performed radical operation. In patients receiving surgery, the tumor grade may also increase when comparing with the grade of biopsy specimens. Generally, the higher the biopsy specimens Gleason score the closer it is to the post-operative Gleason scores and, moreover, the higher is the coincidence between Gleason scores before and after surgery. Biopsy instruction meaning is less accurate in low biopsy Gleason score. Some studies demonstrate that the consistency rate is low between low biopsy Gleason score and postoperative Gleason score when the score is low\(^{(2)}\).

Our findings showed that underestimation rate of Gleason score was 37.3% and 66.7% when the biopsy Gleason score was 2–5 and 6–7, respectively. The underestimation rate was only 16.7% when the biopsy Gleason score was 8–10. Steinberg et al\(^{(13)}\) reported that 43% of patients with biopsy Gleason score of 2–6 were confirmed to have post-operative Gleason score of 7–10. In the present study, only 15.5% of patients with biopsy Gleason score of 2–6 was confirmed to have post-operative Gleason score of 7–10, which was significantly lower than previously reported. This may be attributed to a pathological examination performed by the same experienced physician. Moreover, simultaneous detection of P504S, 34 β E12 and P63 by immunohistochemistry also increased the accuracy of early diagnosis of PC with high differentiated tumor.

Our results showed that serum PSA level was positively correlated with biopsy Gleason score and post-operative Gleason score, which was in accordance with a recent report of Freedland et al\(^{(14)}\). In this last study, 2312 men treated with RP for PC were recruited from 1992 to 2004, and their results showed high preoperative PSA level predicted high cancer grade and patients with high preoperative PSA level were more likely to have extraprostatic diseases. PSA is secreted by the prostate epithelial...
cells and stored in the cavity catheter with a high concentration. There is a barrier between normal epithelial cells and capillaries, lymphatic system existing between the integrity of the basal cell layer and basement membrane formation, which prevents the leakage of PSA to the blood circulation.

When PC progresses, Gleason score increases accordingly and cancer tissues become more disorganized, which causes disorganized gland growth, deformed glandular cavity and reduced matrix components. Thus, PSA secreted by cancer cells increases at the same time, and the barrier between basal cell layer and basement membrane is damaged severely. In addition, angiogenesis is also active in PC at this time. These finally lead to the increased leakage of PSA into the blood circulation, leading to elevated level of serum PSA.

Studies have revealed that the cancer microvessel density was positively correlated with the Gleason score and serum PSA level, which suggests that the leakage of PSA into blood increases with the increase of microvessel density in PC with high Gleason score\(^{(15)}\).

Recently, Bettendorf et al\(^{(16)}\) investigated 350 patients receiving radical prostatectomy for PC and results revealed that tumor volume was significantly correlated with the degree of tumor differentiation and pathological grade. Our results also showed that the proportion of tumor invading capsule (>T2) in tumors with Gleason score of 8-10 was significantly higher than that in those with Gleason score of 2-7 (31.25% vs 5.08%).

We speculate that the higher the Gleason score, the higher possibility to invade surrounding tissues the tumor has. Even in the same stage, there are different grade levels. Tumors with high Gleason score are usually poorly differentiated and have a larger cancer volume, resulting in increased secretion of PSA and elevated serum PSA level. This may be one of reasons why serum PSA level was positively correlated with Gleason score. Our results also showed that the proportion of tumors with Gleason score of 8-10 (poorly differentiated adenocarcinoma) was significantly higher in tumors with preoperative serum PSA level of >20 ng/mL (38.7%) than in those with serum PSA level of <20 ng/mL (9.1%). Therefore, when the serum PSA level is higher than 20 ng/mL and the biopsy Gleason score ranges from 2 to 6, underestimation of Gleason score may be present. If necessary, biopsy at multiple sites is recommended for re-evaluation.

In conclusion, serum PSA level was positively related with post-operative Gleason scores, which may lead toward correct prediction of cancer histopathological grading and can make up for the deficiencies of biopsy specimen Gleason score which always underestimates radical specimen Gleason score. When serum PSA level is unmatched with the biopsy Gleason score, determination of therapeutic strategies should be made carefully. Clinically, the serum PSA level can be combined with biopsy specimen Gleason score to predict the tumor grade. For PC patients who are suitable for radical prostatectomy, radical prostatectomy should be performed as soon as diagnosis is confirmed by biopsy.

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