Running title: Prostatitis and Upstaging/Upgrading in Prostate Cancer Active Surveillance

Role of chronic inflammation as a predictor of upstaging/upgrading in prostate cancer: Finding a new group eligible for active surveillance.

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ABSTRACT

Purpose: We aimed to investigate the correlation between presence of inflammation and pathology upgrading/upstaging in patients with prostate cancer.

Materials and Methods: A retrospective study accomplished on 315 patients with prostate cancer, eligible for active surveillance except prostate-specific antigen (PSA) level (PSA<30ng/dL), who underwent radical prostatectomy between 2005 and 2015. Patients divided into two groups based on needle biopsy: A; with evidence of inflammation (chronic prostatitis) and B; without inflammation. The frequency of upstaging and upgrading in both groups was compared in different ranges of PSA level (<10, 10-20 and 20-30ng/dL). Upgrading/Upstaging was defined as increase from one prognostic grade group to another. Statistical analyses were performed to investigate the relation between inflammation and upgrading/upstaging.

Results: The mean age of the patients was 68.2 years and the mean PSA level was 10.2 ng/ml. Chronic prostatitis was identified in 82 of 315 cases therefore upgrading/upstaging were seen in only three patients (3.7%) while 39 of ***233*** (16.7%) patients without inflammation had upgrading/upstaging in final pathology (p-value = 0.003). Other variables including the patient's PSA before surgery, PSA density, and the presence of hypoechoic areas in ultrasound had a significant relationship with the incidence of postoperative upgrading/upstaging. Among studied variables, presence of inflammation in biopsies was found to be the most important predictor of upstaging/upgrading (OR: 0.205).

Conclusion: Our data demonstrated that patients with concurrent prostatitis and PCa may have a better prognosis even if the PSA level is higher than 10ng/mL.

INTRODUCTION

Prostate cancer is considered as the most common cancer and the second most common cause of cancer-related mortality in adult men and the incidence of disease is increasing globally [1, 2]. Due to widespread use of PSA screening the number of diagnosed prostate cancer patients has increased in recent years. However, many patients may receive unnecessary treatments for clinically localized and insignificant cancer [3, 4].

Active surveillance is considered as a management method for low-risk prostate cancer but the main challenge is to determine low risk prostate cancer patients. Therefore, in order to achieve an accurate prediction of pathologic stage, it is necessary to have more sensitive markers and more accurate criteria. We conducted this study to evaluate baseline factors that might predict upstaging/upgrading in those who are candidates for active surveillance. One of the baseline characteristics that has the potential to predict upstaging/upgrading is the presence of chronic prostatitis in biopsy specimens. Prostate specific antigen (PSA) is elevated in patients with chronic prostatitis and this elevation though related to inflammation may erroneously exclude patients from active surveillance program[5-7]. We hypothesized that presence of chronic prostatitis may overestimate the risk of disease and therefore patients with chronic prostatitis and higher serum PSA levels who are otherwise appropriate for active surveillance may benefit from surveillance.

PATIENTS AND METHODS

Our institution prospectively records demographic, clinical, and pathological data for patients who undergo radical prostatectomy for prostate cancer. Among all men who underwent radical prostatectomy between 2005 and 2015, 213 patients had PSA $\leq$ 10 ng/mL, clinically localized prostate cancer (cT1), biopsy Gleason score $\leq$ 6 and involvement of 2 cores or less and met inclusion criteria for active surveillance. Patients with total biopsy cores less than 12 were

excluded from analysis. In addition, 84 patients with PSA level between 10 and 30 ng/mL who met the remaining criteria for active surveillance were also included in the analysis to assess the possibility of expanding criteria for active surveillance. Upstaging and upgrading were defined as pathologic stage ≥ T3 and presence of Gleason pattern 4 in radical prostatectomy specimens. Incidence of upstaging/upgrading was determined in both groups and the impact of baseline characteristics in predicting upstaging/upgrading was evaluated.

All baseline characteristics including age, Body mass index (BMI), pre-operative PSA, prostate volume, PSA density, transition zone volume, PSA transition zone density, Gleason score, presence of hypoechoic lesions in ultrasound and chronic inflammation in biopsy specimens were compared between patients with and without upstaging/upgrading.

Clinical staging was determined based on digital rectal exam findings, whole body bone scan and cross sectional imaging (MRI or CT). In our institution, patients with low risk prostate cancer also routinely undergo bone scan and cross sectional imaging prior to surgery.

Chronic prostatitis was defined according to the consensus classification system proposed by Nickel et al. Presence of multifocal stromal, glandular or periglandular infiltration with inflammatory cells, including lymphocytes, plasma cells and macrophages.

Multivariable analysis was also performed to assess which factors can independently predict upstaging/upgrading in each PSA category

Statistical analysis

The results for quantitative variables were expressed as the mean and standard deviation (mean ± SD) and for qualitative variables as percentages. Kolmogorov-Smirnov (K-S) test was used to evaluate the normal distribution of quantitative variables. In the case of normal distribution, the comparison of the mean quantitative variables in two qualitative groups was done by independent

t-test. The comparison between qualitative variables was done using Chi-square test or Fisher's exact test. Furthermore, examining the predictive power of variables, binary logistic regression analysis was done. Data analyses were performed using Package for Social Sciences (SPSS) version 16. The p values of < 0.05 were considered significant.

RESULTS

In this study, 273(87%) patients had no upstaging/upgrading postoperatively, and only 42 (13%) patients showed upstaging/upgrading. Table 1 compares baseline characteristics between the study groups. As shown in the table, PSA, PSA density, presence of hypoechoic lesion and chronic prostatitis has the potential to predict upstaging/upgrading. Upstaging/upgrading was more frequent among patients with hypoechoic lesion in ultrasound compared to those who did not show hypoechoic lesion (20.4% vs. 9.9% respectively; p=0.010), whereas it was less frequent in patients with chronic prostatitis (3.7% upstaging/upgrading in patients with chronic prostatitis vs. 16.7% in patients without prostatitis, p=0.003).

In a second analysis we assessed the impact of chronic prostatitis and hypoechoic lesions on predicting upstaging/upgrading in patients with PSA>10 ng/mL.

In patients with PSA between 10 and 30 ng/mL, chronic prostatitis was significantly associated with upstaging/upgrading. Among 24 patients with chronic prostatitis and PSA>10, only 2(8.3%) showed upstaging/upgrading whereas reclassification happened in 19 (31.7%) patients without prostatitis (p=0.026). We found no statistically significant association between hypoechoic lesions and upstaging/upgrading in patients with serum PSA>10.

Multivariable logistic regression analysis also showed that serum PSA level, presence of hypoechoic lesions and chronic prostatitis can independently predict upstaging/upgrading in potential candidates for prostate cancer active surveillance.

DISCUSSION

In the present study we showed that presence of chronic inflammation in association with prostate cancer in biopsy specimens may be a predictor of low risk disease and many of these patients can be a suitable candidate for AS regardless of serum PSA level. It also should be considered that there is no consensus on the role of PSA level in predicting outcomes and GS is considered as the most important factor for treatment decision making [(11)]. Therefore, in contrast to Epstein's criteria for AS, some patients with elevated serum PSA level, even those with PSA between 20 and 30, may be suitable candidate for AS.

In the current study, the upgrading/upstaging rate between patients with preoperative PSA level less than 10 ng/mL and patients with PSA level between 10 and 20 ng/mL had a significant difference. However, those with chronic inflammation had a significantly lower risk of upstaging/upgrading.

The previous study by Faisal et al., showed that patients with PSA between 10 and 20 ng/mL could not be considered as suitable candidates for the Active Surveillance management strategy. Moreover, they suggested that concurrent existence of prostate cancer and prostatitis may make these patients candidates for AS [(12)]. Moreover, those with PSA density <0.15 ng/mL/gr are appropriate cases for AS. This simply means patients with more prostate volume will be less likely to be at risk [(12)]. Besides, Kwak et al. have shown that increased prostate volume was associated with the severity of inflammation [(13)]. On the other hand, Jiwoon Yu et al., concluded that

upstaging/upgrading in patients with PSA level >20 ng/mL was significantly higher than patients with a PSA level <20 ng/mL [14]. However, Spahn M et al., suggested that 10 year mortality rate for prostate cancer with PSA >20 ng/ml and Gleason score≤7 or GS>7 is 5% and 35% respectively [15].

Considering histological inflammation in needle biopsy sample and serum PSA level of non-prostate cancer men, Okada K et al. proposed that aging, prostate volume and histological evidence of inflammation were significantly associated with increased levels of PSA, especially in those with a larger prostate [15]. This was in contrary to the study of Chang SG et al., in which they found that the chronic inflammation of prostate is not associated with increased PSA level and prostate volume mentioned as the most important cause of increased serum PSA levels in patients with negative prostate biopsy for cancer [17].

Our results revealed that among studied factors, presence of inflammation as well as hypoechoic areas in ultrasound, and PSA are the parameters that are significantly associated with upstaging/upgrading. Additionally, binary logistic regression showed that the presence of inflammation and hypoechoic lesions are independent factors that have the potential for predicting upgrading/upstaging. The retrospective nature was one of the limitations of the current study.

CONCLUSIONS

Our study showed that the presence of inflammation in biopsies as well as presence of hypoechoic areas in ultrasound are independent predictors of upstaging/upgrading. The presence of inflammation in the prostate tissue is associated with a reduced risk of prostate cancer. Therefore, concurrent prostatitis and an elevated PSA level (>10 ng/mL) can lead to an error in selection of patients for the AS strategy.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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Table1- Comparing baseline characteristics between study groups

		Upstaging/Upgrading		P-Value
		Present	Absent	
Age mean(SD)		69.5(9.0)	68.0(8.2)	0.29*
BMI mean(SD)		25.23(4.02)	25.58(3.39)	0.37*
Prostate Volume mean(SD)		38.60(17.77)	35.52(17.87	0.21*
PSA mean(SD)		15.33(8.32)	9.46(4.84)	<**0.001***
PSA Density mean(SD)		0.47(0.36)	0.33(0.21)	**0.039***
PSA Transition Zone Density mean(SD)		0.99(1.71)	0.72(2.51)	0.238*
Hypoechoic lesion in transrectal ultrasound Number (%)	Present	21(20.4)	82(79.6)	0.010†
	Absent	21(9.9)	191(90.1)	
Chronic prostatitis in biopsy specimen Number (%)	Present	3(3.7%)	79(96.3%)	0.003†
	Absent	39(16.7%)	194(83.3%)	

* Independent T-test

† Chi-square test

Table 2- Binary logistic regression analysis to determine independent predicting factors of upgrading/upstaging

		Hazard ratio (95% CI)	P-value
PSA	≤10 ng/mL (referent)	3.517 (1.757-7.039)	<0.001
	10-30		
Hypoechoic lesion	Absent (referent)	2.231(1.120-4.443)	0.022
	Present		
Inflammation	Absent (referent)	0.171(0.050-0.580)	0.005
	Present		