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Original Article

Is active surveillance an appropriate approach to manage prostate cancer patients with Gleason Score 3+3 who met the criteria for active surveillance?

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ABSTRACT

Objective: Prostate cancer is one of the common malignant tumors in men worldwide. Nowadays it seems that Gleason Score 3+3 may not need definite treatment and some of the experts even ignore it as a cancer but we should be aware that in some patients with Gleason Score 3+3 there is a higher risk for harboring higher-grade cancer. We had done this study to evaluate patients with prostate cancer with Gleason Score 3+3 to determine the value of tumor volume in these cases.

Material and methods: From September 2010 to October 2017, radical prostatectomy was done for 123 sequential patients with localized prostate cancer in two referral centers of Shahid Beheshti Medical University, Tehran, Iran, and 42 cases with Gleason Scores 3+3 which who were candidates for active surveillance were included in the study.

Results: We interestingly found that 30 of 42 (71.4%) patients had significant tumor volumes (≥0/5 cm^3). We concluded that when tumor volume was less than 0.5 cm^3, none of the patients had extra prostatic tumor extension. In patients with tumor volume greater than 0.5 cm^3, two cases (6.6%) had extra prostatic extension, 4 cases (13.3%) had positive margins, four cases (13.3%) reactive lymph nodes and 16 cases (53.3%) perineural invasion.

Conclusion: Authors suggest that some patients with Gleason Score 3+3 have tumor volume >0.5 cm^3 who are considered having significant cancer pathology and active surveillance may not be appropriate approach to manage all cases with Gleason Score 3+3.

Keywords: Active surveillance; Gleason Score; prostate cancer; tumor volume; transrectal ultrasound guided biopsy of the prostate.

Introduction

Prostate cancer (PCa) is one of the common cancers in men worldwide, and the annual death rate from PCa were 28,170 and 69,960 in the United State and Europe, respectively in 2012.[1-4] A few studies done about incidence of PCa in Iran have shown that it is the third most common cancer diagnosed in men.[5-7] In the last two decades early detection of PCa has been improved by Prostate Specific Antigen (PSA)screening.[8,9] Active surveillance (AS) is a therapeutic strategy for early-stage PCa to balance early detection of aggressive disease and overtreatment of indolent tumor.[10]

Our understanding of PCa biology has significantly developed in the last decade, leading to wide interest in AS as a viable management strategy for patients with Gleason Score (GS) 3+3 who met the criteria for AS.[11] There are different accepted eligibility criteria for AS in different institutes.[12] Although multiparametric magnetic resonance imaging or genomic tests can help us determine the probability of disease upgrading or upstaging, confirmatory biopsies and surveillance prostate biopsies are currently considered as the most reliable means of identifying patients who need curative therapy while on AS. However the risk of misclassification still exists.[13]

Table 1.RP findings in GS 3 + 3 PCa stratified by TV

Overall		<0.5 cm^3	≥0.5 cm^3	
No. Pts (%)	**42**	**12 (28.6)**	**30 (71.4)**	**p**
Age, mean±SD (years)	66.1±8.9	68.7±10.7	65.1±8	0.3
Abnormal DRE (No, %)	40 (95.2)	12 (100)	28 (93.3)	1
PSA mean±SD (ng/mL)	5.4±3	4.6±2.8	5.6±3	0.3
Mean prostate volume±SD (mL)	53.9±35.4	50.3±9.5	51.8±37.4	0.9
PSAD	0.13±0.11	0.12±0.02	0.14±0.12	0.8
pT2a	19 (45.2%)	12 (100%)	7 (23.3%)	0.0001
pT2c	21 (50%)	0 (0%)	21 (70%)	0.0001
pT3a	2 (4.7%)	0 (0%)	2 (4.7%)	1
EPE	2 (4.7%)	0 (0%)	2 (6.6%)	1
Positive margin	4 (9.5%)	0 (0%)	4 (13.3%)	0.3
Positive lymph nodes	4 (9.5%)	0 (0%)	4 (13.3%)	0.3
Perineural invasion	16 (38%)	0 (0%)	16 (53.3%)	0.001

GS: Gleason Score; RP: radical prostatectomy; PCa: prostate cancer; TV: tumor volume; DRE: digital rectal examination; PSA: prostate-specific antigen; EPE: extraprostatic extension; PSAD: prostate-specific antigen density

It has been believed that low risk PCa does not need immediate intervention because of its low-risk potential for metastases. However, some men may initially appear to have low-risk disease but in fact they have disease reclassified to higher risk.[14] On the other hand, repeated prostate biopsy is frustrating for our patients and sometimes lead to serious complications.[15] Since low-risk PCa is a heterogeneous disease, total removal of the prostate is a valid option with very effective and improved functional outcomes.[16]

Benefits of AS that include avoidance of treatment induced side effects such as erectile dysfunction (ED) and urinary incontinence must weigh against the risk of cancer progression.[17] The term Tumor Volume (TV) was firstly defined by Stamey and McNeal based on radical prostatectomy (RP) specimens.[18] They found an association between TV and stage of cancer, and threshold of 0.5 cm^3 for insignificant cancer was suggested.[18] We did this study to evaluate patients with PCa with GS 3+3 who met the criteria of AS but pursue RP because of patients' fear of missing opportunity for cure.

Material and methods

From September 2010 to October 2017, 123 patients with low-risk PCa were scheduled for curative treatment in two referral centers of Shahid Beheshti Medical University, Tehran, Iran. The patients who met the following ROYAL MARSDEN criteria were included in the study: GS≤3+3, PSA≤15 clinical stage ≤T2a, ≤3 positive cores, and single core positivity of ≤50%.[19,20] The patients who had history of palliative therapy before surgery or incomplete preoperative data were excluded. Forty-two of 123 patients were enrolled in this study. Preoperative clinical history, physical examination, prostate volume, PSA level and transrectal ultrasound biopsy (TRUS Bx) data were evaluated.

Specimens of RP were examined according to the Stanford protocol under microscope. The specimens were received in 10% formalin in three separate containers which included prostate lobes, seminal vesicles, vas deferens, respectively. Each prostate lobe was divided into two parts; anterior and posterior sections. Whole specimens were sliced into 5-μm cuts and stained with H&E. every slide was examined under 40x magnification. For each slice, relative volume of tumoral part was calculated. Total TV was obtained by summation of these parts. All histological samples were again reviewed by one pathologist. Then the TV was calculated.

The ethical committee of Shohada-e-Tajrish Hospital approved this study and let us for review of patients' medical data.

Statistical analysis

Statistical analysis was done using a commercially available software package for the Social Sciences version 20 software. Qualitative data were analyzed by chi-square, and quantitative data were analyzed by independent T-test and Mann-Whitney U test. A p value of 0.05 or less was considered statistically significant in this study.

Results

Forty-two patients with GS 3+3 following RP were enrolled in our study. Demographic data are available in Table 1. Thirty of 42 patients with GS 3+3 had significant cancer (TV> 0/5 cm^3). Four RP pathology report upgrade to GS 3+4 and one upgrade to GS 4+3 and all of them had TV> 0/5 cm^3.

A total of two cases (4.5%) had extra prostatic extension (EPE), which was focal in one and non-focal in another case (Table 1). pT2 and pT3 cases did not differ by patient's age or gland weight. A single tumor nodule was seen in three pT2c cases (14.2%) and in one of two pT3 cases (50%). Surgical margin was positive at apex in three cases and at bladder neck in one case. These cases were considered significant cancers since they were not amenable to complete resection due to the distal location in the prostate, where additional resection would risk incontinence. Additionally, in one case there was positive surgical margin at the area of EPE. None of the cases had seminal vesicle invasion or lymph node (LN) metastasis.

In patients with TV less than 0.5 cm^3, none of the cases had seminal vesicle invasion or LN metastasis or EPE. In patients with TV greater than 0.5 cm^3, two cases (6.6%) had EPE, four cases (13.3%) positive margins and four cases (13.3%) reactive LN.

Sixteen of 30 patients (53.3%) had perineural invasion, and a significant relationship existed between TV greater than 0.5 cm^3 and perineural invasion (p=0.001). There was significant relationship between TV and pathologic stage, and all cases with TV less than 0.5 cm^3 (100%) had pT2a stage (p<0.001). The incidence of pT2c increased when TV was greater than 0.5 cm^3 (21 of 30, p<0.001).

Discussion

There is evidence that screening tests for PCa with PSA or digital rectal examination (DRE) are able to detect PCa at an early stage, but it is not clear if this earlier detection and treatment leads to any change in the natural history and outcome of PCa.[21]

There are many factors other than GS that need to be considered to determine whether low-risk PCa is significant.[22] In 1994 Epstein et al.[23] defined correlation between TV and pathological stage in RP specimens. Authors revealed that combination of TV with other diagnostic assessment tools such as serum PSA level, PSA density, and biopsy pathology report helps to predict outcomes of PCa. Another study of Epstein et al.[23] on 185 men who underwent RP concluded that TV is a desirable parameter for the management of patients with PCa. It is crucial to predict outcomes of patients with GS 3+3 before surgery to avoid unnecessary treatment. AS is a preferred treatment for selected cases with GS 3+3, however, men under AS protocol may experience anxiety, distress or face complications due to the frequent biopsies include pain, embarrassment, hematuria, hematochezia, hematospermia, urinary retention, infection and sepsis.[10,15,24,25]

Approximately one-quarter of men will eventually be upgraded, and definite treatment such as RP should be offered.[26] RP is the most common approach for patients with early diagnosed localized PCa but it may cause ED and urinary incontinence[27], however most of them recover from ED and urinary incontinence after RP.[27-29] In this study we evaluated patients with GS 3+3 who met the criteria for AS and interestingly found that 30 of 42 (71.4%) cases had significant TV (≥0/5 cm^3). This may suggest that even low-risk cancer needs definite treatment.[30] In our study we showed that high pathological stage, positive surgical margins, positive LN and perineural invasion are associated with TV>0.5 cc. In the current study, none of the cases with TV less than 0.5 cm^3 had EPE, positive margins, LN involvement and perinural invasion. In contrast, 6.6% of the cases with TV greater than 0.5 cm^3 had EPE and were not candidates for AS and 53.3% of the patients with TV greater than 0.5 cm^3 had perineural invasion. In this study we found that some patients with GS 3+3 who were suitable for AS, had significant PCa and might lose their opportunity for cure if they prefer AS.

In conclusion, this study may suggest that some patients with PCa with GS 3+3 need definite treatment. Finally, we found that some patients with GS 3+3 have TV>0.5 cm^3 who are considered having significant cancer pathologically and AS may not be appropriate approach to manage these cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Shohada-e-Tajrish Hospital.

Informed Consent: In accordance with retrospective nature of study ethical committee wave inform consent from patients.

Peer-review: Externally peer-reviewed.

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