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ORIGINAL ARTICLE

Validation of revised Epstein's criteria for insignificant prostate cancer prediction in a Greek subpopulation

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Abstract

Background: Different treatment options for patients with prostate cancer (PCa) are applicable after stratifying patients according to various classification criteria. The purpose of our study is to evaluate the revised Epstein's criteria for insignificant PCa prediction in a Greek subpopulation.

Methods: During a 4-year-period, 172 Cretan patients were submitted to radical retropubic prostatectomy in our institution. 23 out of them met the revised Epstein's criteria for the presence of clinically insignificant PCa (clinical stage T1c, prostate specific antigen density < 0.15 ng/ml/g, absence of Gleason pattern 4-5, <3 positive biopsy cores, presence of <50% tumor per core) during pre-treatment evaluation and were retrospectively included in the study. Post-surgery outcomes were evaluated including pathological stage, surgical margins and Gleason score upgrade.

Results: Organ confined disease and insignificant PCa were predicted with a 74% and 31% accuracy, respectively. These figures are remarkably lower than those derived from similar studies worldwide.

Conclusions: Due to the high variation in the revised Epstein's criteria prediction accuracy observed worldwide, the development and implementation of novel tools/nomograms with a greater predictive accuracy is still warranted. Hippokratia 2015, 19 (1): 30-33.

Keywords: Epstein's criteria, Gleason score, insignificant prostate cancer, Gleason upgrade

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Introduction

The widespread use of prostatic specific antigen (PSA) combined with new biopsy protocols have led to overdiagnosis and overtreatment of prostate cancer (PCa) during the last years[1,2].There have been many studies and a lot of nomograms[3–6] have been created in an attempt to detect patients with clinically insignificant PCa. The most widespread predictive tool of insignificant PCa is the implementation of the Epstein's biopsy criteria as modified by Bastian in 2004[7,8]. The Epstein's criteria have been reported to predict organ-confined disease and a high likelihood of cure after radical prostatectomy including biochemical relapse-free survival. These criteria have been studied in many countries but there is no validation to date in Greece.

Epstein *et al* in 1994[7] developed PSA and needle biopsy-related criteria (PSA density <0.15 ng/ml/g, absence of adverse pathologic findings on biopsy (i.e., biopsy Gleason score ≤ 6), presence of PCa in fewer than 3 cores (in 6-core biopsy samples), no more than 50% PCa involvement in any of the cores) for identifying insignificant PCa. According to these criteria the accuracy of predicting organ-confined (<pT3a stage) tumors with volume less than 0.5 ml and without high grade components is 79%. 10 years later, Bastian *et al*[8] revised these criteria and reported a higher predictive accuracy, up to 83.9%. In the present study we attempt to validate Epstein's modified criteria in a Greek subpopulation from Crete and compare our results with similar studies in different populations.

Materials and Methods

During the period 2008-2012, 172 patients were submitted to radical retropubic prostatectomy (RP) in our institution. We retrospectively studied the medical files of these patients focusing on clinical pre-treatment staging and pathological post-treatment reports. 23/172 (13%) patients met the revised Epstein's criteria for the presence of clinically insignificant PCa (clinical stage T1c, PSA density <0.15 ng/ml/g, absence of Gleason pattern 4-5, <3 positive cores in biopsy, <50% tumor in each core) during

Table 1. Data of the 23 patients (out of the 172 patients submitted to radical retropubic prostatectomy during a 4-year-period) that met the revised Epstein's criteria for the presence of clinically insignificant prostate cancer.

Age, year, mean (range)	58.6 (53-74)
PSA before surgery, ng/ml, mean (range)	6.2 (2-9.5)
Prostate volume, ml, mean (range)	68.9 (40-110)
PSAD, ng/ml/g, mean (range)	0.09 (0.03-0.14)
Gleason score	
< 6, no (%)	5 (21%)
6, no (%)	17 (79%)
Number of positive cores	
1, no (%)	12 (52%)
2, no (%)	11 (48%)
Percentage of positive cores, %, mean (range)	13% (5-45%)

PSA: prostate specific antigen, PSAD: prostate specific antigen density.

pre-treatment evaluation.

Clinical stage assessment was based on the TNM staging system 2002. Prostate volume evaluation was based on CT scan and TRUS during biopsy. The average number of biopsy cores taken was 10 (6-18) and the median core size was 15 mm. Pathological reports evaluated biopsy as well as surgical specimens with typical Gleason grading system. No patient was under androgen deprivation therapy or 5-Reductase inhibitors treatment and serum PSA measurements were made prior to biopsy. The characteristics of the patients that met the criteria are summarized in Table 1.

Results

The diagnostic accuracy of organ-confined disease was 74%. 6/23 patients (26%) presented non-organ-confined disease. Thirteen of the 23 patients(57%) presented Gleason score 7 and none 8-10. 3 of these patients (23%) presented extra-prostatic extension. None of them presented infiltration of lymph nodes or seminal vesicles. 3/10 patients (30%) with Gleason score 6 presented extra-prostatic extension but none had infiltration of seminal vesicles or lymph nodes. Figuring out the patients with Gleason score upgrade (13) and the patients with Gleason score ≤ 6 but extra-prostatic extension (3), a total of 16/23 patients (69%) with clinically insignificant PCa presented a pathological stage incompatible with non-insignificant PCa. Therefore, in our study, the sensitivity of the criteria reached only 31% in predicting patients with insignificant PCa. Histopathological findings in these 23 patients after RP are summarized in Table 2.

Table 2. Histopathological findings in the 23 patients that met the revised Epstein's criteria, after radical prostatectomy.

Positive surgical margins, no (%)	6 (26%)
Non organ confined disease, no (%)	6 (26%)
Invasion of prostate capsule, no (%)	6 (26%)
Invasion of seminal vesicles, no (%)	0 (0%)
Positive lymph nodes, no (%)	0 (0%)
Gleason score	
< 6, no (%)	0 (0%)
6, no (%)	10 (43%)
7 (3+4), no (%)	10 (43%)
7 (4+3), no (%)	3 (14%)
Gleason score upgrade, no (%)	13 (57%)
Same Gleason score, no (%)	10 (43%)

Discussion

Epstein *et al* created criteria for the pre-treatment evaluation of patients in order to reduce the number of patients that require immediate therapeutic treatment and the number of over-treated patients. These criteria were used for identification of insignificant PCa discriminating them from low-risk patients according to D'Amico[9] risk group stratification (PSA <10 ng/mL and GS< 7 and cT1-2a). Table 3 summarizes different PCa classifications. Similar criteria were used in several studies[10–12] for selecting patients for active surveillance and not radical therapy, and reported disease-specific survival up to 97.2% at 10 years, establishing active surveillance as an acceptable option for eligible patients. Currently, several other treatment options for localized disease are available, such as prostate brachytherapy and cryoablation, but in our institution these patients are mostly managed with surgery.

Originally, Epstein's criteria could detect patients with organ confined disease with an accuracy of 79%, tumors with volume less than 0.5 ml and without any high grade components. After the revision of these criteria by Bastian *et al* in 2004[8], the detection accuracy of organ-confined disease was reported to have increased up to 91.6%. 18 (7.6%) of the 237 patients with organ-confined disease had a Gleason score 7 or greater. Thus, 199 of the 237 (83.9%) had both disease limited in prostate and Gleason score ≤6. In a more detailed analysis of the results, the revised criteria underestimated both disease stage and Gleason score in 16%. Therefore, the prediction was accurate in 84% of the cases. During the evaluation of these criteria in European populations in 2008[13] researchers found similar results in predicting organ-confined disease (91.7%). However, Gleason score upgrade was greater than the one found in the study of Bastian (accuracy 76% vs. 84%). The evaluation of the criteria in Middle East patients[14] yielded similar results in predicting the prostate confined disease (91.7%) but Gleason score upgrade was higher (40%) with the inaccuracy of the Epstein criteria to predict insignificant prostate cancer reaching 46%. The evaluation of the criteria in Korean patients[15,16] the diagnostic inaccuracy of insignificant PCa was 42.1% and 30.5%. Finally, in Australian patients, Epstein's criteria showed 55% accuracy for insignificant PCa and a 55% Gleason upgrade[17].

The application of the revised Epstein's criteria yielded 74% and 31% accuracy in predicting organ confined disease and insignificant PCa, respectively in the Cretan population, which are significantly lower compared to other studies around the world. These great dis-

Table 3. Criteria of PCa in different classifications.

Insignificant PCa (Epstein's criteria)	Low risk PCa (D'Amico classification)	Organ-confined PCa
PSAD<0.15 ng/ml/g and Biopsy Gleason score ≤ 6 and PCa in fewer than 3 cores (in 6-core biopsy samples) and <50% PCa involvement in any of the cores	PSA<10 ng/mL and Gleason Score < 7 and cT1-2a	Pathological stage <T3a Any PSA Any Gleason score

PCa: prostate cancer, PSA: prostate specific antigen, PSAD: prostate specific antigen density.

crepancies might be attributed to our study limitations including small sample size, retrospective design and absence of standardized biopsy protocol application. Biopsy protocols were applied by several urologists/radiologists and were not standardized regarding the number of cores taken or the technic used, although the effect of intra-observer variation in prostate volume measurement on PSA density calculations among PCa has been reported not to be sufficient to elicit a value >0.15 in 95% of the cases studied[18].

Another reason that might be responsible for these differences observed is that Epstein's criteria could not be accurate enough in the population of Crete in line with reports from Middle East and Korean populations, due to a different biological behavior of PCa among different races/populations. This hypothesis includes a greater proportion of high risk PCa and a significantly higher probability of biochemical failure after curative treatment[19] , but it has not yet been verified in our population. It has also been proved that after the 2005 International Society of Urological Pathology (ISUP) modification of the Gleason grading system the accuracy of Epstein's criteria to predict insignificant PCa declined from 73-84% to 39-76%[19]. The accuracy for predicting Gleason score ≤6 was also reduced from 90.3% to 54.3-75.9%, but organ confined status predictive ability remained favorable[20]. In conclusion, Epstein's criteria were proven to have a very high accuracy in predicting organ confined disease but they were not accurate enough in predicting insignificant disease[21,22]. The great difference found between the results of the present study and the results of other similar studies should alert towards the use of more prognostic factors in the evaluation of patients with theoretical insignificant cancer. The use of various markers has been studied in this respect, especially prostate cancer gene 3 (PCA3) for predicting insignificant PCa with satisfactory results[23,24]. Research was also made towards the use of transperineal template-guided mapping biopsy in diagnosing patients with insignificant PCa and proved that 39.1% of the patients who were diagnosed with insignificant PCa using TRUS biopsy had actually more advanced disease and needed additional treatment[25]. In addition, the use of various nomograms during the pretreatment evaluation of these patients would help in reducing prediction error of insignificant PCa and may also reduce the differences among the various populations.

Conclusion

The challenge of using tools which could differentiate a significant from an insignificant PCa prior to treatment should be a primary goal for the urologists to achieve best treatment results. Epstein's biopsy criteria are used to predict insignificant PCa, but special attention should be paid in patient selection to avoid misclassification. Nevertheless, revised Epstein's biopsy criteria represent a useful tool for insignificant PCa prediction. However, due to the high variation in prediction accuracy observed worldwide with the application of the revised Epstein's biopsy criteria, development/implementation of novel tools/nomograms with a greater predictive accuracy is still warranted.

Conflict of interest

Authors report no conflict of interest.

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