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Original Article

Clinical efficacy of transrectal ultrasound-guided prostate biopsy in men younger than 50 years old with an elevated prostate-specific antigen concentration (>4.0 ng/mL)

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Abstract

Background: Prostate cancer (PCa) is not commonly found in men younger than 50 years of age. However, serum prostate-specific antigen (PSA) concentration has been examined more frequently at a younger age in Asia partially due to an increased awareness of prostate cancer. The purpose of our study was to investigate the efficacy and complication of PSA-triggered transrectal ultrasonography-guided prostate (TRUSP) biopsies. We retrospectively reviewed TRUSP biopsies in young men with elevated PSA concentration in Taipei Veterans General Hospital.
Methods: We reviewed the cases of patients younger than 50 years of age with elevated PSA concentration (>4.0 ng/mL), who received 12 cores TRUSP biopsies at TPEVGH from January 2008−December 2013. The age, family history, digital rectal examination (DRE) results, PSA concentration, free/total PSA ratio, total prostate volume, PSA density, lower urinary tract symptoms and complications after the procedure were reviewed. The pathologic findings of TRUSP biopsy and clinical follow-up were reviewed and analyzed according to the Epstein criteria.
Results: A total of 77 patients were included and were divided into 2 groups: 1) the younger group consisted of 20 patients <40 years of age; and 2) the elder group had 57 patients who were 40−50 years of age. The overall detection rate of PCa was 11.69% (9/77), and all of the PCa cases were diagnosed in the elder group (group detection rate: 15.8%). There was a significant difference in the severity of lower urinary tract symptoms (LUTS) between these 2 groups. All PCa patients were clinically significant according to the Epstein criteria. Two patients experienced fever (2.60%) after TRUSP biopsy.
Conclusion: From our patient cohort, it appears that no benefit was apparent for patients younger than 40 years old who received TRUSP biopsy, even with elevated PSA. However, PCa detected in men between 40 and 50 years of age were all clinically significant. Overall, our results supported current major practice guidelines which recommend an initial PSA checkup at 40 years of age.

Keywords: Biopsy; Epstein criteria; Prostate; Prostate neoplasm; PSA

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

In the United States, PCa was the most commonly found cancer among all males, according to the US Centers for Disease Control and Prevention (CDC).[1] In Taiwan, PCa was the fifth most common and the sixth most lethal cancer found in that country's population.[2] The incidence of PCa in Taiwanese men (30 per 100,000 person-year in 2010) was significantly lower than its American and European counterparts. Though not as prevalent as in Western countries, the incidence rate of PCa in Taiwan has continued to increase for more than 10 years.

Young men 40–50 years of age in Taiwan had a very low 10-year cumulative incidence of PCa, unless their PSA was greater than the 99th percentile (4.07 ng/mL).[3] However, little was known about the PCa features detected by TRUSP biopsy, as well as the side effects of TRUSP biopsy in young patients (under 50 years old) especially in Taiwan.

Several recent studies indicated that overzealous diagnosis and overtreatment of PCa might be induced by PSA screening, particularly in young men. This elevated level of diagnosis and overtreatment has also led to increased economic costs, added social burdens, and unnecessary compromise of both the quality of life and psychological wellness.[4,5] According to the EAU guideline and several other recent studies, a baseline PSA determination for men 40 years of age was suggested to identify a high-risk group for PCa. Such testing to identify a baseline PSA not only provides beneficial risk stratification, but also has helped to guide screening protocols.[6–8] The 2013 American Urological Association (AUA) guideline discourages screening for men younger than 40 years of age, considering the relatively low prevalence of PCa in this age group and the lack of sufficient evidence demonstrating the benefits.[9]

Several studies suggested that for young males, the risk of TRUSP biopsy may outweigh its benefit. Yoo et al.[10] reported that in Korean subjects younger than 40 years of age who received TRUSP biopsy, febrile urinary tract infections occurred in 3 patients (6%), 2 (4%) of whom needed hospitalization. Hematuria persisting longer than 1 week was noted in 2 (4%) patients, and hematospermia was noted in 1 (2%). In this cohort, only one patient (2%) was found to have low risk PCa. However, major guidelines suggested a baseline PSA at 40 years of age, which are based on studies performed on western populations. Thus, we set out to study the clinical efficacy of TRUSP biopsy, and the features of cancer detected in men younger than 50 years of age. To this end, we retrospectively reviewed the records of TRUSP biopsy in men younger than 50 years of age, with high PSA (>4.0 ng/mL) in Taipei Veterans General Hospital (TPEVGH).

2. Methods

We reviewed the medical records of patients younger than 50 years old with high PSA (>4.0 ng/mL) who received 12 cores TRUSP biopsies at TPEVGH from January 2008 to December 2013. Parameters were collected and analyzed including age, family history, initial presentation, digital rectal examination (DRE) results, serum PSA, free/total prostate-specific antigen ratio (%fPSA), total prostate volume, PSA density (PSA/total prostate volume), lower urinary tract symptoms (LUTS), complications related to biopsy, pathologic findings of TRUSP biopsy specimen, pathologic findings of operation specimen if available, PCa stage, treatment and follow-up data. The abnormal DRE findings were defined and identified as either a hard nodule or induration. The study protocol was approved by the institution review board of TPEVGH (VGHIRB No.: 2014-12-002CC).

All prostate biopsies were guided by ultrasonography (Type 2202, BK medical, Herlev, Denmark) in two-dimensional planes [sagittal and axial]. The TRUSP biopsy procedure followed the standard template including parasagittal medial and lateral plane, with each plane comprising the apical, middle, and basal regions of bilateral prostate. Each region was sampled with a biopty gun for a total of 12 cores.[11] The needle cores were submitted separately. The Gleason score, percentage of the tissue involved by the tumor, and presence or absence of perineural invasion were reported for each core. Patients with a biopsy finding of atypical prostatic gland, prostatic intraepithelial neoplasia (PIN), and atypical small acinar proliferation (ASAP) were not included in the malignancy group.

We specified the total percentage of cancer in each individual biopsy core, which was a percentage of a single focus of carcinoma or a sum of separate tumor foci percentages if extensive distance was seen between them.[12] The Epstein criteria was applied to determine insignificant PCa and to see if any of these cancers were eligible for active surveillance. A generally accepted definition of the Epstein criteria was as follows: (1) PSA density (PSAD) ≦0.15; (2) biopsy Gleason score ≦6; (3) ≦2 positive cores; and (4) ≦50% involvement in any single core.[13]

2.1. Statistical analysis

Descriptive and comparative analyses were performed using IBM SPSS ver. 20.0 software (IBM Co., Armonk, NY, USA). Additionally, the Mann–Whitney *U* test or Fisher's exact test were used to compare clinical and pathological data. A P value of less than 0.05 was defined as statistically significant. All given *p*-values were two-tailed.

3. Results

There were 81 patients younger than 50 years of age who received 12 cores TRUSP biopsy at TPEVGH from January 2008 to December 2013. Four patients who received TRUSP biopsy for abnormal DRE or prostate sonography findings were excluded for PSA <4 ng/ml. A total of 77 patients were included for analysis. The baseline characteristics of the study cohort are shown in Table 1. 5 Patients had positive family history and none of them were diagnosed as being PCa patients. Also, 11 of 77 (14.3%) patients had abnormal DRE findings; for all patients, the average PSA was

Table 1
Baseline characteristics of study population.

Age (Mean ± SD) (y/o)	43.36 ± 6.11
PSA (Mean ± SD) (ng/ml)	9.07 ± 11.52
FPSA/PSA (Mean ± SD)	0.12 ± 0.11
Prostate volume (Mean ± SD) (cm^3)	29.83 ± 13.92
PSAD (Mean ± SD) (PSA/volume)	0.33 ± 0.29
Abnormal DRE (%)[a]	11.69
Significant LUTS (%)[b]	42.86
Family history of Prostate cancer (%)	6.5

LUTS = lower urinary tract symptoms; SD = standard deviation.
[a] Abnormal DRE: either a hard nodule or induration was identified.
[b] Significant LUTS: International Prostate Symptom Score (IPSS)≧8. IPSS 0 to 7, 8 to 19, and 20 to 35 signify mild, moderate, and severe symptoms, respectively.

9.07 (±11.52) ng/ml. The average total prostate volume was 29.83 (±13.92) mm^3.

The overall cancer detection rate was 11.69% (9/77). There were 20 patient who were younger than 40 years of age (the younger group). All of the patients were informed of their elevated PSA levels by means of health checkups at other hospitals. Of these subjects, 57 patients were between 40 and 50 years of age (the elder group) and PCa were all in this group. There was no significant difference between the younger and elder groups in terms of PSA level, %fPSA, prostate volume, PSAD, DRE, family history and PCa detection rate. The only significant difference was the incidence of moderate to severe LUTS (Table 2).

According to the pathology results, the patients were divided into PCa and benign groups. However, there was no significant difference in terms of PSA level, %fPSA, prostate volume, PSAD, DRE and family history (Table 3).

Table 4 showed the clinic-pathologic results of the 9 patients with PCa. All PCa were clinically significant according to the Epstein criteria. There were 4 patients who received radical prostatectomy, and 1 patient was currently stage IV, and died of disease after castration therapy. Free-form PSA (fPSA) was available in 4 of them, and all of the %fPSA were less than 25% (Table 4).

Table 2
Subgroup analysis of clinical parameters of Age ≦ 40 y/o and 40 < Age ≦ 50 y/o group.

	Age ≦ 40 y/o	40 < Age ≦ 50 y/o	*p*
Patients number (n)	20	57	0.33
PSA (ng/ml) (Mean ± SD)	7.75 ± 2.21	9.54 ± 13.33	0.33
FPSA/PSA (Mean ± SD)	0.08 ± 0.03	0.13 ± 0.13	0.08
Prostate volume (Mean ± SD) (cm^3)	26.10 ± 8.57	31.13 ± 15.21	0.08
PSAD (Mean ± SD) (PSA/volume)	0.34 ± 0.17	0.32 ± 0.33	0.78
Abnormal DRE (n)	1	10	0.17
Symptomatic LUTS (n)	4	29	0.02[a]
Family history (n)	1	4	0.24
Prostate cancer detected (n)	0	9 (15.79%)	0.06

Abbreviations and definitions as Table 1.
[a] Statistic significant.

Table 3
Comparison of clinical parameters between prostate cancer and benign group.

	Prostate cancer	Benign	*p**
Patient number (n)	9	68	
PSA (ng/ml) (Mean ± SD)	16.60 (±28.43)	8.08 (±6.74)	0.40
FPSA/PSA ratio (Mean ± SD)	0.10 (±0.05)	0.12 (±0.12)	0.52
Prostate volume (cm^3) (Mean ± SD)	29.81 (±10.32)	29.83 (±14.39)	1.00
PSAD (PSA/volume) (Mean ± SD)	0.47 (±0.58)	0.31 (±0.24)	0.11
Abnormal DRE (n)	1	10	1.00
Symptomatic LUTS (n)	5	28	0.49
Family history (n)	0	5	1.00

* $p < 0.05$ was defined as statistically significant.
Abbreviations and definitions as Table 1.

2 TRUSP biopsies were complicated by post biopsy fever. The two patients were 30 and 50 years of age, respectively. There was no AUR, anal bleeding or septic shock after the TRUSP biopsy.

4. Discussion

In our study, there was no PCa detected in patients younger than 40 years of age. In those patients between 40 and 50 years old, the PCa detection rate was 11.69%, and all of them were clinically significant according to the Epstein criteria. Overall, there were 2 people who developed fever after TRUSP biopsy. Our study suggested that for men younger than 40 years of age with PSA elevation, the risk of post TRUSP biopsy complication may outweigh the benefit.

Despite several retrospective analyses of the TRUSPBx in young male, there has not been a purposefully designed prospective trial.[10,14,15] Current guidelines published by major organizations such as the American Urology Association, the European Association of Urology, the American Cancer Society, and the National Comprehensive Cancer Network do not recommend screening for patients <40 years of age for the following reasons: (1) low prevalence of PCa; (2) no evidence of benefit (population subset not represented in randomized trials); and (3) potential harms of screening.[16]

We did not perform PSA screening on patients under 50 years of age. For patients in our study, most people with elevated PSA concentration (>4.0 ng/mL) under 50 years of age were patients who sought a second opinion due to incidental findings of elevated PSA at other institutions. According to AUA guideline, for men 40–54 years of age, screening in this age group is actively discouraged, although it is generally recognized that some men with higher risk due to family history or race may benefit from screening. For these patients, decisions regarding screening should be individualized.

EAU guidelines have recommended Early PSA testing for men over 50 years of age. The current AUA guideline suggests a baseline PSA determination for men aged 40 years old. Therefore, our patients were divided into 2 groups: 1) younger than 40 years of age; and 2) 40–50 years of age.

Table 4
Clinicopathologic data of prostate cancer detected in this cohort.

Age[a] (y/o)	PSA (ng/ml)	Prostate volume (ml)	PSAD (PSA/volume)	DRE	FPSA/ PSA ratio	Pathology (adenocarcinoma)			Epstein criteria[b]	TNM stage
						Gleason grade	Positive cores	Involvement		
42	7.85	11.05	0.71	−	−	3 + 4	6/12	100%	Significant	cT3aN0Mx
45	6.5	20.99	0.31	−	0.09	3 + 3	1/12	10%	Significant	pT2bN0M0
46	11.44	36.15	3.16	−	0.07	3 + 3	4/12	40%	Significant	pT2bN0M0
47	7.85	16.7	2.13	−	−	3 + 3	2/12	30%	Significant	pT3aN0M0
48	5.52	19.26	0.29	−	−	4 + 4	7/12	80%	Significant	cT1cN0M0
48	92.2	46.11	0.29	+	−	4 + 3	13/13	100%	Significant	cT3bN1M1
49	6.62	40.67	0.16	−	0.17	3 + 3	1/12	15%	Significant	cT1cN0M0
49	11.72	26.35	2.25	−	0.05	4 + 4	3/12	100%	Significant	cT1cN0M0
49	4.28	34.55	8.07	−	−	3 + 3	1/12	70%	Significant	pT2aN0M0

[a] No malignancy finding in <40 y/o male.
[b] Epstein criteria: (1) PSA density (PSAD) ≦ 0.15, (2) biopsy Gleason score ≦6, (3) ≦2 positive cores, and (4) ≦50% involvement in any single core.

Serum PSA and digital rectal examination (DRE) are the standard tools for early detection of PCa. In our study, abnormal DRE findings were present in 14.29% (11/77) of our cohort, and the average PSA level was 9.07 ± 11.52 ng/mL. Both serum PSA and DRE are not significantly different in men younger than 40 years of age versus those patients between 40 and 50 years old, and they are also not different in PCa versus non-PCa patients. But the lack of significance may be limited by the small number of patients.

According to recent reports, the incidence of PCa in men younger than 50 years of age accounts for 3−4% of the total PCa.[17,18] Sun et al.[14] reported that the detection rate of PCa by PSA triggered TRUSP biopsy is 4.4% in men younger than 50 years of age, compared to 14.2% of men older than 50 years of age in US. In this study, the investigator suggested a PSA velocity threshold of 0.60 ng/mL/year for men younger than 50 years of age. This is lower than the traditional 0.75 ng/mL/year.[14] However, The PSA velocity (PSAV), and PSA doubling time (PSADT) are of limited use in the diagnosis of PCa due to background noise (total volume of prostate, BPH), the variations in interval between PSA determinations, and acceleration/deceleration of PSAV and PSADT over time. Moreover, some prospective studies have shown that these predictors do not provide additional benefit compared to PSA alone.[19−22]

Also in the US, Kosaka et al.[23] investigated clinical characteristics of men younger than 50 years of age. In that study, 106 patients were included and PCa was noted in 15 patients (12.3%); Gleason score was 6 or lower in 9 patients, and 7 in the other 6 patients. There were no significant differences between non-PCa and PCa patients with regard to PSA value, prostate volume, and PSAD, which are consistent with our study. The Kosaka et al. study proposed a cut value of PSAD <0.32 to predict clinical insignificant PCa, a number which we did not validate. The rationale for this discrepancy does merit further study.

Yang et al. reported PSA triggered TRUSP biopsy in Korea.[24] This study included 75 patients younger than 40 years of age, with PSA > 4.0 ng/mL; the PCa detection rate was 1.3% in the Korean study. In comparison, there were substantially more abnormal DRE findings and significant LUTS findings in our study. The results suggested that PSA alone was not an effective mechanism for detecting PCa for young men, and the detection rate of PCa from PSA screening was very low. This is consistent with the result of our investigation, which suggested that PSA triggered TRUSP biopsy detected no PCa in men under 40 years of age.

The AUA guidelines recommend against PSA-based screening in men less than 40 years of age. However, for high-risk men (i.e. those with a strong family history of prostate cancer or Afro-American ethnic group) aged 40−54 years, and all men from 55 to 69 years of age, individualized discussion of PSA detection of prostate cancer was suggested.[9] In our cohort, all PCa patients had no family history, while the 5 patients with a family history of prostate cancer had negative TRUSP biopsy.

The EAU guidelines recommended baseline PSA measurement at a young age. It was a robust predictor of aggressive PCa, metastasis, and PCa-specific mortality years later. Thus, the baseline PSA testing for young men could be useful for risk stratification, and to individualize protocols for early detection of PCa.[8] With the primary purpose being risk assessment and the establishment of a baseline PSA or PSA velocity, initial PSA checkup provides important prognostic information. TRUSP biopsy triggered by PSA or PSA velocity had higher AUC (area under curve) on ROC (receiver operating characteristic) analysis for PCa detection in men in their 40s than those in their 50s, which has been reported in multiple studies.[14,25]

In 1994, Epstein et al. first reported criteria-based prostate-specific antigen and needle biopsy pathology for identifying potentially insignificant CaP, that might be safely managed by active surveillance.[26] These criteria are associated with a significantly lower risk of adverse findings upon surgery than those with low-risk disease (stage T1c/T2, PSA ≦10 ng/mL, and Gleason score ≦6).[27] The Epstein criteria have been used prospectively in a trial with more than 700 men to aid in selecting patients suitable for active surveillance rather than early intervention.[28]

In our study, PCa was detected in 9 patients, and all PCa cases were clinically significant according to the Epstein criteria. One patient was stage IV at present, and died

following castration therapy. Free form PSA was available in 4 of the 9 patients, and all of the %fPSA were less than 25%. In our study, there was no statistically significant difference in PSA derived parameters including PSA density or %fPSA between cancer and non-cancer patients. However, among those cancer patients, %fPSA were uniformally lower than 25%.

Bill-Axelson et al. have shown the survival advantage of radical prostatectomy over watchful waiting for male patients younger than 65 years old.[29] The younger PCa patients also have lower treatment-related morbidities such as incontinence and erectile dysfunction.[30] Previous reports have also shown a better biochemical progression-free survival after prostatectomy, and less advanced disease at prostatectomy for younger males.[31,32] Younger men have fewer comorbid conditions that might complicate treatment course.[33] These findings suggest that in younger men, active treatment may be more effective, with fewer associated complications.[8]

In our study, 2 (2.60%) TRUSP biopsies were complicated by post biopsy fever. There was no AUR, anal bleeding or sepsis shock after the TRUSP biopsy. There were a number of potential detriments caused by PCa screening, which include hematuria, hematochezia, hematospermia, dysuria and retention, pain and infection.[34] Our group reported on a nationwide study analyzing complications after TRUSP biopsy in Taiwan. The most frequently seen complication of prostate biopsy was voiding difficulty (9.76%), followed by infection (6.59%), and significant bleeding (1.14%). Age was a significant factor in infection requiring treatment.[35] These findings supported the present study that severe complication such as infection following TRUSP biopsy in young men was not higher than the average in Taiwanese patients.

There were several limitations to this study. First, for some patients, initial PSA values were detected at other institutions, and these patients came to our facility for further diagnosis, thus rendering less available complete PSA-derived parameters such as PSA velocity. Second, the DRE, transrectal biopsies and ultrasonographies were not performed by a single urologist. Third, this study may have insufficient power to show the predictive value of several promising parameters such as PSAD due to the limited number of patients. However, our study was conducted to study the efficacy of biopsy at detecting prostate cancer in patients younger than 50 years of age with elevated serum PSA at a single hospital. This is the 1st study focusing on the PSA triggered TRUSP biopsy in Taiwanese young male. And by applying the Epstein criteria, the results suggested that cancer detected in this age group are clinically significant.

In conclusion, our results suggested that PSA triggered TRUSP biopsy provided no benefit for patients younger than 40 years of age, even with elevated PSA value. On the contrary, PCa detected in men 40−50 years of age were all clinically significant. Our result supported current major practice guidelines which recommend an initial PSA checkup at 40 years of age. Further studies are needed to evaluate other markers, to improve cancer detection efficacy and prevent overdiagnosis in this young age group.

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