

Research Paper

Prostate Cancers Detected During 5 α -Reductase Inhibitor Use Are Smaller, De-Differentiated, But Confined when Compared To Controls

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Abstract

Rationale: To compare cancers detected during use of 5 α -reductase inhibitors (5 α RI) with cancers detected in untreated controls stratified for tumor size.

Methods: Prostate biopsies were performed on 235 consecutive patients “for cause” (elevated or rising PSA, positive digital rectal examination, or focal hypoechoic lesion). Fifty patients were excluded for a prior diagnosis of cancer, leaving 185 as the study group (5 α RI=41, control=144). Patients in the 5 α RI group had been treated for a mean of 3.5 years. Cancer was ultimately diagnosed in 114/185 patients.

Results: Cancer was diagnosed in 31/41 (76%) of patients treated with 5 α RI and 83/144 (58%) of the control group ($p=0.04$). Control tumors were larger (14.3 mm) than those in 5 α RI treated patients (9.4 mm, $p=0.0007$). No differences in mean PSA or PSA kinetics were detected between groups. For tumors less than 1.0 cm, the proportion of high grade cancers (Gleason 7-10 and Gleason 4+3-10) was higher in 5 α RI subjects than in controls ($p<0.05$). Fewer 5 α RI patients had proven extracapsular extension than controls, but this difference did not reach statistical significance ($p=0.13$). Normal DNA ploidy was more likely to be diagnosed in the 5 α RI group versus controls, but this difference was not statistically significant (81% vs. 65%, $p=0.14$).

Conclusions: Cancers diagnosed in patients presenting “for cause” treated with 5 α RI drugs are more likely to be de-differentiated compared to controls. However, these tumors are also smaller and less likely to have extracapsular extension and abnormal DNA ploidy than controls.

Key words: Prostate Cancer, Benign Prostatic Hyperplasia, 5 α -reductase inhibitors, Gleason score, DNA ploidy, cancer staging.

Introduction

Treatment of benign prostatic hyperplasia (BPH) with 5 α -reductase inhibitors (5 α RI) is now widespread (1,2). The 5 α RI drugs block the conversion of testosterone into the more active dihydrotes-

tosterone, leading to shrinkage of androgen sensitive tissues in the prostate. Besides the use for treatment of BPH, the anti-androgenic effects of 5 α RI have been extensively explored for the chemoprevention of

prostate cancer. In the largest studies to date, both finasteride and dutasteride were associated with a decrease in the overall number of prostate cancer cases (3,4). However, an unexpected finding was an increase in the rate of high grade cancer detected in the 5 α RI groups compared to controls and raises questions about a possible association between 5 α RI and biologically aggressive tumors (5).

Multiple studies have demonstrated a strong association between prostate cancer size, pathologic grade and curability. Before the era of 5 α RI drugs, most tumors < 1 cm in size were of low Gleason grade, confined to the prostate, and considered "curable" (6-9). Small tumors with high Gleason grades and aggressive biologic behaviors were unusual. The motivation for this study was the recent anecdotal observation in our practice of an unexpected number of small prostate cancers with high Gleason grades in men treated with 5 α RI drugs. Therefore, the purpose of this study was to retrospectively compare the characteristics of *size matched* cancers in patients treated with 5 α RI vs. a control group consisting of cancers in untreated patients.

Materials and Methods

Between 1/1/2008 and 9/15/2010, 235 consecutive transrectal-ultrasound guided prostatic biopsies were performed by a single radiologist (FL) using a Hitachi model EUB 6000 (Hitachi Medical Systems, Terrytown, NY) with 5-7.5 MHz transducer with color flow Doppler. Indications for biopsy included: 1) an abnormal PSA (10) or digital rectal examination (DRE) and/or 2) a focal hypoechoic lesion detected by ultrasound (11,12). When a focal lesion was not visible but the PSA was elevated above predicted for gland volume, sextant biopsies were performed. When a focal hypoechoic lesion was visible, both targeted (2-3 cores) and sextant biopsies were performed (13). Mean tumor size was calculated by the formula (Width + Height + Length)/3 (11). Tumors were assigned to one of four groups based on mean tumor size (<5 mm, 5-9 mm, 10-15 mm, >15 mm). Tumors that were diagnosed only by sextant biopsies (i.e. no hypoechoic lesion was visible) were placed in the < 5 mm group (9). Tumors were grouped into two size categories (<1.0 cm and \geq 1.0 cm for the purposes of statistical comparisons. Retrospective chart review included DRE, PSA level and kinetics, length of time on 5 α RI, and prostate gland volume. The pathologic results included tumor size in millimeters, Gleason score and extracapsular extension determined by biopsies of neurovascular bundles and seminal vesicles (14). DNA ploidy was obtained and considered ab-

normal if tetraploid and aneuploid phases were detected (15,16).

Statistical Analysis

For all statistical analysis results reported, two-sided p-values of 0.05 or less were considered to indicate statistical significance. Two-sample t-tests, ANOVA, Wilcoxon-Mann-Whitney tests and Kruskal-Wallis tests were conducted for continuous variables, and Chi-square tests or Fisher's exact tests for associations were performed for contingency tables. Relative risks were used to compare the risks of high-grade cancer or abnormal pathologic results between the 5 α RI treated group and controls. For our study, Mantel-Haenszel estimates adjusting for tumor size were used to calculate all relative risks and associated confidence intervals; for other 5 α RI related studies we considered, logarithm transformation was used to calculate the confidence intervals of relative risks.

RESULTS

Study group: Of the 235 patients who underwent prostatic biopsies during the study period, 50 were excluded due to a previous diagnosis of prostate cancer. Of the remaining 185 subjects, 41 were being treated with a 5 α RI at the time of biopsy (21 on finasteride alone, 12 on dutasteride alone, and 8 on both), and 144 were not. Prostate cancer was diagnosed in a total of 114 of the 185 subjects, and these 114 patients constitute the study group. When stratified for 5 α RI use, 31/41 (76%) of patients treated with 5 α RI and 83/144 (58%) of the control group had cancer (p=0.04). Among the 31 5 α RI treated subjects with cancer, the mean duration (standard deviation) of 5 α RI use was 3.5 (2.3) years. The treatment durations were not significantly different between subjects with different tumor sizes [p=0.53].

Patient ages in the 5 α RI and control groups were not statistically different, with a mean (standard deviation) of 66.5 (8.6) years and 65.8 (8.8) years, respectively [p=0.70]. Gland volumes of subjects in the 5 α RI group were significantly larger than controls, with a mean (standard deviation) 53.7 (30.4) and 45.4 (24.3) cubic centimeters, respectively [p=0.13].

Tumor sizes: The distribution of tumor sizes between groups was significantly different, with larger tumor diameters found in controls (14.3 [7.0] mm) vs. the 5 α RI subjects (9.4 [4.0] mm) [p=0.0007]. In particular, there was a significantly higher proportion of small prostate cancers (< 1 cm) in the 5 α RI group when compared to controls, Figure 1 [64.5% vs. 26.5%, p=0.0002].

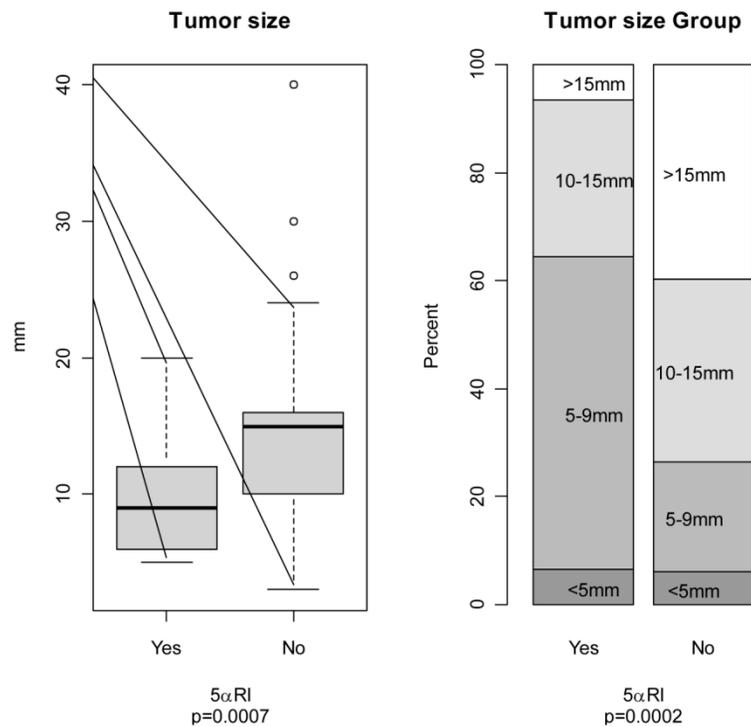


Figure 1: Tumor sizes Distributions. : Distribution of tumor size by 5αRI use. Left: Boxplot for tumor size in millimeters; Right: Percentage of tumor sizes <5mm, 5-9mm, 10-15mm, and >15mm.

Physical examination findings: Digital rectal examination overall was not as likely to be positive in 5αRI patients (16% positive) as controls (41% positive, $p=0.01$). The likelihood of a positive DRE increased as tumor size increased for both 5αRI and controls. For tumors < 1 cm, DRE was positive in 15% and 9%, and in tumors \geq 1 cm DRE positive tumors increased to 18% and 52% for 5αRI patients and controls, respectively [$p=0.04$]. After adjusting for tumor sizes, the relative risk of a positive DRE between 5αRI and no 5αRI groups was 0.60, with 95% C.I. (0.23, 1.56).

Prostate specific antigen: PSA was either elevated (≥ 4) or increased in the majority of patients in both the 5αRI and control groups, regardless of tumor size (Table 1). No significant differences were detected between groups for either total PSA or PSA kinetics (Figure 2).

Gleason scores: Table 1 summarizes the distribution of histologic high grade cancer (Gleason 7-10 or Gleason 4+3-10) stratified by tumor size and 5αRI use. Overall, patients on 5αRI drugs diagnosed with cancer had a higher likelihood of having a high grade tumor, but this difference did not quite reach statistical significance (Gleason 7-10: 77% vs. 64%, $p=0.17$; Gleason 4+3-10: 45% vs. 30%, $p=0.13$). For small (< 1 cm) tumors, the proportion of high grade cancers (Gleason 7-10 and Gleason 4+3-10) was higher than in controls [85% vs. 27% ($p=0.0002$) and 55% vs. 5%

($p=0.0003$), respectively].

Relative risk of high grade prostate cancer: The relative risk of high-grade cancer for 5αRI patients in our study is presented in Table 2 along with the results of other trials examining 5αRI use in chemoprevention. The studies listed include: Finnish Prostate Cancer Screening Trial (17), Prostate Cancer Prevention Trial (PCPT) (3), Radical Prostatectomy (RP) Cases of PCPT (18) and Effect of Dutasteride on the Risk of Prostate Cancer (REDUCE) (4). For the relative risks of Gleason 7-10 and associated confidence intervals, our result of 1.54 with 95% C.I. (1.06, 2.24) was consistent with those from the Finnish study, 7-year PCPT, RP cases of PCPT, as well as REDUCE at 3-4 years. Our relative risk of Gleason 4+3 to 10 was 2.84 with 95% C.I. (1.28, 6.27) was also similar to the relative risk of RP cases of PCPT (where only results of Gleason 8-10 are available), and similar to results from the REDUCE study (3-4 years).

Extracapsular extension: Analysis of systematic biopsy was available in 7/31 (23%) of 5αRI subjects, and 45/83 (54%) of controls ($p=0.003$). Among patients whose systematic biopsy results were available, a higher proportion of control patients had positive extracapsular extension, but this difference did not quite meet statistical significance (14% vs. 44%, $p=0.13$, 5αRI and control subjects respectively). In particular, for tumor size \geq 1 cm, 0/5 of 5αRI subjects

and 20/42 (48%) of non-5αRI subjects had positive ECE (p=0.06).

DNA Ploidy: Analysis of DNA ploidy was available in 26/31 (84%) of 5αRI subjects, and 75/83 (90%) of controls. The remaining 13 patients had insufficient tissue for evaluation. The proportion of

cancers with normal DNA in the 5αRI group was higher than in controls, but this difference was not statistically significant [81% vs. 65%, p=0.14, Table 2]. Adjusting for tumor sizes, the relative risk of abnormal DNA ploidy in the 5αRI group patients was 0.73 with 95% C.I. (0.27, 2.02).

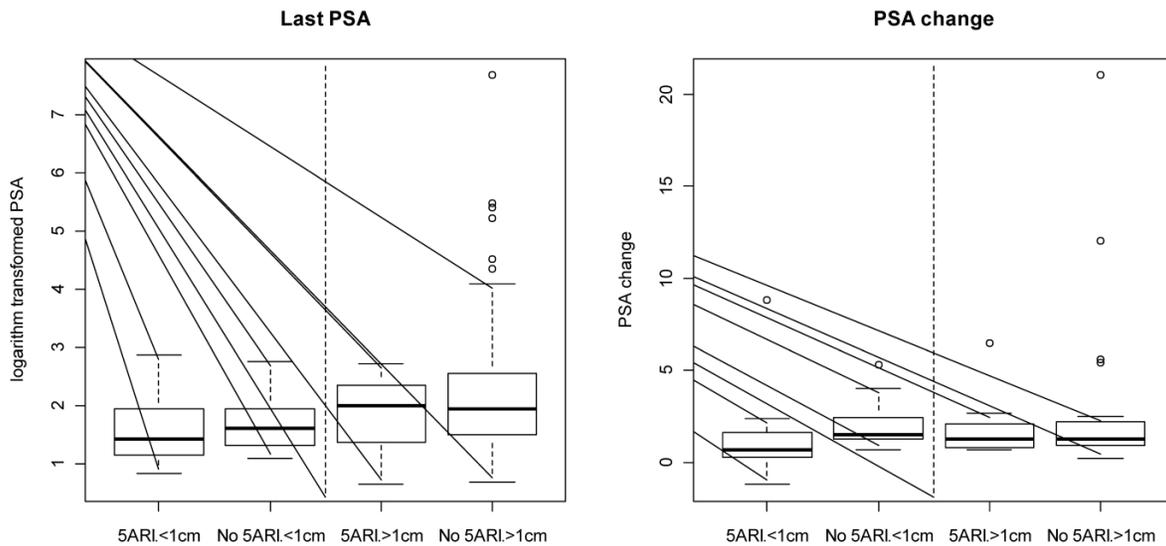


Figure 2: PSA kinetics. Distribution of last PSA measurement (left) and PSA measurement change (right) by 5αRI use and tumor size.

Table 1: PSA Kinetics and Gleason Scores of Prostate Cancers.

TRUS Tumor Size	Group	1 st PSA ≥ 4 or change > 0	PSA Change Median (Range)	Gleason 7-10	Gleason 4+3 to 10	Total
<1 cm	5αRIs	18 (90%)	0.8 (0.2)	17 (85.0%)	11 (55.0%)	20
	No 5αRIs	20 (90.9%)	1.5 (0.7)	6 (27.3%)	1 (4.5%)	22
≥1 cm	5αRIs	11 (100%)	1.3 (0.7)	7 (63.6%)	3 (27.3%)	11
	No 5αRIs	55 (90.2%)	1.3 (0.2)	47 (77.0%)	24 (39.3%)	61
Combined	5αRIs	29 (93.5%)	1.3 (0.2)	24 (77.4%)	14 (45.2%)	31
	No 5αRIs	75 (90.4%)	1.5 (0.2)	53 (63.9%)	25 (30.1%)	83
Subtotal		104 (91.2%)	1.3 (0.2, 21)	77 (67.5%)	39 (34.2%)	114

Table 2: Relative Risk of High-Grade Cancer in 5αRI patients.

Study	Relative Risk (95% C.I.)	
	Gleason 7-10 vs. Gleason ≤ 6	Gleason 4+3-10 vs. Gleason ≤ 3+4
1. Current study	1.54 (1.06, 2.24)	2.84 (1.28, 6.27)
2. Finnish study ¹⁷	1.59 (1.01, 2.50)	-
3. PCPT (All Cancer) ³	1.69 (1.46, 1.96)	2.43 (1.75, 3.36)*
4. PCPT (RPs) ¹⁸	1.68 (1.30, 2.17)	3.26 (1.87, 5.69)*
5. REDUCE (1-2 years) ⁴	1.09 (0.91, 1.31)	1.19 (0.81, 1.75)
6. REDUCE (3-4 years) ⁴	1.67 (1.21, 2.34)	5.09 (2.27, 11.40)
7. REDUCE (1-4 years) ⁴	1.22 (1.04, 1.42)	1.68 (1.21, 2.34)

*: Relative risk between Gleason 8 to 10 vs. Gleason ≤ 7.

Table 3: Tumor Characteristics.

Tumor Size	Group	Extracapsular extension		DNA ploidy	
		Positive	Total	Normal	Total
<1 cm	5 α RI	1	2	14 (77.8%)	18
	No 5 α RI	0	3	14 (82.4%)	17
\geq 1 cm	5 α RI	0	5	7 (87.5%)	8
	No 5 α RI	20 (47.6%)	42	35 (60.3%)	58
Combined	5 α RI	1 (14.3%)	7	21 (80.8%)	26
	No 5 α RI	20 (44.4%)	45	49 (65.3%)	75
Subtotal		21 (40.4%)	52	70 (69.3%)	101

Discussion

The randomized controlled trials investigating the potential chemopreventive attributes of 5 α RI drugs published to date were designed primarily to detect a difference in the incidence of prostate cancer in a large population treated with 5 α RI drugs. As a result, routine biopsies performed at fixed time intervals (without a particular clinical indication) were a critical component of the trial design. The results of these timed biopsies demonstrated a decrease in the overall number of cancers detected in 5 α RI-treated subjects compared to untreated controls. This decreased number of detected cancers led the authors to conclude that 5 α RI drugs were chemopreventive against prostate cancer. By way of contrast, our study is a retrospective analysis of a series of prostatic biopsies performed for specific clinical indications (an abnormal physical examination, rising or abnormal PSA, or a hypochoic lesion detected at ultrasound), i.e. "for cause." Therefore, the focus of our study is on those patients that already have met the criteria to undergo prostatic biopsy, not an epidemiologic study of the effect of 5 α RI treatment on a population. In this setting, the positive biopsy rate was slightly higher for patients treated with 5 α RI when compared to controls (76% vs. 58%, $p=0.04$). We believe that biopsying "for cause" such as in this study, is representative of most clinical practices, and is best used to inform physicians and patients when management decisions are being made. Interestingly, in the two randomized studies of 5 α RI for chemoprevention of prostate cancer published to date (PCPT and REDUCE), biopsies performed "for cause" found no significant difference in prostate cancer detection rates between groups (3,4).

Assuming that treatment of a population with 5 α RI decreases the number of cancers detected, the overall salutatory effect of this result on a population bears close scrutiny in light of other data from the

trials and the results of this study. Prior to the 5 α RI era, virtually all small (<1cm) prostate cancers were of low histologic grade, only rarely had extracapsular extension, and were highly curable (6-9, 11,12). Prior pathologic studies strongly suggest that 5 α RI drugs either shrink or inhibit the growth of many prostate cancers (18,19). The results of our study support this hypothesis--65% of patients treated with 5 α RI had tumors <1cm as compared to only 27% in untreated controls. The question that remains is whether shrinking or inhibiting tumor growth ultimately changes biologic behavior. In the absence of a long-term longitudinal randomized controlled trial, examination of surrogate markers of tumor aggressiveness lead to a mixed picture. For example, in this study, Gleason scores were higher in patients treated with 5 α RI compared to controls. This finding was even more dramatic in small tumors where 85% of patients in the 5 α RI group were found to have aggressive tumors (Gleason 7-10) compared to 27% in the control group. The relative risk of having an aggressive tumor in this study was 1.54, a comparable result to other studies where this ranged from 1.1-1.7 (Table 2). Thus, while the overall number of tumors may be decreased, the histologic aggressiveness of the remaining tumors appears to be increased.

Questions have been raised as to whether the high grade cancers detected during PCPT and REDUCE were a result of artifactual morphologic changes that could result in an over-estimation of the biologic potential of high-grade cancers in patients treated with 5 alpha-reductase inhibitors (20). Lucia, et al. evaluated the pathology of cancers found during PCPT and concluded that finasteride did not induce histomorphologic changes in prostate cancer, but may have contributed to the increase in high-grade cancers (18). Civantos, et al. observed that finasteride could induce foci of low grade prostate cancer to resemble high grade cancer (21). In response to this controversy, the FDA Oncologic Drugs Advisory Committee

had the histopathology from the PCPT and REDUCE trials re-evaluated by multiple urologic pathologists. Results of this analysis demonstrated that insignificant histopathologic differences were detected between cancers in patients treated with 5 alpha-reductase inhibitors and placebo, and intra-observer variability between Gleason scores among pathologists was low (22,23).

The association of low volume tumors and high Gleason scores found in this study most likely is a reflection of the time our patients had been on 5αRI drugs prior to diagnosis (mean 3.5 years). Despite the fact that our study is limited by data collection at a single time point, the longitudinal data from other studies demonstrates similar results in patients who have been on 5αRI drugs for ≥ 4 years. For example, a higher proportion of high grade cancers were detected in the later data (but not at earlier time points) in the Finnish (17) and REDUCE (4) studies. Throughout the seven years of the PCPT (3) high grade cancers occurred. However the end of study biopsies at year 7 discovered 38% (211/557) of these high grade cancers (23). This raises the possibility that 5αRI drugs selectively inhibit the growth of hormonally sensitive low grade cancers by reducing the levels of intracellular dihydrotestosterone within the prostate. In the case of high grade or heterogeneous cell populations, 5αRIs may selectively allow growth of only the hormonal refractory high grade components.

Besides Gleason score, other markers of biologic activity include extracapsular extension of tumor and tumor ploidy (14,15,16). In this study, the risk of extracapsular extension was most dependent on tumor size rather than Gleason score. In fact, the overall risk of extracapsular extension was less in 5αRI treated patients vs. untreated controls, likely reflecting the smaller tumor size in 5αRI patients. The etiology of decreased extracapsular extension in this series may be similar to earlier studies where adjuvant treatment of large prostate cancers prior to radiation therapy with androgen deprivation shrunk tumors and decreased overall mortality (24,25). Based on the results of this study, it could be argued that 5αRI is protective against extracapsular invasion in patients ultimately diagnosed with cancer, despite higher Gleason scores. The other marker of aggressive biologic behavior examined in this study, tumor ploidy, demonstrated a more normal DNA appearance in 5αRI treated patients vs. controls, but this difference was not statistically significant ($p=0.14$). Therefore, it appears as if patients treated with 5αRI who are eventually proven to have prostate cancer tend to have higher grade (but smaller) tumors with less evidence of extracapsular extension vs. controls, and more normal (but not sta-

tistically significant) appearing DNA. These findings correlate with the findings of the PCPT where high grade cancers were associated with lower surrogate findings of tumor aggression in patients treated with Finasteride (18). Whether this translates into a survival difference compared to untreated prostate cancer remains to be seen.

The main limitation of this study is the retrospective consecutive case-series design and the lack of randomized controlled data. However, while this is a weakness in determining the impact of 5αRI treatment on a population, it is advantageous when applying the findings to a clinical practice where the target population is patients who have undergone a positive biopsy and are being treated with 5αRI drugs. An additional limitation is our use of ultrasound to stratify patients according to tumor size. We have proven the accuracy of tumor size measurements using ultrasound in our practice (11,12,14), however, it is unclear whether this method is generalizable to all practitioners. In the interest of completeness, we have also included conglomerate data based on sextant biopsies similar to studies where targeted ultrasound techniques were not available (13). The data on extracapsular extension was also obtained using targeted biopsies according to our previously published methods (14). This could lead to an undersampling bias since generally only tumors >1 cm received extra-capsular biopsies. Lastly, this study was limited to a 32 month period and the mean duration of 5αRI use was only 3.5 years. Whether treatment with 5αRI over longer time periods would change the results is not known, but a longer term study will be needed to answer these questions and determine any impact on survival.

In summary, our study and others suggest that prostate cancer diagnosed in patients who are treated with 5αRI over extended periods are associated with increased tumor grade, even in small tumors < 1 cm. Extracapsular extension of cancer and abnormal tumor ploidy appear to be decreased in patients on 5αRI drugs. Therefore, besides Gleason score, the other surrogate markers of tumor aggressiveness suggest that small tumors (even if high grade) in 5αRI-treated patients may still be low risk if detected when small. This information suggests the need for an aggressive screening strategy for patients who are expected to remain on 5αRI drugs for long time periods.

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Conflict of Interest

The authors have declared that no conflict of interest exists.

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