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Original Article

Characteristics of incidental prostate cancer after radical cystoprostatectomy for bladder carcinoma in Chinese men

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Abstract: The purpose of this study was to analyze and characterize the clinicopathological features of incidental prostate cancer (PCa) after radical cystoprostatectomy (RCP) for bladder cancer in Chinese patients. We retrospectively reviewed 378 male patients who underwent RCP for muscle invasive bladder cancer at our center and identified 47 men with incidental PCa. The clinicopathological data of incidental PCa after RCP were compared with those of clinical T1c PCas who had radical prostatectomy at our institute. Forty-seven of the 378 patients (12.4%) were diagnosed with PCa. The incidental PCa was well-differentiated in 68.1% of patients, compared to 33.5% of patients with T1c PCa, and was significantly more unifocal than the T1c PCas. When compared to T1c PCa, the incidental PCa was more likely to be organ-confined, have negative margins and be classified as clinically insignificant. After a mean 48-month follow-up, only one patient with incidental PCa was confirmed to have bone metastasis. While 9 patients with clinical T1c PCa were found to have tumor recurrence or metastasis and 5 patients had died caused by PCa. In our study, the prevalence of incidental PCa in RCP specimens was 12.4%. These incidental PCas were likely to be unifocal, organ-confined, and clinically insignificant. The technique of capsular and apex preservation of the prostate was not a first option for patients with bladder cancer, as it increased the risk of a positive surgical margin.

Keywords: Prostate cancer, bladder tumor, radical cystoprostatectomy, radical prostatectomy, clinical T1c prostate cancer

Introduction

Prostate cancer (PCa) is a common cancer and the second leading cause of death in male in the United States. Its incidence is significantly increasing in China. Autopsy studies have shown that incidental PCa occurs in 30% of 50-year-old men and in 70% of 80-year-old men in the US [1]. Moreover, the prevalence of fortuitous PCa in American males was much higher than that for Chinese males. In China, the prevalence was 9.3% of 51- to 69-year-old men and 25% in men over 69 years old [2]. An increasing number of studies have demonstrated that the incidence of prostate cancer was high in patients with bladder cancer [3, 4]. Reportedly, the coexisting PCas were typically small, well differentiated, localized entirely within the gland, and usually regarded as clinically insignificant. The reported rate of coexisting PCas is 14% to 60% in other countries [3, 5, 6]. However, there had been a few reports regarding incidental PCa in Chinese males with bladder cancer.

To determine the prevalence, characteristics and outcomes of incidental PCa in Chinese men, we compared the pathological features of PCa in radical prostatectomy (RP) specimens after screening detection of PCa without clinical signs of PCa (T1c) with those fortuitously found in radical cytoprostatectomy (RCP) specimens of patients treated for bladder cancer. We compared the short-term clinical outcomes in these two groups as well.

Material and methods

Patients

From January 2005 to December 2010, 383 consecutive male patients with bladder cancer

had performed RCP at our hospital. The preoperative clinical evaluations included B ultrasound, a digital rectal examination (DRE), a chest X-ray, an intravenous pyelogram (IVP) and either contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI). All patients had their serum prostate-specific antigen (PSA) tested before surgery. Five patients with bladder cancer were diagnosed with synchronous PCa before surgery and excluded from the current study. In 378 patients, standard RCP with bilateral pelvic lymphadenectomy via an open or laparoscopic method was performed on patients with urothelial carcinoma of the bladder. Urinary diversion consisted of an ileal conduit in 265 cases, a cutaneous ureterostomy in 56 cases, and an orthotopic ileal neobladder in 57 cases. To compare the pathological characteristics and the short-term outcome of incidental PCa with that of other PCas, we also included patients with clinical T1c PCa (prostate carcinoma having been diagnosed solely on the basis of elevated PSA levels) who had undergone RP during the same period at our institution. Patients who had received preoperative androgen ablation therapy were excluded, which resulted in our enrolling 158 T1c PCa patients. This study was reviewed and approved by our institutional internal review board.

Pathologic examination

All specimens from RCP and RP were immersed intact in 10% neutral buffered formalin solution for 24 hours. The entire prostate was submitted for histopathologic analysis. A routine pathologic examination was conducted by completely transverse sectioning the prostate from apex to base at 4-mm intervals. Two experienced genitourinary pathologists microscopically reviewed all the specimens. When prostate adenocarcinoma was identified, tumor location and tumor volume (which were calculated according to Chen et al. based on the formula: 0.4 (slope of the regression line) × length × width × CST thickness (number of cross sections × sectional thickness)) were recorded. The Gleason score, presence of extracapsular extension, evidence of seminal vesicle invasion, and lymph node metastasis were also documented. The pathological stage of PCa was based on the 2010 revision of the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) tumor, node and metastasis (TNM) system. The Gleason score was determined using the 2005 International Society of Urological Pathology (ISUP) modified Gleason system. If needed, immunohistochemical staining was performed using specific antibodies against PSA, 34βE12, P504S or p63.

In our study, clinically significant PCa was defined as the presence of extraprostatic extension, seminalvesicle invasion, positive surgical margin, lymph node metastases, tumor volume ≥ 0.5 cm^3 or a Gleason score ≥ 7, as modified by Epstein's criterion.

Follow-up and clinical evaluation

All patients were scheduled for DRE, serum PSA evaluation and contrast-enhanced CT every 3 months for the first postoperative year and biannually thereafter. Biochemical recurrence (BCR) was defined as a sustained PSA level higher than 0.2 ng/mL on two or more consecutive occasions. We evaluated differences between the clinical characteristics and the short-term outcome of unsuspected PCa and clinical T1c PCa.

Statistical analysis

Continuous variables (age and serum PSA level) were compared using Student's *t-test*. Categorical and binary variables were compared using the Kruskal-Wallis and Chi-square tests, respectively. Statistical analysis was performed using Social Sciences (SPSS, Version 16.0) and GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA). Descriptive statistics are presented as the mean ± SD, median, number, and percentage. An unpaired *t*-test (two-sided) was used for comparison between the two groups. Statistical significance was defined as a two-sided p-value ≤ 0.05.

Results

Characteristics of concomitant PCa with bladder cancer

Of the 378 patients who underwent RCP, incidental PCa was detected in 47 patients (12.4%). Detailed features of those 378 patients are summarized in **Table 1**. The mean preoperative serum PSA level was 3.02 ng/mL in the 47 patients with fortuitous PCa and 2.93 ng/mL in patients without incidental cancer, which was not a significant difference (P = 0.32) (**Figure 1B**). Only 4 of those patients who underwent

Table 1. The Characteristics of patients who had radical cystoprostatectomy

Characteristics	Total	Incidental PCa	Non-incidental PCa	*P* Value
Patients (n)	378	47	331	
Age of patients at procedure (yr), mean ± SD	68.4±1.05	73.9±0.89	65.3±1.21	<0.001[a]
TPSA (ng/ml), median (range)	2.98±0.79	3.02±0.58	2.93±0.85	0.32[a]
F/T (%)	29.6±6.1	28.5±6.7	30.2±5.6	0.45[a]
Pathological stage of bladder cancer				0.71[b]
pT1 (%)	112 (29.7)	14 (29.8)	98 (29.6)	
pT2a (%)	72 (19.0)	8 (17.0)	64 (19.3)	
pT2b (%)	106 (28.0)	13 (27.7)	93 (28.1)	
pT3a (%)	88 (23.3)	12 (25.5)	76 (23.0)	

Footnotes: [a]Student's *t-test*. [b]Kruskal-Wallis test.

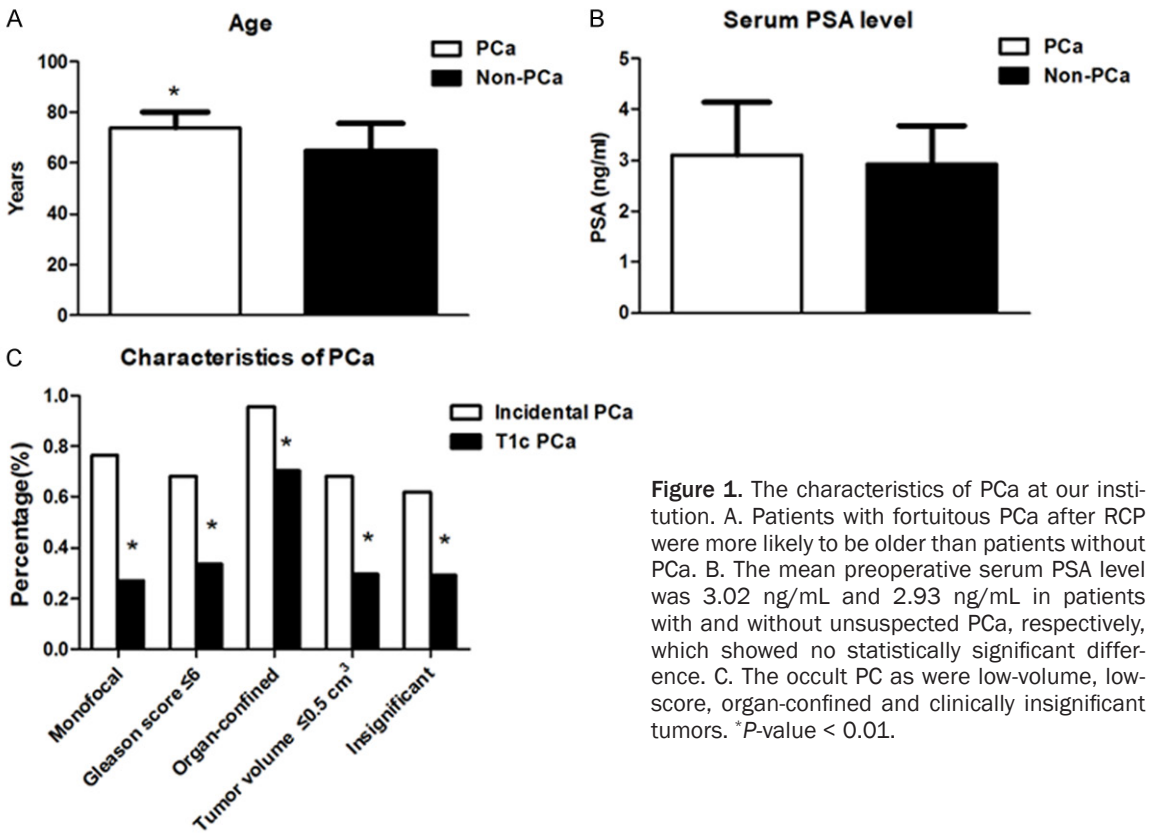

Figure 1. The characteristics of PCa at our institution. A. Patients with fortuitous PCa after RCP were more likely to be older than patients without PCa. B. The mean preoperative serum PSA level was 3.02 ng/mL and 2.93 ng/mL in patients with and without unsuspected PCa, respectively, which showed no statistically significant difference. C. The occult PC as were low-volume, low-score, organ-confined and clinically insignificant tumors. *P-value < 0.01.

RCP had a preoperative serum PSA level higher than 4 ng/mL (rang, 4.3 to 5.8 ng/mL), but they all had a normal PSA free percentage and PSA density. Patients with occult PCa after RCP were more lik lence in other pathological stages (**Table 2**). No case had positive regional lymph nodes from PCa. In 15 specimens (31.9%), the total tumor volume was more than 0.5 cm^3. Of the 47 incidental cases of PCa, 18 (38.3%) were defined as clinically significant (**Figure 1C**).

Features of clinical T1c PCa versus unsuspected PCa with bladder cancer

The comparison of the 158 T1c PCas and 47 incidentally detected PCas in RCP specimens is listed in **Table 2**. The patients with fortuitous PCa were significantly older than those with T1c PCa (P < 0.001 =. The concomitant PCas showed more favorable features than the clinical T1c PCas. The coexistent PCas were well-differentiated (Gleason ≤ 6) in 68.1% of PC as

Table 2. The clinicopathological features of incidental PCa after RCP and clinical T1c PCa

Characteristics	Incidental PCa (%)	cT1c PCa (%)	*P* Value
Patients (n)	47	158	
Age of patients at procedure(yr), mean ± SD	73.9±0.89	69.4±0.45	<0.001[a]
PSA level (ng/ml), median (range)	3.02±0.58 (43)	12.6±1.30	0.0047[a]
Focality			<0.001[b]
Monofocal	36 (76.6)	43 (27.2)	
Multifocal	11 (23.4)	115 (72.8)	
Gleason score			<0.001[c]
≤ 6	32 (68.1)	53 (33.5)	
7 (3+4)	7 (14.9)	43 (27.2)	
7 (4+3)	3 (6.4)	26 (16.5)	
8-10	5 (10.6)	36 (22.8)	
pT (TNM system)			<0.001[c]
pT2a	38 (80.8)	27 (17.1)	
pT2b	2 (4.3)	25 (15.8)	
pT2c	5 (10.6)	59 (37.3)	
pT3a	2 (4.3)	18 (11.4)	
pT3b		23 (14.6)	
pT4		6 (3.8)	
Seminal vesicle invasion			0.006[b]
Negative	47 (100)	135 (85.4)	
Positive	0	23 (14.6)	
Extraprostatic extension			0.04[b]
Negative	44 (95.7)	141 (84.2)	
Positive	2 (4.3)	25 (15.8)	
Regional lymph nodes from PCa			0.034[b]
Negative	47 (100)	144 (91.3)	
Positive	0	14 (8.7)	
Surgical margin status			0.003[b]
Negative	45 (95.7)	121 (76.6)	
Positive	2 (4.3)	37 (23.4)	
Total tumor volume, cm^3			
Mean ± SD (Range)	0.23±0.32	1.4±1.07	<0.001[c]
≤ 0.5	32 (68.1)	63 (29.9)	
≥ 0.5	15 (31.9)	95 (60.1)	
Apex involvement	10 (21.2)	61 (38.6)	0.028[b]
Clinical significant	18 (38.3)	112 (70.9)	<0.001[b]
Clinical insignificant	29 (61.7)	46 (29.1)	
Follow-up (months)	48.7±11.3 (45)	51.1±9.8 (138)	0.292[b]
Tumor recurrence or metastasis	1 (2.1)	9 (5.7)	0.315[b]
Death cause by PCa	0	5 (3.2)	0.217[b]

Footnotes: [a]Student's *t-test*. [b]Chi-square test. [c]Kruskal-Wallis test.

versus 33.5% of T1c PCa. The incidental PC as were more prone to being unifocal (**Figure 1C**) and to having an average six-fold smaller tumor volumes when compared to T1c PCas (0.23 cm^3 versus 1.4 cm^3, respectively). Furthermore, the coincidence of PCa was not significantly an extraprostatic extension (4.3% versus 15.8%) or in regional lymph node metastasis (0% versus 8.7%). The tumors were significantly organ-confined (95.7% versus 70.2%) (**Figure 1C**) and had negative margins (95.7% versus 76.6%). The occult PC as were likely to be classified as

Table 3. Incidental PCa after RCP: data from the literature

Reference	Country	No. of patient	Mean Age (Yr)	Section (mm)	No. of PCa (%)	No. of significant PCa (%)
Winkler et al. [3]	UK	97	NA	2	58 (60)	31 (53)
Kouriefs [7]	UK	128	NA	NA	23 (18)	NA
	UK	225			81 (36)	
Rocco et al. [8]	Italy	63	67	3	34 (54)	12 (35)
Mazzucchelli et al. [9]	Italy	248	68	3	123 (49.6)	23 (18.7)
	Italy	311			157 (50.4)	
Ruffion et al. [10]	France	100	62	2.5	51 (51)	6 (12)
Delongchamps et al. [6]	France	141	62	4	20 (14.2)	14 (70)
	France	241			71 (29.5)	
Joung et al. [11]	Korea	36	66	4	18 (50)	7 (19.4)
Weizer et al. [12]	USA	35	65	NA	16 (47)	4 (25)
Abbas et al. [13]	USA	40	64.3	2-3	18 (45)	6 (33)
Revelo et al. [14]	USA	121	67.4	5	50 (41)	24 (44.8)
Bruins et al. [15]	USA	1476	67	3-5	559 (37.9)	123 (22)
Ward et al. [16]	USA	129	69	NA	30 (23)	18 (60)
	USA	1801			673 (37.4)	
Conrad et al. [17]	Germany	133	60	3	58 (43.6)	11 (19)
Gakis et al. [18]	Germany	95	68	4-5	26 (27)	7 (27)
	Germany	228			84 (36.8)	
Yang et al. [19]	Taiwan	49	67	8.3	16 (33)	NA
Lee et al. [20]	Taiwan	248	63.5	NA	10 (4.0)	NA
	Taiwan	297			26 (8.8)	
Abdelhady et al. [21]	Canada	204	67	NA	58 (28.4)	18 (31)
Sivalingam et al. [4]	Canada	83	71	5	25 (30)	12 (14.5)
	Canada	287			83 (28.9)	
Moutzouris et al. [22]	Greece	59	66.5	5	16 (27)	NA
Nakagawa et al. [23]	Japan	349	65	5	91 (26.1)	68 (74.7)
Kurahashi et al. [24]	Japan	251	65.3	3-5	31 (12)	9 (29)
	Japan	600			122 (20.3)	
Aytac et al. [25]	Turkey	300	62	3-5	60 (20)	40 (66.6)
Aydin et al. [26]	Turkey	121	67.1	NA	17 (14.3)	NA
	Turkey	421			77 (18.3)	
Hosseini et al. [27]	Iran	50	62.5	NA	7 (14)	5 (57)
Jin et al. [28]	China	264	70.9	5	37 (14)	12 (32.4)
Present study	China	378	72	4	47 (12.4)	18 (38.3)
	China	642			84 (13.1)	
	Overall	5198			1499 (28.8)	

clinically insignificant (61.7% versus 29.7%) (**Figure 1C**). Additionally, clinical T1c PCa was more likely to involve the apex of the prostate in our study (**Table 2**), compared to the coincidence of PCa. After mean 48-month follow-up, only one patient with incidental PCa had confirmed bone metastasis and no patients died from the incidentally detected PCa. Nine cases of T1c PCa were found to have tumor recurrence or metastasis, and 5 patients with PCa died.

Discussion

The incidence of PCa varies significantly among countries, and it is remarkably lower in Asia than in the west. Previous studies showed that the proportion of unsuspected PCa varies from

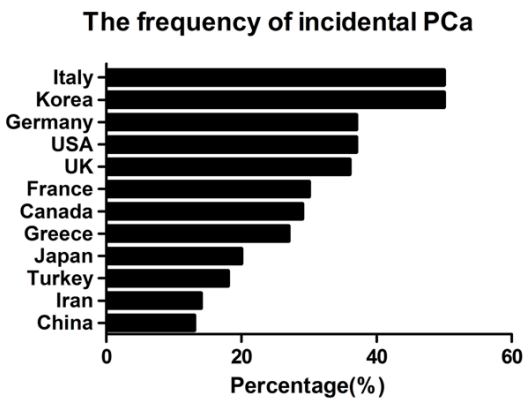

Figure 2. The frequency of incidental PCa in different countries. In developed countries, such as the United State of America, Germany, Korea and Italy, the prevalence of concomitant PCa in RCP specimens was very high. The highest morbidity of incidental PCa was 50.4%, which was reported from Italy. However, the mean frequency of incidentally discovered PCa in developing countries (i.e., Turkey, Iran and China) was approximately 15%.

12% to 60% [3, 4, 6-28] (**Table 3**). Furthermore, the mean global prevalence of incidental PCa in RCP specimens was 28.8% (**Table 3**). Therefore, in developed countries, such as in the US, Germany, Korea and Italy, the concomitant PCa in RCP specimens is significantly more common than that in developing countries (**Figure 2**). Regarding the published studies in **Table 3**, Winkler et al. [3] reported a 60% rate of incidental PCa in RCP specimens. Bruins et al. analyzed 1,476 RCP specimens at the University of Southern California and diagnosed 559 patients with coexistent PCa (559/1476, 37.9%). On the contrary, the frequency of incidental PCa after RCP was lower in developing countries. The prevalence of unexpected PCa in our study was in accordance with a previous study performed by Hosseini et al. [27] in Iran. The high range for the incidences of coexistent PCa may be related with hereditary and exogenous factors, such as food consumption and patterns of sexual behavior.

The pathologic sampling techniques may be another significant factor for the lower cancer incidence. In the case of the pathologies, the thickness of the slice of the prostate and whether the prostate is totally embedded represent two important issues to be considered. The frequency of PCa was present in 12.4% of RCP specimens in our series, with a slice taken every 4 mm from the base to the apex of the gland. Joung et al. [11] reported that PCa was present in 18 out of 36 patients (50%) who had undergone RCP when prostates were transversely sectioned at 4-mm intervals. Insignificant cancers are also more frequently identified by more accurate evaluation. Winkler et al. [3] presented the highest prevalence of coexisting PCa at 60% in 97 RCP specimens after sectioning at 2-mm intervals, and 52% of the unexpected PCa cases were considered clinically significant (tumor volume of 0.5 mL or more, Gleason score >6 and no organ confinement). These results are consistent with the data reported by Ruffion et al. [10], who detected a rate of incidental PCa of 51% among their patient population using 2.5-mm section intervals, but found that only 12% of the cancers were clinically significant PCa. These findings provide strong evidence that the prevalence of PCa in RCP specimens is related to the slice thickness of the studied prostate.

The incidentally detected PC as in RCP specimens are shown to generally involve small lesions confined within the prostate. Similar findings were confirmed by our study that is, the coincidence of PCa was regarded as having more favorable characteristics in term of serum PSA, pathological stage, Gleason grade, perineural invasion and capsular penetration than that of clinical T1c PCa. Furthermore, in our study, 61.7% of incidental PCa was judged to be insignificant cancer. However, the proportion of insignificant disease in T1c PCa patients was only 29.1% in our center. This prevalence is similar to a previously reported rate of insignificant cancer of 27% in screen detected PCa at the ERSPC Rotterdam [29]. This finding indicated that incidental PCa is lower than T1c PCa with regard to stage, Gleason score, and surgical margin status.

Androulakakis et al. have suggested that the association of PCa with bladder cancer did not enhance the progression of both cancers. The prognosis appeared to be related to the characteristics of each tumor, respectively. During the mean 48-month follow-up in this study, there was only one patient with confirmed bone metastasis, and no patients died due to unsuspected PCa. Other authors [6, 13] have obtained results similar to ours. These results suggest that the outcome of patients with incidental PCa after RCP depends on the progression of the bladder cancer.

Recently, several investigators have suggested that prostate-sparing cystectomy (PSC), pre-

serving the prostatic capsule and apex, can help to improve functional recovery, such as sexual function and urinary continence. However, quality-of-life considerations should be balanced against concerns of cancer control. PSC increases the risk of surgical margin and residual cancers, as the fortuitous PCa and prostatic urothelial cancer are common in RCP specimens. Revelo et al. [14] have analyzed the presence and location of concomitant PCa in 121 RCP specimens. Of the 50 PCas that were diagnosed, 60% involved the apex, including 19 of 24 (79%) that was significant cancers. Compared with the coincidence of PCa, clinical T1c PCa was more likely to involve the apex of the prostate in our study. Therefore, there is strong evidence that the technique of capsular and apex preservation increased the risk of a positive surgical margin.

Although serum PSA is widely used to screen for PCa, our study showed that preoperative PSA could not detect incidental PCa in patients with bladder cancer. Some other publications have also confirmed these results [23, 28]. However, Winkler et al. [3] found the mean preoperative PSA to be 3.1 ng/mL in patients with incidental PCa compared with 1.1 ng/mL in those without incidental PCa. We attributed to this result mainly to the small cancer volume and low Gleason grade of concomitant PCa, because, in most cases of PCa, the serum PSA levels correlate well with tumor volume and the Gleason score [30]. Therefore, the preoperative PSA value had proven to be a poor screening tool for the detection of fortuitous PCa.

Taken together, the prevalence of unsuspected PCa in our patients was 12.4%, and the majority of this type PCa was small-volume, low-score, and organ-confined tumors. The preoperative PSA level was a poor screening tool for the detection of concomitant PCa. The technique of capsular and apex preservation of the prostate is not recommended for patients with bladder cancer, as it increases the risk of a positive surgical margin. Our data suggest that the morbidity of fortuitous PCa in developing countries is significantly lower than that in developed countries, and the outcome of incidental PCa after RCP depends on the prognosis of the bladder cancer.

Disclosure of conflict of interest

None.

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