Differences in cancer characteristics of Chinese patients with prostate cancer who present with different symptoms

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ABSTRACT

Introduction: Currently there is no structured prostate cancer screening programme in Asia. Early diagnosis of prostate cancer in Asia is by an opportunistic case-finding approach, that is, offering prostate-specific antigen testing to an individual without obvious symptoms of prostate cancer. In this study, we investigated the relationship between the mode of presentation and the characteristics of prostate cancers diagnosed in our hospital.

Methods: We recruited 120 consecutive Chinese patients with prostate cancer newly diagnosed from September 2011 to February 2013 in a regional hospital in Hong Kong. Patient demographics, symptoms, presentation, staging, and risk profiles were collected and analysed.

Results: The number of subjects diagnosed during a health check (group 1), investigated for symptoms with no/low suspicion of prostate cancer (group 2), investigated for symptoms where prostate cancer was suspected (group 3), or who had undergone transurethral prostatectomy (group 4) were 12 (10.0%), 53 (44.2%), 46 (38.3%), and nine (7.5%), respectively. Overall mean age was 71.0 (range, 54-90) years, and patients in group 3 were significantly older than those in groups 1 and 2 (P<0.001). Patients in group 3 had a significantly higher level of serum prostate-specific antigen, higher incidence of abnormal digital rectal examination, and more metastatic disease at presentation than the other groups. Nonetheless, more than 50% of the prostate cancers in groups 1 and 2 were of intermediate risk or higher staging at presentation. After a median follow-up of 32 months, cancer-specific survival was 100% for each of groups 1, 2, and 4 but was only 76.8% for group 3 (P=0.006).

Conclusions: Patients with prostate cancer who presented with prostate cancer–related symptoms had more metastatic disease and poorer survival than patients diagnosed by a case-finding approach. Moreover, more than half of those patients diagnosed by case finding belonged to intermediate- or higher-risk groups for which active treatment was recommended.

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New knowledge added by this study

- In the local Chinese population, patients with prostate cancer who presented with prostate cancer–related symptoms had more metastatic disease and poorer survival than asymptomatic patients.
- More than half of those patients with prostate cancer diagnosed by prostate-specific antigen (PSA) testing (case-finding approach) had intermediate- or higher-risk disease warranting treatment.

Implications for clinical practice or policy

- Health care professionals could offer PSA testing to appropriate male patients when they are seen for non-prostate-cancer–related symptoms after appropriate counselling. This may help to improve outcome and survival of prostate cancer patients.

Introduction

Prostate cancer is the second most frequently diagnosed cancer of men worldwide, with the highest incidence and prevalence rates occurring in more developed societies.[1] The incidence of prostate cancer is also increasing in Asian countries.[2] Many reasons have contributed to this recent rise in incidence in Asia, including the increase in the ageing population, the westernised diet, and also the increased use of serum prostate-specific antigen (PSA) for cancer detection.[3,4] Although current evidence supports the use of PSA testing to decrease

the incidence of metastatic disease and prostate cancer–specific mortality,[5] the use of serum PSA for the early detection of prostate cancer is still controversial.[6,7] One of the concerns is the risk of overdiagnosis and overtreatment of low-risk cancer that may result in more potential harm than benefit to patients.[8-10] There are many types of prostate cancer screening approaches. Currently, there is no structured prostate cancer screening programme in Asia. Therefore, early diagnosis of prostate cancer in Asia is by an opportunistic case-finding approach, that is, offering PSA testing to an individual without obvious signs and symptoms of prostate cancer. Information on the characteristics of prostate cancer diagnosed by various approaches in Asia is lacking, however. We postulated that patients diagnosed by a case-finding approach, such as during a routine health check or a consultation for symptoms with a low suspicion of prostate cancer origin, would have a better prognosis than those who presented with symptoms related to prostate cancer, with or without metastatic disease. We investigated the relationship between the mode of presentation and the characteristics of prostate cancers diagnosed in our hospital.

出現不同症狀的前列腺癌華籍患者的癌症特徵差異

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引言：亞洲尚未有前列腺癌篩查計劃，目前主要是透過機會性病例篩檢方式作早期診斷，意謂向沒有明顯前列腺癌症狀的人提供前列腺特異性抗原（PSA）測試。本研究旨在探討本院前列腺癌患者疾病表現模式和前列腺癌特點之間的關係。

方法：我們於2011年9月至2013年2月期間招募了120位新確診前列腺癌的華籍患者，收集並分析病人的特徵、症狀、癌病分期和風險因素。

結果：病人分為四組：第一組是於常規健康檢查期間被診斷前列腺癌的病人（12例，10.0%）；第二組是因症狀與前列腺癌無關或低關係而求診的病人（53例，44.2%）；第三組是因與前列腺癌相關症狀而求診的病人（46例，38.3%）；第四組是因接受經尿道切除前列腺術而確診前列腺癌的病人（9例，7.5%）。病人平均年齡71.0歲（介乎54-90歲）。第三組病人明顯比第一、二組年長（P<0.001）。與其他組別比較，第三組病人的血清PSA水平較高，肛門指診有異常結果以及就診時發現有轉移性疾病的情況較多。第一、二組病人中超過50%就診時發現的前列腺癌均屬於中度風險或以上階段。經過32個月的中位隨訪後，第一、二、四組與前列腺癌相關的存活率均為100%，第三組只有76.8%（P=0.006）。

結論：相比於健康檢查時確診或是因非前列腺癌相關症狀求診而確診的患者，確診時已經有前列腺癌相關症狀的患者有更多擴散性疾病和較低存活率。此外，超過一半透過機會性病例篩檢而確診的患者屬於中／高風險群組，需接受積極治療。

Methods

This was a prospective cohort study to assess consecutive adult male patients diagnosed with prostate cancer at Prince of Wales Hospital, a regional hospital in Hong Kong, between September 2011 and February 2013. Institutional ethics approval was obtained for the study. Informed consent was obtained from all study subjects prior to enrolment in the study.

All patients aged 18 years or above at our hospital with histological confirmation of prostate cancer were identified and approached for inclusion in this study. After informed consent was obtained, information on the initial presentation of the patient's condition, prostate cancer characteristics at diagnosis, and the initial treatment plan were collected. Patients were then followed up for a minimum of 2 years, and the clinical outcome was assessed. All cancer was graded using the Gleason grading system that is based on the histological pattern of the cancer tissue. The tissue was graded from 1 (well-differentiated) to 5 (poorly differentiated). Each biopsy was given two scores, the first indicated the most common pattern and the second, the highest grading.[11] Our scoring system for prostate cancer consists of staging according to TNM staging 2010[12] and risk stratification according to the National Comprehensive Cancer Network (NCCN) guideline.[13]

Subjects were divided into four groups according to the initial clinical presentation of their prostate cancer by two investigators who were blinded to the clinical outcome during the assessment and then confirmed by a senior investigator. Any discrepancy was discussed and a final allocation made. The health check group (group 1) included patients in whom a raised PSA was detected during a routine health check. Group 2 comprised patients diagnosed with prostate cancer by the case-finding approach after they presented with symptoms with no/low clinical suspicion of prostate cancer (eg renal cysts, non-specific abdominal pain). Group 3 comprised patients with a high clinical suspicion of prostate cancer or malignant disease, for example, lower urinary tract symptoms with abnormal digital rectal examination (DRE), bone pain, or weight loss. Finally, those patients with a histological diagnosis of prostate cancer made following transurethral resection of the prostate (TURP) but with no preoperative suspicion of prostate cancer were assigned to the TURP group (group 4).

Since prostate cancer arises mostly from the peripheral zone (in contrast to benign prostate hyperplasia [BPH] that commonly arises from the transition zone), patients with early-stage prostate cancer are usually asymptomatic.[14] Not until the tumour becomes locally advanced (with clinical signs of abnormal DRE) do patients have voiding

symptoms attributed to prostate cancer. Therefore, in a patient who presents with lower urinary tract symptoms (LUTS) and normal DRE, the symptoms are more likely related to BPH, not secondary to prostate cancer. Testing of PSA is not routine for male patients with LUTS.[15,16] According to the Guidelines from the European Association of Urology, PSA measurement should only be performed to assess the risk of progression of LUTS or if a diagnosis of prostate cancer would change disease management.[16] For patients who present with LUTS but with a low clinical suspicion of prostate cancer (ie normal DRE), PSA testing is considered case-finding for prostate cancer. In this study, such patients were assigned to group 2. This also applied to other presenting symptoms with no or low suspicion of being related to prostate cancer. Nonetheless, in subjects with LUTS and clinical symptoms or signs suspected to be secondary to prostate cancer, such as abnormal DRE findings, PSA testing would be part of the diagnostic process for prostate cancer, not case-finding. As a result, these patients would be assigned to group 3.

After all data were collected, descriptive statistics were applied. A Chi squared test or Fisher's exact test was used to determine any relationship between the categorical outcome measures. Analysis of variance or Kruskal-Wallis test was used for normal or skewed data, and then followed by post-hoc comparisons with Bonferroni adjustment. Kaplan-Meier survival analysis was applied to analyse survival among the four groups. Data management and analysis were performed using the Statistical Package for the Social Sciences (Windows version 22.0; SPSS Inc, Chicago [IL], US). A two-tailed test was used with significance set at P<0.05.

Results

From September 2011 to February 2013, 126 consecutive patients with newly diagnosed, histologically confirmed prostate cancer were managed in our centre. One patient refused to participate in this study, and five patients were not capable of providing informed consent. Therefore 120 patients were enrolled in this study: group 1 (n=12), group 2 (n=53), group 3 (n=46), and group 4 (n=9) [Table 1]. The initial presenting symptoms of patients in groups 2 and 3 are listed in Table 2. In group 2, 43 patients presented with LUTS (including three with acute urinary retention) with low clinical suspicion of prostate cancer. Ten patients presented with other symptoms—seven with other urological symptoms and three with other general surgical problems. Among them, three patients (one with loin pain, one with erectile dysfunction, and one with hernia) were found to have abnormal DRE during consultation. In group 3, 33 patients presented with LUTS (nine patients with acute urinary retention) and abnormal DRE. Three patients presented with haematuria and DRE during initial workup was abnormal and a subsequent diagnosis was made of prostate cancer. Nine patients presented with metastatic symptoms, eg bone pain, acute spinal cord compression, and abnormal soft tissue mass. One patient presented with weight loss and was subsequently diagnosed to have non-metastatic prostate cancer (Table 2).

The overall mean age was 71.0 (range, 54-90) years (Table 1). Age and serum PSA level were statistically significantly different across groups. Multiple comparisons with Bonferroni correction revealed that patients in group 3 were significantly older than those in groups 1 and 2 (P<0.001). Patients

TABLE 1. Demographics and cancer-related characteristics

	No., No. (%), or mean ± standard deviation (range)					P value*
	Overall	Group 1	Group 2	Group 3	Group 4	
No. of patients	120	12 (10.0)	53 (44.2)	46 (38.3)	9 (7.5)	-
Age (years)	71.0 ± 8.1 (54-90)	65.3 ± 8.8 (56-85)	68.8 ± 6.4 (54-84)	75.2 ± 8.1 (54-90)	70.8 ± 7.2 (62-82)	<0.001
Abnormal DRE	44 (36.7)	0	3 (5.7)	41 (89.1)	0	<0.001
Serum PSA level	116.51 ± 395.51 (0.8-3438.0)	19.55 ± 36.05 (4.2-133)	21.40 ± 43.32 (4.2-285)	269.35 ± 601.58 (54-3438.0)	24.67 ± 30.86 (0.8-95.2)	<0.001
Presence of metastasis	30 (25.0)	1 (8.3)	4 (7.5)	24 (52.2)	1 (11.1)	<0.001
Gleason sum ≥7	55 (45.8)	7 (58.3)	12 (22.6)	32 (69.6)	4 (44.4)	<0.001
NCCN risk group						-
Very low/low†	32 (36.8)	4 (36.3)	23 (46.9)	3 (15.8)	2 (25.0)	
Intermediate†	33 (37.9)	4 (36.3)	15 (30.6)	11 (57.9)	3 (37.5)	
High†	22 (25.3)	3 (27.5)	11 (22.4)	5 (26.3)	3 (37.5)	
Locally advanced	3	0	0	3	0	-
Metastatic	30	1	4	24	1	-

Abbreviations: DRE = digital rectal examination; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen

* Comparison between the four groups

† Percentage was calculated for localised disease

in group 3 also had a significantly higher serum PSA level compared with those in group 1 (P=0.044) and group 2 (P=0.045) by Kruskal-Wallis test. In group 3, 41 (89.1%) patients had an abnormal DRE (P<0.001).

With regard to disease status, the numbers of patients with a Gleason sum of ≥7 were seven (58.3%) in group 1, 12 (22.6%) in group 2, 32 (69.6%) in group 3, and four (44.4%) in group 4. In accordance with the NCCN guideline, the number of patients with disease more severe than very low or low risk were eight (66.7%) in group 1, 30 (56.6%) in group 2, 43 (93.5%) in group 3, and seven (77.8%) in group 4 (Table 1). In group 3, 24 (52.2%) patients had metastatic disease at initial presentation, a much higher rate than in the other groups (P<0.001, Fisher's exact test).

Since both groups 1 and 2 had no prostate cancer–related symptoms, we tried to combine the two groups to assess the characteristics of prostate cancer diagnosed by a case-finding approach. Group 3 patients had significantly older age, higher serum PSA level, more aggressive disease (Gleason sum ≥7), and more metastatic disease at presentation than the combined groups 1 and 2 patients (P<0.001 for all parameters; Table 3).

TABLE 2. Initial symptoms of patients in groups 2 and 3

Symptom	Group 2	Group 3
LUTS (including AUR)	43	33
Other urinary tract symptoms		
Erectile dysfunction	1	-
Loin pain	1	-
Haematuria	3	3
Haemospermia	1	-
Renal cyst	1	-
Other surgical problems	3	-
Bone pain	-	5
Acute spinal cord compression	-	2
Soft tissue mass	-	2
Weight loss	-	1
Total	**53**	**46**

Abbreviations: AUR = acute urinary retention; LUTS = lower urinary tract symptoms

TABLE 3. Comparison of the demographic and cancer-related characteristics of patients diagnosed by PSA testing (groups 1 and 2) and those who presented with symptoms (group 3)

	Mean ± standard deviation (range), No. (%), or No.		P value
	Groups 1 + 2 (n=65)	Group 3 (n=46)	
Age (years)	68.1 ± 6.9 (54-85)	75.2 ± 8.1 (54-90)	<0.001
Abnormal DRE	3 (4.6)	41 (89.1)	<0.001
Serum PSA level	21.06 ± 41.81 (4.2-285)	269.35 ± 601.58 (54-3438.0)	<0.001
Presence of metastasis	5 (7.7)	24 (52.2)	<0.001
Gleason sum ≥7	19 (29.2)	32 (69.6)	<0.001
NCCN risk group			
Very low/low*	27 (45.0)	3 (15.8)	
Intermediate*	19 (31.7)	11 (57.9)	
High*	14 (23.3)	5 (26.3)	
Locally advanced	0	3	
Metastatic	5	24	

Abbreviations: DRE = digital rectal examination; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen
* Percentage was calculated for localised disease

TABLE 4. Primary treatment in each patient group

Treatment	Group 1 (n=12)	Group 2 (n=53)	Group 3 (n=46)	Group 4 (n=9)
No treatment*	1	5	4	6
Radical surgery	8	23	6	0
Radical radiotherapy	2	21	5	1
Primary ADT	1	3	26	2
ADT + TURP	0	1	5	0

Abbreviations: ADT = androgen deprivation therapy; TURP = transurethral resection of the prostate
* Includes watchful waiting and active surveillance

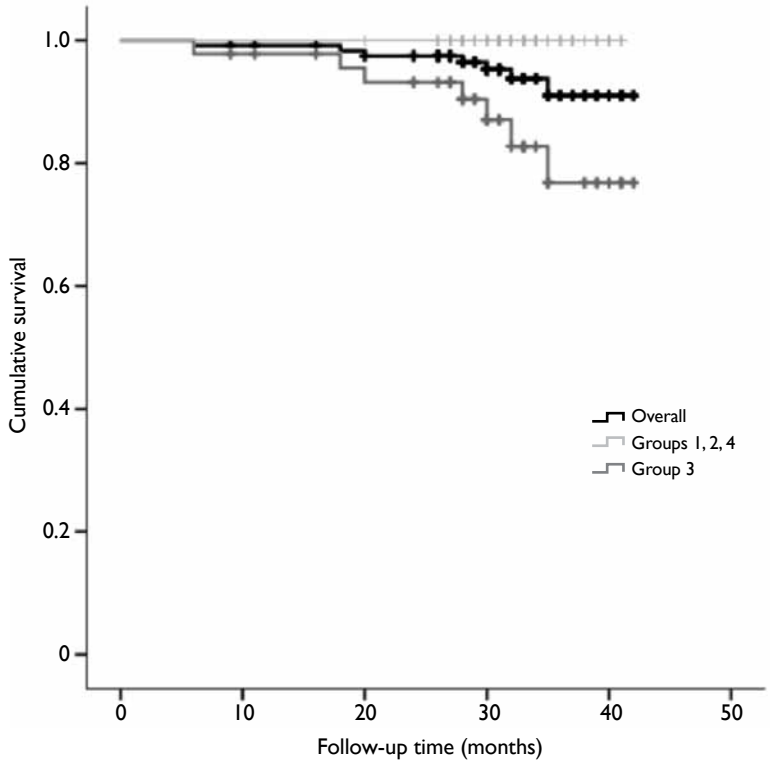

FIG. Cancer-specific survival for all and individual groups

The types of primary treatment administered are listed in Table 4. The number of patients receiving radical local therapy (either surgery or radiotherapy) was 10 (83.3%) in group 1, 44 (83.0%) in group 2, 11 (23.9%) in group 3, and one (11.1%) in group 4. Systemic androgen deprivation therapy was prescribed to one (8.3%) patient in group 1, three (5.7%) in group 2, 26 (56.5%) in group 3, and two (22.2%) in group 4 (P<0.0005). Because group 3 had significantly more patients with locally advanced and metastatic disease, significantly fewer could be managed with curative-intent local therapy. Among those patients with very low– or low-risk disease in groups 1 and 2, one (25%) and five (21.7%) respectively elected to have conservative management, either watchful waiting or active surveillance.

The median follow-up period was 32 months (interquartile range, 28-35 months). No patients were lost to follow-up. Eleven (9.2%) patients died—10 (21.7%) in group 3 and one (11.1%) in group 4. No patient in groups 1 or 2 died during the follow-up period. The causes of death in group 3 patients were directly related to prostate cancer in seven patients, metastatic bladder cancer in one patient, and acute myocardial infarction in two patients. The cause of death of the patient in group 4 was secondary to advanced rectosigmoid carcinoma. Therefore, the overall rate of cancer-specific survival for the total cohort was 91.0%, but 100% for each of groups 1, 2, and 4 compared with only 76.8% for group 3 (P=0.006, log-rank test; Fig).

Discussion

Since the introduction of PSA testing, there has been a worldwide change in the presentation of prostate cancer. More and more prostate cancers are diagnosed at a lower risk level and earlier stage for which curative treatment can be offered.[17,18] As a result, the use of PSA testing for early detection of prostate cancer is believed to be one of the factors that has led to the decrease in overall prostate cancer mortality in many developed areas.[2] From our cohort, we also observed that patients with prostate cancer diagnosed by case-finding approach using PSA testing (groups 1 and 2) had significantly more clinically localised disease and hence a higher chance of receiving curative-intent treatment than those patients who presented with prostate cancer–related symptoms (group 3).

We also observed that the short-term cancer-specific mortality rate of patients who presented with prostate cancer–related symptoms (group 3) was significantly higher than that in the other groups. In our cohort, more than half of the patients in group 3 already had metastasis at diagnosis. Because patients presenting with metastasis have a much poorer outcome than other patients,[19,20] it was not surprising that the mortality rate for patients who presented with symptoms was also higher. This indirectly supports the case-finding approach by PSA testing in patients with symptoms but no/low clinical suspicion of prostate cancer, as it might help to decrease the incidence of metastatic disease and hence the mortality related to prostate cancer.[21]

Although PSA testing is widely performed in western countries to detect early prostate cancer, its use in Asian countries is still not a common practice. From a population-based telephone survey involving 1002 Chinese men aged ≥50 years in Hong Kong, only 9.5% had ever had a PSA test, and only 3.7% of the total sample had PSA test done during a routine health check.[22] Even in more developed Asian countries such as Japan and South Korea, only 15% to 20% of the population had had a PSA test.[23] Only 10% of the prostate cancers in our cohort were diagnosed during a self-initiated health check with PSA testing. Therefore, offering a PSA test as case-finding for prostate cancer during a patient's consultation for non-prostate-cancer–related symptoms is an alternative approach for early detection of prostate cancer. We believe that this case-finding approach is feasible for the detection of early prostate cancer in our region, where public awareness and use of PSA testing is still low. Certainly, patients need to be well informed about the nature and implications of PSA testing before the test is performed.[24,25]

The main concerns surrounding the use of PSA testing for the detection of early prostate cancer are overdiagnosis and overtreatment.[8-10] Only approximately 36% of patients in the study cohort had very low– or low-risk disease that might not require aggressive intervention.[13,26] Even in those patients with prostate cancer diagnosed by PSA testing (ie groups 1 and 2), more than 50% were in the intermediate- or higher-risk groups. Testing of PSA level did help to detect patients with significantly high-risk prostate cancer that warranted further treatment. To minimise the risk of overtreatment, the Melbourne Consensus Statement advises uncoupling of the prostate cancer diagnosis from the intervention.[5] Offering active surveillance to patients with low-risk disease will help to minimise the potential harm of overtreatment. In our cohort, for patients in groups 1 and 2 with very low– or low-risk disease, six (22.2%) opted for observation with no active treatment. We believe this concept should be promoted to both clinicians and patients, rather than limiting the use of PSA testing for the case finding of prostate cancer.

Currently, some newly proposed strategies, such as determination of the baseline PSA level earlier in life[27,28] and the use of newer diagnostic tools,[29,30] might help to reduce unnecessary prostatic biopsies and overdiagnosis of low-risk prostate cancer. Nonetheless, since most of these studies were conducted in Caucasian-based populations, further studies in Asian populations are necessary to verify their suitability in our region.

Although our data show that the short-term outcome of patients who present with prostate cancer–related symptoms seems to be worse than those diagnosed by PSA testing, this might be due to potential lead-time bias, that is, the increase in survival is actually due to the length of time between the detection of a disease by PSA testing and its usual clinical presentation and diagnosis. This will result in an increase in survival time for patients diagnosed by PSA testing. Other potential bias is length-time bias which suggests that annual PSA may only detect slow-growing tumours, that screening for prostate cancer does not detect the very tumour for which it is intended.

The aim of our study was not to assess the role of PSA testing in the detection of early prostate cancer or its effect on long-term outcome and survival of patients. Rather, we aimed only to compare cancer characteristics and short-term outcome among patients with different presentations. We also did not analyse the potential harm of PSA testing, prostatic biopsy, or morbidities related to treatment. The positive rate for prostatic biopsy depends on the level of serum PSA and DRE finding. From local experience, for patients with a normal DRE, the positive rate of prostatic biopsy for serum PSA level of 4-10 ng/mL and 10-20 ng/mL was only 6.7%-13.4% and 10.3%-21.8%, respectively.[31-33] Therefore, information on this would be helpful during patient counselling for prostatic biopsy. Another limitation of our study was the relatively small sample size from a single centre in Hong Kong, therefore our results might not represent the general situation in Hong Kong. Further studies, especially with multicentre collaboration, may help to confirm the applicability of our results in the local population.

Conclusions

Patients with prostate cancer presenting with related symptoms had more metastatic disease and poorer survival than those diagnosed by a case-finding approach using PSA testing during a health check or management of symptoms with a low suspicion of prostate cancer. More than half of the patients diagnosed by this case-finding approach belonged to intermediate- or higher-risk groups for which active treatment was recommended. Apart from a self-initiated health check with PSA testing, offering PSA testing to appropriate patients who present with symptoms with no/low clinical suspicion of prostate cancer is an alternative approach to early diagnosis of prostate cancer. Pre-test counselling, including the discussion of potential bias (such as lead time or length-time bias), is essential. This may hopefully help to improve the short-term outcome for these patients.

Declaration

All authors have disclosed no conflicts of interest.

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