Clinical Usefulness of Serum CYFRA 21–1 in Patients with Colorectal Cancer

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Abstract

Purpose Among diverse tumor markers, pretreatment evaluation and follow-up detection of recurrence in colorectal cancer are generally evaluated by serum carcinoembryonic antigen (CEA) levels. However, there have been some reports about the low accuracy and high false-positive results of CEA in colorectal cancer. We investigated the clinical utilities of CYFRA 21–1 by comparing CEA and cancer antigen 19–9 (CA 19–9) in pretreatment and recurrent colorectal cancer.

Methods Using a solid-phase immunoradiometric assay, serum levels of CYFRA 21–1, CEA and CA 19–9 were analyzed in 132 patients with primary colorectal cancer, 124 healthy controls, 104 patients with benign colorectal disease and 19 patients with recurrent colorectal cancer. We determined three different cutoff values to evaluate the sensitivity of diagnostic performance in pretreatment and recurrent colorectal cancer.

Results CYFRA 21–1 (≥ 1.13 ng/ml) had a sensitivity of 47 %, compared with 37 % for CEA (≥ 3.05 ng/ml) and 32.6 % for CA 19–9 (≥ 23.1 ng/ml) in the initial staging of primary colorectal cancer. Using different cutoff values, CYFRA 21–1 showed higher sensitivity for pretreatment colorectal cancer than CEA and CA 19–9 in adenocarcinoma and adenosquamous carcinoma of this study. A mildly significant correlative relationship was noted between Dukes' stages and three tumor markers ($p < 0.01$). The areas under the receiver operating characteristic curves of CYFRA 21–1, CEA and CA 19–9 were 0.81 ± 0.03 , 0.74 ± 0.03 and 0.62 ± 0.04 , respectively, for discriminating colorectal cancer patients from patients with benign colorectal disease. In addition, CYFRA 21–1 was determined as the most sensitive tumor marker for evaluating recurrent colorectal cancer for all cutoff values.

Conclusion This study showed that CYFRA 21–1 could be a useful and dependable tumor marker for pretreatment and recurrent colorectal cancer. Further prospective studies on its usefulness with respect to the prognosis and utility of combined tumor markers are needed.

Keywords Colorectal cancer · CYFRA 21–1 · CEA and CA 19–9

Introduction

Colorectal carcinoma (CRC) is one of the significant causes of gradually global increased cancer death rate and morbidity, with rising incidence in Korea. The American Cancer Society reported 101,340 new cases of colon cancer and 39,870 cases of rectal cancer and 49,380 related deaths in the USA in 2011 [1]. Although the overall survival of CRC is relatively good compared with other malignant diseases, the local recurrence rate is relatively high despite radical curative surgery [2]. Early detection of local recurrence or resectable hepatic metastasis and performance of curative surgery in low staged patients can be important in prolonging the survival of CRC patients [3–5].

Carcinoembryonic antigen (CEA) has been generally used in screening, pretreatment staging, posttherapeutic monitoring and detecting recurrence in CRC. CEA is manufactured by normal colonic cells and colon carcinoma cells and affected by multiple factors including smoking [6]. Although clinical CEA survey is the most cost-effective indicator for CRC, unusually elevated levels of CEA are frequently reported in smokers [3, 6–8] and multiple benign gastrointestinal diseases—including ulcerative colitis, active alcoholic cirrhosis, viral hepatitis, and cryptogenic or biliary cirrhosis—may show increased CEA levels not associated with CRC [6, 9–11]. For these reasons, Australia's previous National Health and Medical Research Council (NHMRC) guidelines did not favor routine measurement of CEA for all CRC

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patients [7]. The presence of normal preoperative serum CEA has confounded the use of CEA in follow-up in other countries [6]. Cancer antigen (CA19-9) has been known to be an efficient biologic marker for evaluating pancreatic cancer and various hepatobiliary carcinomas [12]. In addition, CA 19-9 could play an important role in detecting recurrent colorectal cancer and in evaluating carcinomatosis peritonei of colon cancer [13–15].

CYFRA 21-1 is known to be a biologic tumor indicator reflecting fragments of cytokeratin 19, which is one of the various kinds of cytokeratins comprising keratin including intermediate filaments of epithelial cell [16–18]. To our knowledge, this marker has been mostly studied in non-small cell lung cancer [19, 20], breast cancer [18], cervical cancer [21] and bladder cancer [22], proving its utility in the diagnosis and predicting capability of prognosis and treatment efficacy. Until recently, because many studies about CYFRA 21-1 and oncology have mostly been studied with squamous cell carcinoma [21, 23, 24], only a few studies have been conducted on the relationship between CYFRA 21-1 and CRC mainly composed in adenocarcinoma.

The objectives of this study were: (1) to evaluate the sensitivity of three tumor markers (CEA, CYFRA 21.1 and CA 19-9) in patients with CRC, respectively, (2) to study the relationships among the tumor markers and some prognostic parameters including histological grade, stage and tumoral ^{18}F -fluorodeoxyglucose (F18-FDG) uptake, and (3) to evaluate the potency of detecting recurrence according to these three markers.

Materials and Methods

Patients

Between September 2009 and November 2012, a total of 147 patients [59 women and 88 men; age (mean $\pm$ SD) 59.9 $\pm$ 12.6 years; range 18–86] were diagnosed with new onset of primary colorectal cancer in our hospital. Among them, 132 patients underwent not only conventional workups, including enhanced CT and F18-FDG PET/CT, but also preoperative evaluation of tumor markers, including CYFRA 21-1, CEA and CA 19-9. Essential prerequisites in this study included: (1) primary colorectal cancer proven histopathologically, (2) no experience of surgical or chemotherapeutic treatment before diagnosis, and (3) patients with performance state 0 or 1. Patients with liver cirrhosis, renal failure and infectious lung disease were excluded. Other patient characteristics are summarized in Table 1. Because of neoadjuvant chemotherapy or concurrent chemoradiation therapy before surgery, 26 patients were not applicable for the Dukes' staging system. Between May 2011 and November 2012, 19 colorectal cancer patients with pathologically or radiologically proven recurrence

Table 1 Characteristics of 132 patients with primary colorectal cancer, 104 patients with benign colorectal diseases and 124 healthy controls in our study

Primary colorectal cancer	
Median age, years (range)	66 (34–89)
Gender (male : female)	79 : 53
Histology	
Adenocarcinoma	124
Mucinous adenocarcinoma	7
Adenosquamous carcinoma	1
Dukes' staging ($n=106$)	
A	11
B	49
C	39
D	7
Benign colorectal diseases ($n=104$)	
Hyperplastic polyps	37
Diverticular disease	10
Tubular adenoma	26
Melanosis coli	3
Colitis	8
Mixed conditions ^a	20
Healthy control ($n=124$)	
Median age, years (range)	43 (31–61)
Gender (male : female)	71 : 53

^a Mixed conditions defines that one patient had two or more benign colorectal diseases (for example, hyperplastic polyp plus adenoma)

underwent follow-up surveillance of all three tumor markers. Radiologically diagnosed recurrent findings were confirmed for at least 6 months of follow-up of radiological imagings, F18-FDG PET/CT and tumor markers. These patients were enrolled to evaluate the efficiency of tumor markers in detecting recurrence. In addition, blood levels of CYFRA 21-1, CEA and CA 19-9 were checked and collected from healthy controls ($n=124$) and patients with benign colorectal disease ($n=104$) to evaluate the diagnostic discrimination of each markers (Table 1).

CYFRA 21-1, CEA and CA 19-9 Assay

Blood samples of each patient was obtained by venupuncture, separated by centrifugation at 2,500 rpm for 8 min and then stored at -70°C until further analysis. Determination of serum CYFRA 21-1 was performed using a commercially available CYFRA 21-1 kit (CIS Biointernational, Gif Yvette, France) by a solid-phase immunoradiometric assay based on the two-site sandwich method. Both measurements of serum CEA and CA 19-9 were done by a two step sandwich immunoradiometric assay (TBF, Tokyo, Japan). The commercial cutoff values of CYFRA 21-1, CEA, and CA 19-9 were 2.0 ng/ml, 7.0 ng/ml and 38 ng/ml, respectively.

F18-FDG PET/CT

F18-FDGPET/CT studies were performed by means of a Gemini GXL 6 PET/CT system (Philips, Hamburg, Germany). All patients went on a fast for about 5 h before FDG injections to maintain serum glucose concentrations below 150 mg/dl. Patients were educated to have sufficient water intake, and to avoid unnecessary physical activity before 1–2 days. Mean 3.7 MBq/kg F18-FDG was injected into all patients 1 h before standard scan. Patients rested in a tranquil, non-brilliant room for 1 h. Low-dose and nonenhanced CT images (50 mA, 140 kV, 512×512 matrix) were undertaken from the base of the skull to the upper to mid thigh, with weak respiratory movement. Detailed education for respiration and positioning were performed to patients before or during FDG PET scanning. The emission data acquisition was conducted in the opposite direction compared to CT scan in the three-dimensional mode with a 144×144 matrix after CT scanning. The emission scan time was 1 min 30 s at each bed, and 8–10 bed positions (field of view, 180 mm) were acquired. After PET scatter and decay correction, PET data were reconstructed iteratively, with and without attenuation correction. Data were reoriented in the axial, sagittal, and coronal sections and in a three-dimensional rotating projection. A three dimensional iterative reconstruction algorithm based on 3D-RAMLA or LOR was applied. PET/CT images were investigated by two board certified nuclear medicine physicians (J.H.L. and S.G.P.). An important finding on the PET/CT scan was considered positive when abnormal non-physiologic FDG uptake with attenuation change was identified. Incidental FDG uptake lesions of normal abdominopelvic organs without significant attenuation change or enhancement and diffusely irregular gastrointestinal FDG activities were considered as benign findings in consensus. The standard uptake value (SUV) of FDG was calculated based on body weight.

Statistical Analysis

Statistical analysis was calculated using SPSS (version 14.0.0; SPSS, Chicago, IL, USA) and MedCalc (version 8.1.1; MedCalc, Ostend, Belgium). To evaluate the differences of tumor markers between cancer patients and benign disease or healthy controls, the Student *t*-test was used. According to clinicopathologic parameters such as differentiation and tumor FDG uptake, statistical difference of tumor markers was evaluated by the Kruskal-Wallis test. The relationship between tumor staging and tumor markers was evaluated by Spearman's rank correlation. Receiver operating characteristic (ROC) curves were calculated for CYFRA 21–1, CEA and CA 19–9 to evaluated individual diagnostic capabilities in discriminating primary colorectal cancer from healthy conditions or benign colorectal diseases. The areas under the ROC curves (AUCs) of the three tumor markers were compared

with one another; *p* values of less than 0.05 were considered statistically significant.

Results

CYFRA 21–1 Distribution

In patients with primary colorectal cancer of our study, the mean value of CYFRA 21–1 was 1.55 ± 0.17 (interquartile range 0.55–1.85 ng/ml). Significant differences in CYFRA 21–1 levels ($p < 0.0001$) were found between primary colorectal cancer patients and patients with benign colorectal disease (0.47 ± 0.06 ; interquartile range 0.23–0.78 ng/ml) and healthy controls (0.38 ± 0.03 ; interquartile range 0.16–0.48 ng/ml). Although there was a mildly positive correlation between CYFRA 21–1 and CA 19–9 ($r = 0.22$, $p = 0.01$), other clinicopathologic parameters—including CEA and main tumor uptake (SUVmax)—were not related to CYFRA 21–1. Moreover, all three tumor markers did not show any significant difference according to the differentiation of adenocarcinoma (CEA, $p = 0.45$; CYFRA 21–1, $p = 0.32$; CA 19–9, $p = 0.25$).

Efficacy of CYFRA 21–1, CEA and CA 19–9 as Tumor Markers for Primary Colorectal Cancer

Cutoff values were determined with regard to 95 % specificity in the benign disease group and in healthy controls; the cutoff values were 1.13 ng/ml and 1.17 ng/ml for CYFRA 21–1, 3.85 ng/ml and 3.05 ng/ml for CEA, 23.1 ng/ml and 25.45 ng/ml for CA 19–9. Table 2 shows the sensitivity results of CYFRA 21–1, CEA and CA 19–9 in each of the three different histologies of primary colorectal cancer. In adenocarcinoma, CYFRA 21–1 sensitivities were higher than CEA and CA 19–9 sensitivities for all the cutoff values. In the case of mucinous carcinoma, the most sensitive marker was CEA (specifically, 85.7 %, cutoff value 3.05 ng/ml), albeit small numbers. A combination of the abovementioned three tumor markers increased the sensitivity by 35 %, with conventional cutoff values. Table 3 shows the sensitivity results of three tumor markers according to the modified Dukes' classifications [25, 26]. A mild significant correlative relationship can be noted between Dukes' staging and the three tumor markers ($\rho = 0.213$, $p = 0.01$ for CYFRA 21–1; $\rho = 0.235$, $p = 0.001$ for CEA; $\rho = 0.248$, $p = 0.001$ for CA 19–9). Although there is minimal variation according to different tumor markers, there is a tendency of increasing sensitivity as stage increases.

Analysis of ROC Curves

For the diagnosis of colorectal cancer, ROCs were constructed and the areas under the curves (AUC) were calculated to compare the capability of the three tumor markers to

Table 2 Relationship between tumor histology and tumor marker serum levels in patients with primary colorectal cancer

Histology	Tumor marker	Sensitivity (A/B/C) ^a	Mean SD (ng/ml)	Range (ng/ml)
Adenocarcinoma (<i>n</i> =124)	CYFRA 21-1	23.4 %/46 %/46.7 %	1.5±1.9	0.1–16
	CEA	16.9 %/34.6 %/29.8 %	8.5±36.2	0.3–381
	CA 19-9	18.5 %/26.6 %/31.5 %	39.7±122.9	0.1–923
Mucinous carcinoma (<i>n</i> =7)	CYFRA 21-1	0 %/42.9 %/42.9 %	1.2±0.3	0.82–1.64
	CEA	28.6 %/85.7 %/71.4 %	20.1±36	2–93.2
	CA 19-9	28.6 %/42.9 %/42.9 %	15.6±14.7	0.1–40.5
Adenosquamous carcinoma (<i>n</i> =1)	CYFRA 21-1	100 %/100 %/100 %	8.3	ns
	CEA	0 %/0 %/0 %	0.5	ns
	CA 19-9	0 %/0 %/0 %	2.6	ns

^a A: cutoff levels are determined according to conventional value (CYFRA 21-1 2 ng/ml, CEA 7 ng/ml and CA19-9 38 ng/ml). B and C: cutoff levels are determined according to 95 % specificity in healthy controls (CYFRA 21-1 1.17 ng/ml, CEA 3.05 ng/ml and CA19-9 25.45 ng/ml) and benign disease (CYFRA 21-1 1.13 ng/ml, CEA 3.85 ng/ml and CA19-9 23.1 ng/ml)

differentiate patients with colorectal cancer from patients with benign colorectal diseases (Fig. 1) or healthy controls (Fig. 2). The AUCs of CYFRA 21-1, CEA and CA 19-9 for differentiating colorectal cancer from benign colorectal diseases and healthy controls were 0.81 ± 0.03 and 0.84 ± 0.03 , 0.74 ± 0.03 and 0.80 ± 0.03 , and 0.62 ± 0.04 and 0.55 ± 0.04 for CYFRA 21-1, CEA and CA 19-9, respectively. Significant differences were noted between the AUCs for CYFRA 21-1 and those for CA 19-9 ($p<0.0001$); on the other hand, there were no significant differences between AUCs for CYFRA 21-1 and those for CEA, although a slight difference was found in differentiating colorectal cancer from benign colorectal diseases ($p=0.09$).

Table 3 Diagnostic performance of CYFRA 12-1, CEA and CA 19-9 according to Dukes' classification in primary colorectal cancer patients

Dukes' stage	Tumor markers	Sensitivity (A/B/C) ^a
Dukes' A (<i>n</i> =11)	CYFRA 21-1	0 %/18.2 %/18.2 %
	CEA	0 %/0 %/0 %
	CA 19-9	9 %/9 %/9 %
Dukes' B (<i>n</i> =49)	CYFRA 21-1	23.1 %/40.3 %/42.3 %
	CEA	13.5 %/32.6 %/25 %
	CA 19-9	7.7 %/13.4 %/19.2 %
Dukes' C (<i>n</i> =39)	CYFRA 21-1	20.5 %/48.7 %/48.7 %
	CEA	20.5 %/46.2 %/25.9 %
	CA 19-9	25.6 %/41 %/43.5 %
Dukes' D (<i>n</i> =7)	CYFRA 21-1	57.1 %/85.7 %/85.7 %
	CEA	71.4 %/71.4 %/71.4 %
	CA 19-9	28.6 %/42.9 %/42.9 %

^a A: cutoff levels are determined according to conventional value (CYFRA 21-1 2 ng/ml, CEA 7 ng/ml and CA19-9 38 ng/ml). B and C: cutoff levels are determined according to 95 % specificity in healthy controls (CYFRA 21-1 1.17 ng/ml, CEA 3.05 ng/ml and CA19-9 25.45 ng/ml) and benign colorectal disease (CYFRA 21-1 1.13 ng/ml, CEA 3.85 ng/ml and CA19-9 23.1 ng/ml)

Role of CYFRA 21-1 in Detection of Recurrence

Table 4 shows the sensitivity results of detecting local or remote recurrence of colorectal cancer according to the three tumor markers. Irrespective of different cutoff values, CYFRA 21-1 was the most sensitive tumor marker for evaluating recurrent colorectal cancer (A: 52.6 %, *n*=10; B: 68.4 %, *n*=13; C: 73.7 %, *n*=14). Even when the conventional cutoff value (2 ng/ml) was applied, the sensitivity of the combination of all tumor markers was slightly higher than that of only CYFRA 21-1 (57.8 % vs 52.6 %).

Fig. 1 Receiver operating characteristic (ROC) curves combined with CYFRA 21-1, CEA and CA 19-9 between colorectal cancer patients and patients with benign colorectal diseases were constructed. The areas under the ROC curves (AUCs) for CYFRA 21-1, CEA and CA 19-9 were 0.81 ± 0.03 , 0.74 ± 0.03 and 0.62 ± 0.04 ($p<0.0001$, $p<0.0001$ and $p=0.002$)

Fig. 2 ROC curves combined with CYFRA 21–1, CEA and CA 19–9 between colorectal cancer patients and healthy controls were constructed. The AUCs for CYFRA 21–1, CEA and CA 19–9 were 0.84 ± 0.03 , 0.80 ± 0.03 and 0.55 ± 0.04 ($p < 0.0001$, $p < 0.0001$ and $p = 0.17$)

Discussion

In primary colorectal cancer, CEA has been applied universally from pretreatment staging to evaluation of recurrence and various chemotherapy efficacies. Although CEA is widely utilized as a practical tool for assessing hematogeneous metastasis or relapse and a predicting marker showing that high preoperative level not reducing to normal ranges after extirpation is associated with a worse prognosis [8], high false-positive results or low sensitivity of CEA in pretreatment evaluation reflect that CEA measurement might be an unsuitable modality for population screening [27].

Epithelial cell markers such as EPCAM-1 and cytokeratins 7 and 8 are sensitive and specific markers for the detection of circulating tumor cells [12]. Among them, cytokeratin 19

(CYFRA 21–1), which is a constituent of the intermediate filament protein responsible for the structural integrity of epithelial cells [12], can be detected using anti-CYFRA 21–1 antibody [18]. CYFRA 21–1 is distinctive in that its epitope is a polypeptide, which is mainly discharged following cell death [18, 28]. On the other hand, most epitopes that are manifested by known valuable tumor markers such as CA-50, CA 72–4, CA19-9 and CEA are glycoproteins [18]. First, in primary lung cancer (PLC), CYFRA 21–1 was described to be most likely distinguishable tumor marker compared with CEA, squamous cell carcinoma antigen (SCC) and neuron-specific enolase (NSE), and thus, this test may play a role in clinical tracing marker during treatment and posttreatment follow-up [16, 29]. Besides PLC, CYFRA 21–1 has been reported to be a valuable marker for esophageal cancer [30], cervical cancer, breast cancer, gastric cancer, and bladder cancer. Although there is little information regarding the clinical role of CYFRA 21–1 in colorectal cancer, some reports have suggested that CYFRA 21–1 plays a role in the initial evaluation of colorectal cancer. Xu et al. [31] demonstrated that cytokeratin 19 mRNA was detected in 41.9 % of colorectal cancer patients and in 3.3 % of controls. This sensitivity was higher than the CEA mRNA detection rate (35.8 % of colorectal cancer patients and 3.3 % of controls). Holdenrieder et al. [32] showed that CYFRA 21–1 levels was prominently upraised in colorectal cancer patients as compared with healthy controls ($p < 0.001$) and benign gastrointestinal controls ($p = 0.01$), and showed stage dependency ($p = 0.01$), as shown by our study. Contrary to the present study, Wild et al. [33] reported that it was found that CEA revealed the highest sensitivity at 95 % specificity with 43.9 % compared with seprase (42.4 %), CYFRA 21–1 (35.5 %), etc. However, in our study, the sensitivity of CYFRA 21–1 according to different cutoff values was somewhat higher than that of CEA, especially in adenocarcinoma, mostly consisting of colorectal cancer, although the sensitivity of CEA was higher than that of CYFRA 21–1 in mucinous carcinoma. In addition, our results showed that the AUCs of CYFRA 21–1 for discriminating between colorectal cancer and benign gastrointestinal controls and healthy controls were larger than those of CEA and CA19-9. Our AUCs of CYFRA 21–1 (0.81 ± 0.03 and 0.84 ± 0.03 , respectively, according to different cutoff values) were slightly higher than that reported by Wild et al. (0.78). To our knowledge, because the diagnostic test with the ROC curve enclosing the largest area is the most accurate [34–36], these results suggested that serum CYFRA 21–1 could be an informative and dependable tumor marker for primary colorectal cancer. Because CYFRA 21–1 was proven to be less vulnerable to age, sex and smoking [16], this fact demonstrated that CYFRA 21–1 may be more reproducible than CEA in the initial staging of colorectal cancer.

In detecting recurrent colorectal cancer, we demonstrated that the positive rates of CYFRA 21–1 were superior to those

Table 4 Diagnostic performance of CYFRA 12–1, CEA and CA 19–9 in recurrent colorectal cancer patients

Tumor marker	Sensitivity (A/B/C) ^a	Median(range)
CYFRA 21-1	52.6 %/68.4 %/73.7 %	2.45 (0.1–81.2 ng/ml)
CEA	31.5 %/57.9 %/42 %	3.6 (0.9–1128 ng/ml)
CA19-9	31.5 %/31.5 %/36.8 %	10.9 (2.2–15940 ng/ml)

^a A: cutoff levels are determined according to conventional value (CYFRA 21–1 2 ng/ml, CEA 7 ng/ml and CA19-9 38 ng/ml). B and C: cutoff levels are determined according to 95 % specificity in healthy controls (CYFRA 21–1 1.17 ng/ml, CEA 3.05 ng/ml and CA19-9 25.45 ng/ml) and benign colorectal disease (CYFRA 21–1 1.13 ng/ml, CEA 3.85 ng/ml and CA19-9 23.1 ng/ml)

of other tumor markers and similar to that of the combined three tumor markers. In particular, when the best cutoff value at 95 % specificity was applied to benign gastrointestinal groups, the detection rate of CYFRA 21–1 was 73.7 % compared with those of CEA and CA 19–9 (42 % and 31.5 %) in recurrent colorectal cancer. Although CEA has been routinely applied in the follow-up of posttreatment colorectal cancer patients, there are several reports on the inefficient efficacy of CEA in detecting recurrent colorectal cancer [2, 4, 6]. Therefore, in order to address the application of CYFRA 21–1 with or without CEA in the restaging of follow-up colorectal cancer patients, further evaluation such as large prospective study would be necessary.

This study had two limitations. First, we did not evaluate the predictive value of CYFRA 21–1 because of the short follow-up period. Second, because small number of recurrent colorectal cancer patients was enrolled in this study, large scaled multicenter study would be necessary to investigate diagnostic performance of CYFRA 21–1 in recurrent colorectal cancer.

In summary, our study demonstrated that CYFRA 21–1 may be a valuable tumor marker of primary colorectal cancer, considering the relatively high sensitivity compared with that of CEA and CA 19–9 according to different cutoff levels and reflected stepwise different tumor stagings. Furthermore, CYFRA 21–1 could be an important tumor marker in evaluating follow-up colorectal cancer patients.

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Conflicts of Interest None.

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