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Vascular patterns on narrow band imaging (NBI) video bronchoscopy of lung cancer patients and its relationship with histology: an analytical cross-sectional study

Abstract

Introduction: Narrow band imaging (NBI) video bronchoscopy provides better visualisation of submucosal vascular patterns in malignant airway lesions compared to white light bronchoscopy. This analytical cross-sectional study was aimed to look for any relationship between these NBI vascular patterns and the histologic type of lung cancer.

Material and methods: After screening 78 patients with suspected lung cancer, 53 subjects underwent video bronchoscopy. Thirty-two patients showing abnormal bronchial mucosa or endobronchial growth with any of the NBI vascular patterns on bronchoscopy were enrolled in the study. These abnormal areas were then biopsied and sent for histologic examination.

Results: NBI bronchoscopy revealed a dilated tortuous vascular pattern in 54.8% of the patients, a non-specific pattern in 32%, a dotted pattern in 9.7% and an abrupt ending vessels pattern in 3.2% of the patients. We did not find any statistically significant relationship between a dilated tortuous pattern and squamous-cell carcinoma ($p = 0.48$), adenocarcinoma ($p = 0.667$) or small-cell carcinoma ($p = 1$); between a dotted pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 0.54$) or small-cell carcinoma ($p = 1$), and between an abrupt ending capillary pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 1$) or small-cell carcinoma ($p = 1$).

Conclusion: No relationship exists between NBI vascular patterns and the histology of lung cancer. Endobronchial lesions showing any vascular pattern on NBI needs to be adequately sampled for proper histologic and molecular studies in lung cancer patients.

Key words: bronchoscopy, histology, lung cancer, narrow band imaging

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Introduction

Among all cancers, lung cancer is the most common cancer across the world, both in terms of incidence and mortality, accounting for 2.1 million new cases and 1.76 million deaths in 2018 [1]. The World Health Organisation estimates that lung cancer deaths will continue to rise worldwide, largely as a result of an increase in global tobacco use, principally in Asia. Diagnostic bronchoscopic techniques have now become widely available for detection and staging of lung cancer. New tools such as autofluorescence imaging (AFI), narrow band imaging (NBI) and endobronchial ultrasound (EBUS) have found their place in many bronchoscopy suites. Angiogenesis and structural changes of the mucosa are the basic and hallmark lesions of neoplasia [2]. NBI uses two bandwidths of light; 390 to 445 nm (blue) light that is absorbed by superficial capillaries and 530 to 550 nm (green) light that is absorbed by blood vessels below the mucosal capillaries [3]. These wavelengths coincide with the peak absorption spectrum of oxyhaemoglobin and make blood vessels more pronounced. Studies have shown the utility of NBI by identifying capillary loop patterns in early diagnosis of oesophageal and gastric carcinoma [4, 5]. As far

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as bronchoscopy is concerned, NBI is still a tool in search of proper indications. Shibuya *et al.* [6] first described the pathological patterns on bronchial mucosa that are known as Shibuya's descriptors (dotted, tortuous and abrupt ending vessels). We conducted this study to find whether any relationship exists between different NBI vascular patterns and the histology of lung cancer.

Material and methods

This was an analytical cross-sectional study conducted in the department of pulmonary medicine at the All India Institute of Medical Sciences, Jodhpur, India over a period of twelve months. The study protocol was approved by the institutional ethics committee (project no. AIIMS/RES/(02)/2015-16/068). Informed written consent was obtained from each participant before enrolment in the study.

Inclusion criteria

Lung cancer patients in whom bronchoscopy showed endobronchial lesions with different NBI vascular patterns.

Exclusion criteria

Patients with endobronchial growth or abnormal mucosa not showing any enhanced vascularity on NBI mode, uncooperative patient, refractory hypoxaemia, hypercarbia, hypotension, recent/unstable angina, myocardial infarction within last six weeks, arrhythmias, bleeding disorders, uraemia and platelet count < 50,000/mm^3.

Methodology

Video bronchoscopy was performed using a flexible video bronchoscopy system (Olympus EVIS EXERA III model BF-1TH190 video bronchoscope, CLV-190 light source, CV-190 video processor and SONY LMD-2451MD high definition TV monitor). All patients were monitored using standard monitoring and alert systems during each procedure. The bronchial tree of each patient was examined by two experienced bronchoscopists, first, under white light (WL), and then, under narrow band imaging (NBI) mode. An abnormal appearance under NBI mode was defined as any area looking abnormal either by blood vessel concentration or appearance as per Shibuya's descriptors. Based on consensus among the two bronchoscopists, a particular NBI pattern was labelled for each patient. In situations where consensus could not be attained, opinion of a third bronchoscopist was taken — who reviewed and labelled the NBI pattern after watching the stored high-definition video of the procedure. The target biopsy sites were areas showing an endobronchial growth and/or abnormal appearing mucosa as seen by both WL and NBI. A minimum of three biopsies were taken from one site using biopsy forceps (Olympus rotatable biopsy forceps; model no. FB-55CR-1). Different forceps were kept to sample a different abnormal area in the same patient to avoid cross-contamination. Biopsy specimens were sent for histologic examination in a 10% formal saline solution. Immunohistochemistry was performed whenever required. Dysplastic and cancerous lesions were classified according to the WHO classification system [7].

Statistical analysis

Continuous variables were presented as mean ± SD; categorical variables were expressed in actual numbers and percentages. Fischer's exact test was used to compare two categorical variables. All statistical analyses were performed with SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

We screened 78 patients, out of whom 46 persons were excluded. Among those who were excluded, 21 patients did not show enhanced vascularity on NBI video bronchoscopy, 7 individuals had platelet count of less than 50,000/mm^3 and 18 patients had unstable cardiovascular status. There were 32 patients who were finally enrolled in the study. One person was excluded from analysis as histology revealed tuberculosis. The results of 31 patients were analysed. A flow chart of the study patients is shown in Figure 1.

The mean age of the patients was 60.3 ± 12.5 years. The majority of the subjects were males (90.3%) and smokers (87.1%). The most commonly encountered lung malignancy was squamous-cell carcinoma (58.1%), followed by adenocarcinoma (22.3%) and small-cell carcinoma (19.4%). Cough was the most common symptom (64.5%), followed by dyspnoea (58.1%), weight loss (51.6%), chest pain (48.4%) and haemoptysis (22.6%). Computed tomography (CT) of the chest showed mass-lesion (90.3 %), pulmonary nodules (12.9%), pleural effusion (12.9%), superior vena cava (SVC) syndrome (6.5%) and mediastinal adenopathy (35.5 %). Baseline characteristics of the patients are mentioned in Table 1.

A dilated tortuous vascular pattern seen in 54.8% of the study subjects was the commonest

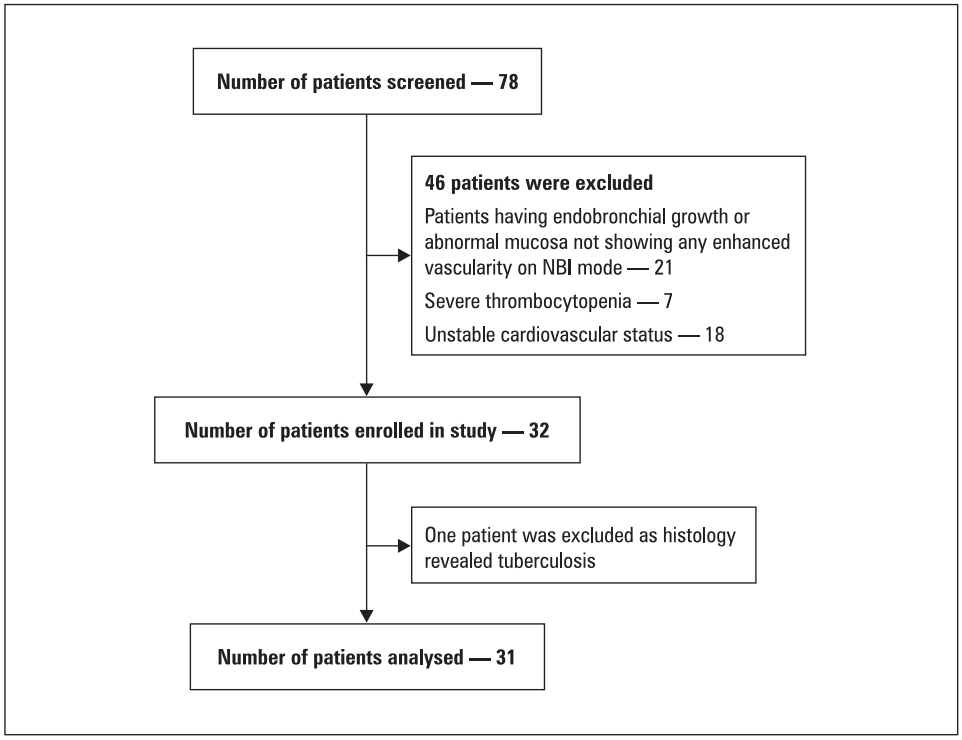

Figure 1. Flow chart of patients included in the study

Table 1. Baseline characteristics

Age, years [mean ± SD]	**60.32 ± 12.5**
Gender	N [%]
Male	28 (90.3)
Female	3 (9.7)
Symptoms	
Cough	20 (64.5)
Dyspnea	18 (58.1)
Weight loss	16 (51.6)
Chest pain	15 (48.4)
Hemoptysis	7 (22.6)
Smoking status	
Smoker	27 (87.1)
Never smoker	4 (12.9)
Comorbidities	
COPD	15 (48.4)
Diabetes mellitus	3 (9.7)
Systemic hypertension	3 (9.7)
Ischaemic heart disease	5 (16.1)
CT chest findings	
Mass	28 (90.3)
Pulmonary nodules	4 (12.9)
Pleural effusion	4 (12.9)
SVC syndrome	2 (6.5)
Mediastinal adenopathy	11 (35.5)

observed pattern on NBI. A non-specific pattern was observed in 32% of the cases, a dotted pattern in 9.7% and abrupt ending vessels in 3.2% of the cases. A dilated tortuous vascular pattern was seen in 61% of the cases of squamous-cell carcinoma, 42.9% of the cases of adenocarcinoma and 50% of the cases of small-cell carcinoma. A non-specific pattern was seen in 50% of the cases of small-cell carcinoma, 42.8% of the cases of adenocarcinoma and 22% of the cases of squamous-cell carcinoma. An abrupt-ending pattern was seen only in one patient of squamous-cell carcinoma. A dotted pattern was seen in 14% of the cases of adenocarcinoma and 11% of the cases of squamous-cell carcinoma. Figure 2 shows the frequency of NBI patterns in the study patients with different histological types of lung cancer. Few of these NBI patterns and the corresponding histopathology images observed in our patients are depicted in Figure 3.

In suspecting squamous-cell carcinoma, the sensitivity and specificity of a dilated tortuous pattern was 61% and 53.8%, respectively, and for a dotted pattern, it was 11% and 92%, respectively. For adenocarcinoma, the sensitivity and specificity of a dilated tortuous pattern was 42.8% and 41.6%, respectively, and for a dotted pattern, it was 14.2% and 91.6%, respectively. Sensitivity and specificity of a dilated tortuous pattern for small-cell carcinoma was 50% and

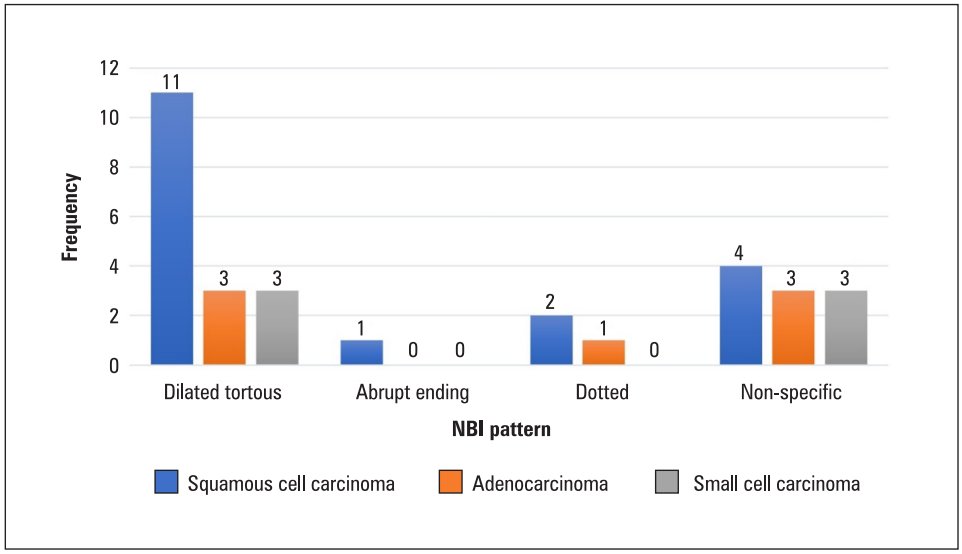

Figure 2. Frequency of various vascular patterns observed on NBI in various histological types of lung cancer

45.8%, respectively. Sensitivity, specificity, positive predictive value and negative predictive values of various vascular patterns observed on NBI in identifying various histological types of lung cancer are shown in Table 2.

There was no statistically significant relationship between a dilated tortuous pattern and squamous-cell carcinoma ($p = 0.48$), adenocarcinoma ($p = 0.667$) or small-cell carcinoma ($p = 1$). There was no statistically significant relationship between a dotted pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 0.54$) or small-cell carcinoma ($p = 1$). There was no statistically significant relationship between an abrupt-ending capillary pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 1$) or small-cell carcinoma ($p = 1$).

Discussion

Despite improved imaging capability of video bronchoscopy, early central lung cancers are difficult to detect solely with white light bronchoscopy as these lesions are usually small, relatively flat with subtle endobronchial changes [8]. Enhanced magnification, improved image quality and better visual contrast have been an area of ongoing research and implementation in the field of endoscopy to differentiate normal from abnormal areas. NBI bronchoscopy has been found to be useful in detecting increased vascularisation and complex vessel networks in the bronchial mucosa ranging from tortuous vessels, dotted vessels to spiral or screw type vessels during the process of carcinogenesis [9]. A combination of high magnification video bronchoscopy with advanced imaging techniques like AFI and NBI has shown promising results [10–12]. A significant association was seen between dotted vessels by NBI-B1 imaging and tissues confirmed pathologically as angiogenic squamous dysplasia [10]. The first study to specifically look for any relation between different NBI patterns and histology of lung cancer was done by Zaric *et al.* [13]. They found that a dotted visual pattern of blood vessels was highly suggestive of adenocarcinoma ($p < 0.0001$), while a tortuous and abrupt-ending blood vessels was significantly suggestive of squamous-cell lung cancer ($p < 0.0001$). This is in contrast to the findings of our study which found no statistically significant relationship between any NBI pattern and the histology of lung cancer. The authors also mention about situations when they faced difficulty in attaining consensus on the NBI pattern but ultimately labelled these pathological patterns based solely on Shibuya's descriptors. This is the second difference from our study where we observed a non-specific NBI pattern in about one-third of the patients not fulfilling the pattern based on Shibuya's descriptors. This pattern consisted of one or two superficial vessels seen over some part of the entire endobronchial growth or abnormal mucosa. Among those whom we screened, 26.9% of the patients actually did not show any increased vascularity or pattern over the endobronchial lesion on NBI mode and were thus excluded from the study as depicted in Figure 1.

After searching PubMed and Google with keywords like histology, narrow band imaging, relation and bronchoscopy, we could find only one

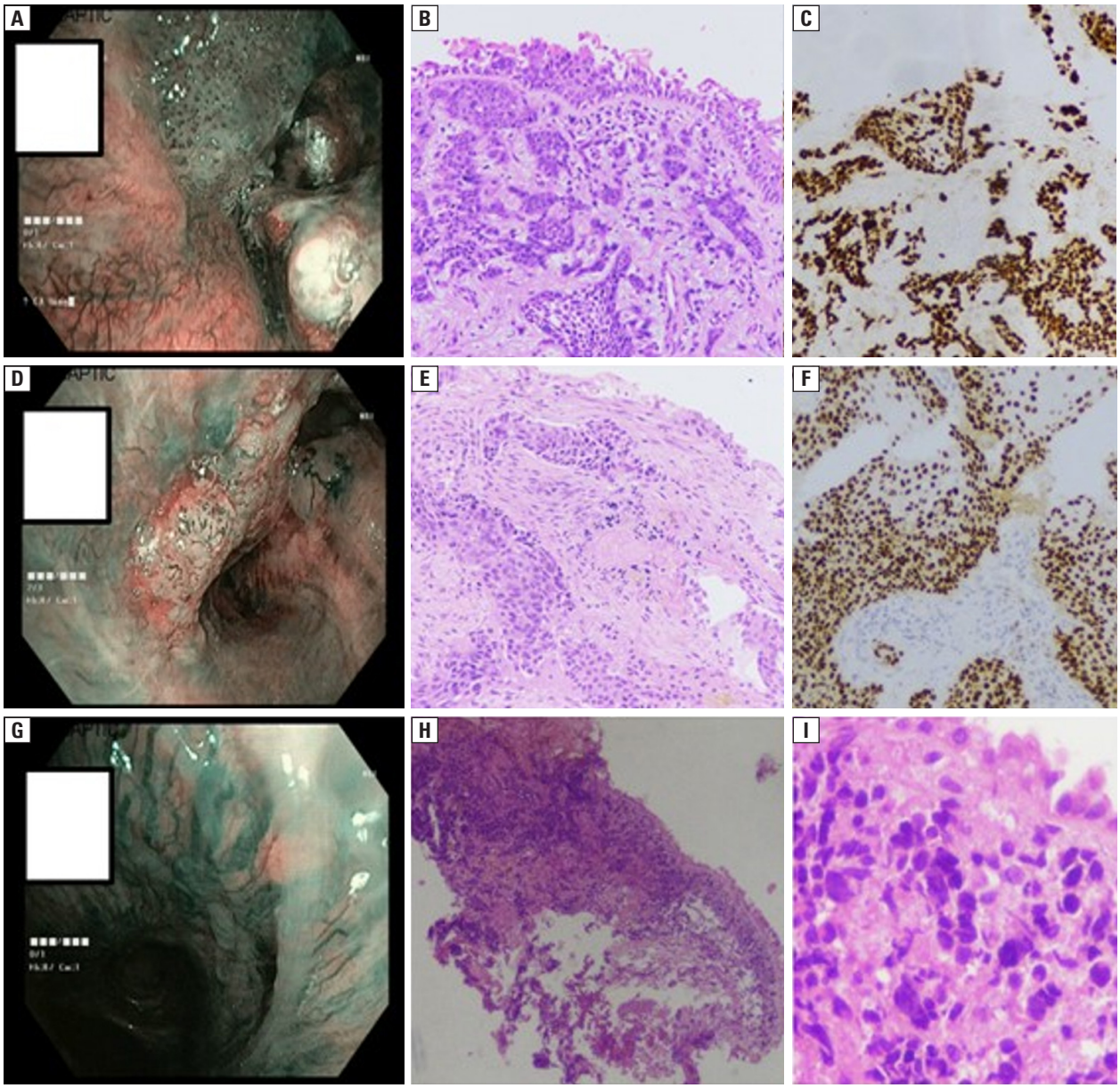

Figure 3. Images of few NBI vascular patterns observed in our patients and the corresponding histopathology slides. **A.** NBI image showing dotted pattern; **B.** Hematoxylin and eosin stained slide of the patient (A), 10×, showing strands and sheets of invasive tumour with squamoid differentiation; **C.** Immunohistochemistry (IHC) for p63 showing intense immunoreactivity; **D.** NBI image showing abrupt ending blood vessels; **E.** Hematoxylin and eosin stained slide of the patient (D), 10×, showing strands and sheets of invasive squamous cell carcinoma; **F.** IHC for p63 showing intense immunoreactivity; **G.** NBI image showing dilated tortuous blood vessels; **H.** Hematoxylin and eosin stained slide of the patient (G), 4×, showing small cell carcinoma; **I.** Hematoxylin and eosin stained slide of the patient (G),10×, showing small cell carcinoma beneath ciliated columnar epithelium

article by Zaric *et al*. [13] that mentions about the relation between different NBI vascular patterns and histology of lung cancer. The majority of clinical research on NBI technology has been in gastroendoscopy. This is due to difference in the luminal vascular anatomy of the airway and digestive tract. The vascular supply of the gastrointestinal tract has an extensive intramural distribution which is well developed with plexuses in the different layers of the bowel wall [14]. The architecture of this prominent vascular network gets distorted in various pathological conditions, which gets detected relatively easier and in a much better way with the use of additional digital imaging technologies like NBI. Various studies in different gastrointestinal pathologies reveal the diagnostic accuracy and relationship of NBI patterns with the histologic diagnosis [15–17]. Unlike these studies, we did not find any relation between the NBI image of airway lesions and histology.

Table 2. Sensitivity, specificity, positive predictive value, negative predictive value of various vascular patterns observed on NBI in diagnosis of histological subtypes of lung cancer

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Fischer's exact test P value
Dilated tortuous in squamous cell carcinoma	61%	53.8%	64.7%	50%	0.48
Dotted pattern in squamous cell carcinoma	11%	92%	66.67%	42.8%	1
Dilated tortuous for adenocarcinoma	42.8%	41.6%	17.64%	71.4%	0.67
Dotted pattern for adenocarcinoma	14.2%	91.6%	33.33%	78.57%	0.54
Dilated tortuous pattern in small cell carcinoma	50%	45.8%	17.64%	78.57%	1

In a recent interesting study on mixed-type early gastric cancers, a fine network pattern was seen in differentiated-type-predominant and a corkscrew pattern was seen in undifferentiated--type-predominant mixed-type lesions [18]. The authors of this study concluded that a combination of these NBI findings with magnifying endoscopy and biopsy could actually change the clinical practice by reducing the number of additional surgeries because of incorrect diagnosis based solely on histology. Although the utility of NBI in detecting precancerous and cancerous lesions in the airways has been proven, our study has shown that it performs poorly in predicting the histology of a cancerous lesion.

We wish to highlight some of the strengths of this study. Firstly, the labelling of NBI vascular pattern was based on consensus. Secondly, we observed a non-specific NBI pattern which affected the results and conclusions of our study. The limitations of our paper are also worth mentioning. Being a single-centre study, despite observing many endobronchial lesions during bronchoscopies, we did not find any NBI abnormality in significant number of patients. This affected our actual sample size for the final analysis. Labelling of NBI patterns is subjective, so the authors feel that a large, multicentric study would help in looking at the reproducibility and variability of NBI assessment between bronchoscopists and finding the relevance of these patterns in malignant as well as benign airway lesions.

Conclusions

No relationship exists between vascular patterns observed on NBI video bronchoscopy and the histologic type of lung cancer. Any abnormality found during bronchoscopy on either WL or NBI, needs to be adequately sampled for proper histologic and molecular studies when suspecting lung cancer. An inconclusive histologic finding of a biopsy sample showing a specific NBI pattern does not obviate the need for repeat tissue sampling.

Conflict of interest

None declared.

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