Are screening and surveillance for Barrett’s oesophagus really worthwhile?

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Oesophageal adenocarcinoma has a low incidence and still remains an uncommon cancer; however, it has been on the rise over the past 20 years. Barrett’s oesophagus, a complication of gastro-oesophageal reflux disease, is the only known precursor of this adenocarcinoma. It can often be asymptomatic and probably goes undiagnosed in the majority of the population. However, many argue that the detection of neoplasms at a curable stage in a high-risk population can perhaps justify screening endoscopy. No prospective, controlled trials have been conducted to support the effectiveness of surveillance, but some indirect evidence does exist. The cost-effectiveness of surveillance programmes needs to be further assessed in prospective studies. Ultimately, the use of better tools to diagnose Barrett’s oesophagus and dysplasia and the identification of high-risk groups for progression to oesophageal adenocarcinoma could potentially make screening and surveillance a cost-effective practice.

The incidence of oesophageal adenocarcinoma has been rapidly rising over the past two decades with an increase in more than 350% in white males between 1974 and 1994. During the same time period, the incidence rates for squamous cell carcinoma of the oesophagus have declined. The reasons for this rapid change in the epidemiology of oesophageal cancer in Western society remain poorly understood. The diagnosis of oesophageal adenocarcinoma usually portrays a poor prognosis but is significantly linked to the stage of the tumour. If the cancer is detected at an early stage, the 5 year survival is 83–90%, compared with a dismal 10–15% 5 year survival of late-stage cancers. Barrett’s oesophagus is present as a pre-malignant lesion in many or most cases of oesophageal adenocarcinoma. Prospective studies in the 1990s demonstrated a wide range of incidence of oesophageal adenocarcinoma in patients with Barrett’s oesophagus. However, this cancer risk may have been overestimated and is probably subject to publication bias. In a recent large prospective study, the incidence of oesophageal adenocarcinoma in patients with Barrett’s oesophagus undergoing surveillance endoscopy was 1/220 patient-years follow up (0.45% per year). Given the lack of robust data on the natural history of Barrett’s oesophagus, rates of progression to cancer, and risk factors involved in the pathogenesis and malignant transformation, there is no consensus among gastroenterologists on when to initiate screening for Barrett’s oesophagus, what the surveillance intervals should be once Barrett’s oesophagus has been diagnosed, what the most optimal biopsy techniques for initial diagnosis and subsequent surveillance are, and what the standards of management of dysplasia should be. This was highlighted in a survey of Members of the British Society of Gastroenterology and in surveys of US based gastroenterologists. The aim of this paper is to review and summarise current data on issues pertaining to the screening and surveillance of Barrett’s oesophagus given the numerous controversies related to this subject. Because there are no randomised trials in this field, a formal systematic review was not conducted; however, recent data are discussed in this paper.

SCREENING FOR BARRETT’S OESOPHAGUS

By definition, screening is the examination of a large sample of the population to detect a specific disease or disorder. In the case of Barrett’s, screening refers to the initial endoscopy to identify individuals with Barrett’s oesophagus, high-grade dysplasia (HGD), or cancer. By establishing the diagnosis of Barrett’s oesophagus on the initial endoscopy, the prevalence of this lesion among the population being evaluated is determined. Screening for Barrett’s oesophagus is a very controversial issue and there is no direct evidence that mortality from oesophageal adenocarcinoma is reduced by entering patients in a screening programme. The yield and benefit of screening endoscopy is related to the prevalence of Barrett’s in different population groups.

The population prevalence of Barrett’s oesophagus

What is the prevalence of Barrett’s in the non-gastro-oesophageal reflux disease (non-GORD) population? Although the exact prevalence of Barrett’s in the general population is unknown, recent data shed some light on the prevalence of...

Abbreviations: BMI, body mass index; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; LOH, loss of heterozygosity; PDT, photodynamic therapy
Barrett’s oesophagus in asymptomatic subjects and in non-GORD patients. Barrett’s oesophagus was identified in 25% of asymptomatic patients >50 years undergoing sigmoidoscopy for colorectal cancer screening.6 Other studies, published as yet only in abstract form, have reported Barrett’s oesophagus to be present in 9.5% of patients undergoing endoscopy for ulcer symptoms9 and in 6% of those with dyspepsia.10 A recent study by Rex et al, in a cohort of patients undergoing colonoscopy who were offered an upper endoscopy, reported an 8.3% prevalence of the Barrett’s oesophagus in subjects with heartburn and 5.6% in patients without heartburn.11 These data reflect a large number of individuals with Barrett’s oesophagus who remain unrecognised until the endoscopy has been performed. Moreover, a 21-fold increase in the recognition of Barrett’s (from 22.6 cases per 100 000 population to 376 cases per 100 000 population) has also been reported when cases of Barrett’s oesophagus found during autopsy were compared with those that were clinically diagnosed, that is by endoscopy.12 Thus, recent data suggest that the prevalence of the Barrett’s oesophagus may be much higher than had been originally appreciated.

**Barrett’s oesophagus in patients with reflux symptoms**

Because Barrett’s oesophagus is a complication of GORD, updated guidelines by the American College of Gastroenterology suggest that patients with chronic GORD symptoms should undergo upper endoscopy for the detection of Barrett’s oesophagus.13 Barrett’s oesophagus can be found in approximately 10–15% of the patients undergoing endoscopy for GORD.14 15 Moreover, GORD symptoms are a risk factor for oesophageal adenocarcinoma. The odds ratio (OR) of patients with at least once a week GORD symptoms for oesophageal adenocarcinoma was 7.7 (95% CI 5.3 to 11.4) as shown in a large case control study.16 The duration of GORD symptoms is also associated with the presence of the Barrett’s oesophagus and oesophageal adenocarcinoma. In a prospective, community based study it was shown that compared with patients with reflux symptoms of duration <1 year, the OR for Barrett’s oesophagus in patients with symptoms for 1–5 years was 3.0 and increased to 6.4 in patients with symptoms for >10 years (p<0.001).17 However, if the only criteria for screening were the presence of GORD symptoms, the population to be screened for Barrett’s oesophagus would be enormous because it is estimated that 20% of the US adult population experiences reflux symptoms.

**Other population groups at risk for Barrett’s oesophagus**

Factors such as male sex, Caucasian race, and obesity have also been shown to be associated with a risk of developing Barrett’s oesophagus and adenocarcinoma in epidemiological studies. The prevalence of Barrett’s oesophagus increases with age—the typical age of diagnosis is approximately 60 years. Data showing a significant association between high body mass (BMI) and symptoms of GORD are now available.18 Compared with those with a BMI <25, the risk of reflux was increased among the severely obese (BMI >35) men (OR, 3.3; 95% CI 2.4 to 4.7) and women (OR 6.3; 95% CI 4.9–8.0). Yet screening even obese patients with reflux symptoms may not be worthwhile, as shown in the population based analysis of Swedish data collected in 1995–1997.19 The number of individuals needed to be screened to detect one case of oesophageal or cardia adenocarcinoma was 2189 in a group of subjects with reflux symptoms and a BMI >25, and was 394 if a similar group had a BMI>30.

**Cost effectiveness of screening programmes**

The cost effectiveness of a screening programme depends on the risk of the particular disease in the population being evaluated—the greater the risk, the more people would potentially benefit from screening. The effectiveness of a screening programme is frequently assessed in the number of life-years saved. The cost effectiveness of endoscopic screening in GORD patients to prevent mortality from oesophageal carcinoma has been evaluated in recent modeling studies. Soni et al calculated the incremental cost effectiveness ratio to be $24 718 per life-year saved, that is the cost difference between two strategies (screening v no screening) divided by the gain in life expectancy. The authors concluded that under favourable conditions (high sensitivity and specificity of the upper endoscopy, high prevalence of Barrett’s oesophagus/HGD, and little or no reduction in health related quality of life by subsequent medical or endoscopic follow up) endoscopic screening of all patients with GORD to prevent death from oesophageal adenocarcinoma may be a cost effective strategy.20

Screening also implies that the patients with Barrett’s oesophagus will enter surveillance programmes for the detection of neoplasia. Although data from two large cohorts indicate that the incidence of cancer in Barrett’s oesophagus is only 0.4–0.5%/year,21 data pooled from a large Barrett’s oesophagus programme in the US indicates that the combined incidence of cancer and HGD is 1.35% per year.22 Depending upon the natural history of HGD, these data suggest that screening and subsequent surveillance could be cost effective.23 24 Unfortunately, there are no controlled trials examining the clinical role or cost effectiveness of endoscopic screening for Barrett’s either in the general population or in patients with reflux symptoms.

**Challenges in screening for Barrett’s oesophagus**

There are a number of problems associated with screening for Barrett’s in the general population or even in patients with reflux symptoms. The risk of oesophageal adenocarcinoma in the general population is too low to be classified as a major health problem and the risk of dying from this cancer, even in patients with Barrett’s oesophagus, is low. The costs of such a screening programme would be enormous. Also, patients with Barrett’s oesophagus, identified through screening, would potentially be enrolled into surveillance programmes, the efficacy of which is also questionable. Although screening the general population for Barrett’s is currently of unproven value in effecting outcomes, some investigators have proposed that the yield and detection of prevalent neoplasia at a curable stage in a high risk population can perhaps justify the role of screening endoscopy. Such a high risk group could include patients with chronic reflux symptoms, elevated BMI, Caucasians, and males, thus targeted screening. Targeted screening for Barrett’s oesophagus has been essentially proposed for a few reasons. The incidence of oesophageal adenocarcinoma is increasing and by the time this carcinoma is detected, survival of patients is extremely poor. It is known that GORD is a risk factor for oesophageal adenocarcinoma and, therefore, the detection of Barrett’s oesophagus in GORD patients could probably help the early recognition of oesophageal carcinoma. This hypothesis has led to attempts to identify a high risk group of individuals in whom targeted screening would be effective.

Deleterious consequences of screening and the potential benefits of one time endoscopic screening for Barrett’s oesophagus in patients with long term heartburn symptoms should also be considered. The presence of erosive oesophagitis at the time of screening may mask underlying Barrett’s oesophagus and biopsies near eroded areas may lead to over diagnosis of dysplasia. The potential impact of false positive diagnoses of Barrett’s oesophagus with attendant generation of patient anxiety, unnecessary follow up examinations, and difficulty obtaining life and other insurance are unintended harms of screening that also must be considered.
SURVEILLANCE OF PATIENTS WITH BARRETT’S OESOPHAGUS

Surveillance is a close and continued observation for the purpose of detecting a newly developed disease in the population at risk. The ultimate goal of surveillance is to improve outcomes in the population involved in the surveillance programme, for example patients with Barrett’s oesophagus. Surveillance in patients with Barrett’s oesophagus refers to the endoscopies performed at regular intervals with the goal to detect dysplasia and early cancer at a curable stage. Potentially, the early detection of oesophageal adenocarcinoma can lead to a decrease in mortality from this disease. Incidence of the disease plays an important role in determining if the surveillance programme is worthwhile. If the incidence of the cancer in patients with Barrett’s oesophagus were high, then surveillance would prove to be cost effective. On the other hand, if the incidence is low (the disease is rare and does not affect a significant portion of the population) an extremely small proportion of the population would probably benefit from the surveillance programme. The incidence of oesophageal adenocarcinoma remains relatively low compared with other types of cancer, for example colon cancer. The overall risk of cancer in Barrett’s oesophagus patients is estimated to be approximately 0.5% per year and the risk of neoplasia including HGD to be 1.3% per year.21

Does surveillance improve outcomes in patients with Barrett’s oesophagus?

Retrospective data have shown that cancers detected during Barrett’s oesophagus surveillance are more likely to have an early stage compared with those detected outside of surveillance.25 26 27 In one study, surveyed Barrett’s patients had a significantly lower stage of cancer than non-surveyed patients. Only 1 (6%) surveyed patient v 34 (63%) non-surveyed had nodal involvement (p 0.0001) and the 2 year survival was 85.9% for the surveyed patients, compared with only 43.3% for the non-surveyed patients (p 0.0029).25 In a recently published population based study of 23 patients (Barrett’s oesophagus diagnosed >6 month before cancer diagnosis), 73% of the patients with Barrett’s oesophagus associated adenocarcinoma detected by surveillance (n = 15) were alive at the end of follow up compared with none in the non-surveyed group (n = 8; p 0.001). All surveillance detected cancer patients had early stage disease leading the investigators to conclude that surveillance detected oesophageal adenocarcinomas were associated with low stage disease and improved survival.24 Thus, the data supporting endoscopic surveillance in patients with Barrett’s oesophagus are weak and based mainly on retrospective studies comparing outcome in surveyed and non-surveyed patients. However, all these reports are subject to both lead time and length time bias and may not represent a true alteration in cancer outcomes. A few studies have demonstrated no difference in the overall survival between patients with Barrett’s oesophagus v the general population and have questioned the utility of endoscopic surveillance. Frequently, patients with Barrett’s oesophagus die from causes other than oesophageal adenocarcinoma, suggesting that oesophageal cancer is an uncommon cause of death in this group. In one report, of 166 patients followed for a mean of 9.3 years, oesophageal adenocarcinoma was the cause of death in only 2 of 79 patients who died during follow up.24 Another observational study followed a cohort of Barrett’s oesophagus patients for 10 years. The majority of the patients who died during the follow up period died from diseases unrelated to oesophageal adenocarcinoma, with only 4 of 409 patients dying from oesophageal cancer.29

Conducting an ‘‘ideal study’’ to demonstrate the effectiveness of surveillance. Is it possible?

The ideal study would be a prospective randomised trial with mortality as the primary outcome. It would have to compare two patient groups, identical in every aspect except surveillance. Using a high estimate of the annual incidence of cancer in Barrett’s oesophagus (1.3%), such a randomised trial would require approximately 5000 patients followed for at least 10 years. It is unlikely that a study meeting these criteria would be conducted because of ethical considerations and the number of patients that would have to be followed over such an extended time period. However, a similar design using two different surveillance intervals in Barrett’s oesophagus patients could potentially be conducted and would provide extremely useful information.

Degree of dysplasia determines the surveillance interval

The histological progression from Barrett’s oesophagus to oesophageal adenocarcinoma is probably a multistep process. Dysplasia is a neoplastic epithelial proliferation, which may remain non-invasive or may progress to cancer. Currently, dysplasia remains the best indicator of the risk of cancer despite the development of new cancer markers. It has specific cytological and architectural features including nuclear enlargement, hyperchromasia, stratification, and increased number of mitosis.34 However, the diagnosis and detection of dysplasia can be complicated by a few problems. There is a high inter-observer variability in the reading of dysplasia. Many pathologists experience difficulties in distinguishing between regenerative changes and low grade dysplasia.35 The terminology used by the pathologists in the East and West is frequently ambiguous; for example, pathologists in Western countries report non-invasive neoplastic epithelium as dysplastic, but in Japan the term carcinoma is used for both invasive and non-invasive neoplastic tissue.35 Moreover, the distribution of the dysplasia in the oesophagus is patchy and sampling errors during surveillance biopsies are common. Currently, endoscopy with four quadrant random biopsies remains the method for obtaining surveillance biopsies and surveillance intervals are based on the grade of dysplasia. Guidelines for the management and surveillance of Barrett’s oesophagus are shown in table 1.

Do patients with HGD benefit from intensive endoscopic surveillance?

The management of patients with HGD remains another controversial area. The options for the management of HGD include intensified endoscopic surveillance, oesophagectomy, or treatment with endoscopic ablation including mucosal resection. First and foremost, the diagnosis of HGD should be confirmed by a second experienced pathologist. Secondly, it is also important to determine if the HGD is unifocal, multifocal, or associated with nodularity. The presence of diffuse or multifocal HGD has a higher (fourfold) increase in the risk of oesophageal cancer development compared with focal HGD (p 0.02),38 whereas the presence of nodularity may signify the presence of underlying or associated cancer.39 Schnell et al showed that cancer did not develop in 63 of 79 HGD patients during a mean follow up period of 7.3 years (range: 0.5–12.3 years).38 They concluded that HGD follows a relatively benign course in the majority of patients and suggested endoscopic surveillance as a management option in these patients. However, other studies have reported a higher rate of progression to cancer in patients with HGD, leading some experts to advocate aggressive treatment with either surgery or endoscopic ablation.34 Surgery has been proposed as a management option given data suggesting that these patients frequently have coexisting oesophageal cancer.35 However, oesophagectomy can be associated with a...
high mortality and morbidity and, therefore, should be reserved for younger patients with good performance status and should be performed in high volume institutions. The advent and use of new ablation techniques can potentially address the problems of high mortality and morbidity rates associated with oesophagectomy. Recently, results from a randomised trial using photodynamic therapy (PDT) in patients with HGD were reported; showing a statistically significant reduction in the rate of progression to adenocarcinoma. After a mean follow up of 24.2 month, 13.0% of patients in the PDT treated group had progression to cancer compared with 28% in the surveillance group (p 0.006). Thus, it appears that the natural history of HGD is variable and intensified endoscopic surveillance is a potential option, but many factors should be considered when choosing the optimal management for HGD and treatment should be individualised.

**Cost effectiveness of surveillance programmes**

Comparisons with other healthcare practices have been made to validate the practice under consideration in order to determine if it is cost effective or not. Often, comparison between two practices is done in view of its incremental cost effectiveness. Using decision analytical models, study results have suggested that surveillance every 5 years in patients with Barrett’s oesophagus is the only viable strategy with the greatest quality adjusted life assuming a cancer incidence of 0.4–0.5% per year. This suggested surveillance increases both the length and quality of life and has an incremental cost utility ratio that is similar to that of accepted medical practices. In another recently published paper, investigators demonstrated that continued surveillance of Barrett’s oesophagus patients without dysplasia offered little benefit over the low incidence of oesophageal adenocarcinoma in this subgroup. Surveillance intervals of less than 5 years for Barrett’s oesophagus patients without dysplasia were associated with a small increase in quality adjusted life years but with higher costs. This model also showed that the benefit from screening was greater than that of surveillance because the prevalence of oesophageal adenocarcinoma in patients with GORD may be greater than the subsequent annual incidence of cancer in patients with identified Barrett’s oesophagus. This model determined that a one time screening endoscopy for Barrett’s oesophagus and oesophageal adenocarcinoma and surveillance of patients with dysplastic Barrett’s was cost effective.

**THE IMPACT OF FUTURE DEVELOPMENTS TO INCREASE THE EFFECTIVENESS OF SCREENING AND SURVEILLANCE**

Screening and surveillance can be improved by better defining the risk groups for Barrett’s oesophagus and dysplasia/cancer and by concurrently developing more accurate methods for the diagnosis of Barrett’s oesophagus, dysplasia, or oesophageal adenocarcinoma rather than relying on random biopsy techniques.

**Identification of risk factors**

Some authors have proposed that the length of the Barrett’s segment and the patient’s age may be risk factors for the development of the oesophageal adenocarcinoma. Both these factors were shown to be independent risks for dysplasia development in a recent multicenter study. There was a 3.3% increase in the risk of dysplasia per year of increase in age. Weston et al, in a prospective study of 108 patients, demonstrated that progression from Barrett’s oesophagus to multifocal HGD and oesophageal adenocarcinoma was associated with the Barrett’s length >2 cm, a hernia size >3 cm, and the presence of dysplasia at any time during surveillance. One of the ways to improve the cost effectiveness of surveillance is to enhance the understanding of the various risk factors involved in the progression of intestinal metaplasia to dysplasia and cancer.

**Potential biomarkers**

Several new biomarkers that have recently been evaluated can potentially also help to identify a group of patients with a high risk of developing HGD and cancer. Recent studies have found that in individuals who progressed from Barrett’s oesophagus to oesophageal adenocarcinoma, one of two normal p53 alleles was inactivated by mutation and the second was lost by a mechanism termed as loss of heterozygosity (LOH). Reid and colleagues followed 256 patients with Barrett’s oesophagus and p53 LOH data at baseline for up to 5 years and found p53 LOH to be a strong predictor of progression to oesophageal adenocarcinoma (relative risk 16; 95% CI 6.2 to 39; p<0.001). In another study, biopsy specimens from 11 of 12 patients with oesophageal adenocarcinoma stained positive for cyclin D1 and a statistically significant risk for progression to adenocarcinoma (OR 6.85; 95% CI 1.57 to 29.91, p 0.0106) was found in the patients who stained positively for this biomarker. Systematic flow cytometry can identify patients with increased 4N or aneuploidy and has also been used in recent studies. A 28% 5 years cumulative oesophageal cancer incidence was found in those Barrett’s patients with either aneuploidy or increased 4N compared to a 0% 5 year cumulative oesophageal cancer incidence in patients with neither aneuploidy nor increased 4N fractions. As yet, none of the molecular markers has shown to be a better predictor or more cost effective than the finding of dysplasia on biopsy. Prospective multicenter validated studies need to be performed to provide more information regarding these predictors and their exact role in surveillance of Barrett’s oesophagus patients.

**Small caliber, non-sedated endoscopy**

Endoscopy with ultrathin endoscopes and without sedation is a promising method of screening that can potentially decrease procedure costs. Recent studies have shown that
unsedated upper endoscopy using smaller caliber instruments is feasible, acceptable, and accurate when compared with conventional sedated endoscopy and offers potential advantages of decreased sedation-related complications and costs. However, limited information is available on unsedated endoscopy in the evaluation of Barrett’s oesophagus, and there are no studies examining its utility in screening. Whether unsedated endoscopy will meet with patients’ acceptance in Western society given the cultural preference for sedation and the variable acceptance and tolerability of unsedated endoscopy in published trials remains unclear.

The cost-effectiveness of a one-time screening was evaluated in a model for 50-year-old patients with chronic reflux symptoms: no screening, standard endoscopy, and screening by ultrathin endoscopy. Ultrathin endoscopy was shown to be more cost-effective than standard endoscopy and both strategies improved quality-adjusted life-years among the patients with chronic reflux at costs that were similar to those of other preventive measures. Defined by decreasing the costs of endoscopy, eliminating the risks associated with sedation, and decreasing the post-procedure recovery time this would make both screening and surveillance endoscopy more attractive propositions.

Other novel endoscopic techniques
Identification of high-risk tissue has been shown to be possible by utilizing new techniques for detecting dysplasia and early cancer such as chromoendoscopy, magnification endoscopy, or fluorescence spectroscopy. Methylene blue staining has been shown to have an overall 95% accuracy for detecting intestinal metaplasia. Specific patterns observed with the help of magnification endoscopy may help in identifying dysplasia and early adenocarcinoma in the absence of endoscopically visible lesions. Indigo carmine staining used in combination with magnification endoscopy has been shown to further increase the diagnostic yield of intestinal metaplasia. Sharma et al. in 2003 reported the use of magnification endoscopy (×115) with indigo carmine staining in 80 patients with Barrett’s oesophagus. The presence of the ridge/villous pattern for detecting intestinal metaplasia had a high sensitivity, specificity, and positive predictive value of 97%, 76%, and 72%, respectively. Thus, the diagnostic yield of biopsies for the detection of dysplasia and cancer can be increased by using target biopsies, which can eliminate unnecessary blind biopsies. These novel endoscopic procedures hopefully will lower the costs of both screening and surveillance programs by improving efficacy. However, more studies need to be performed to compare the cost-effectiveness of new endoscopic techniques to conventional methods.

CONCLUSION
The role of screening and surveillance in patients with Barrett’s oesophagus remains controversial. There is a clear link between screening and surveillance. Patients detected by screening may be committed for further surveillance programmes and this has to be borne in mind before embarking on large-scale screening. Existing data do not show that screening for Barrett’s oesophagus is cost-effective or improves mortality from oesophageal adenocarcinoma. A critical component of a Barrett’s targeted screening programme will be to identify a high-risk group and an inexpensive screening tool. Targeted screening of selected subjects may detect oesophageal adenocarcinoma at an earlier stage and improve survival in these patients. However, currently the exact criteria for screening for Barrett’s oesophagus cannot be determined and it is unclear whether proposed guidelines are cost-effective or alter outcomes. Similarly, the efficacy of endoscopic surveillance for Barrett’s oesophagus is unproven. However, observational studies and computer models do suggest that surveillance may decrease mortality from oesophageal cancer. Identification of patients with Barrett’s oesophagus at high risk for progression to cancer utilizing better diagnostic tools will tremendously benefit surveillance and may decrease the cost burden of Barrett’s oesophagus. Such a group could be better identified by using a panel of biomarkers. Using less expensive methods of performing endoscopy, utilizing advanced endoscopic techniques, minimizing endoscopic complications, and decreasing the cost of surgery for oesophageal cancer and cost of cancer care may also contribute to the ultimate goal of reducing mortality from oesophageal adenocarcinoma.

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