

Modern Management of Colorectal Polyps: Are They All Premalignant?

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Abstract

There are various types of polyps in the colon and rectum. Most colorectal polyps in the colon and rectum are either adenomas or hyperplastic polyps. In general, adenomas are considered to be premalignant. Adenoma-carcinoma sequence is an established theory of carcinogenesis in the large bowel in Western countries. However, small adenomas are ubiquitous phenomena, and it is questionable whether they are actually precancerous. Most small adenomas did not become larger in our colonoscopic follow-up study of small adenomas measuring 5 mm or less. It was considered safe to leave such small adenomas behind, particularly in a situation in which follow-up examination is periodically performed, such as in patients who have undergone colorectal cancer surgery before. In Japan, small flat carcinomas have been reported as an important precursor of advanced colorectal carcinoma. They are also found in Western population. The malignancy rate of small flat and depressed lesions was significantly higher than that of polypoid lesions. Although small flat carcinomas are less frequently seen than polypoid-type carcinomas in the early stages, they are considered to be an important precursor of advanced colorectal cancer.

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Introduction

Polyps of the colon and rectum are relatively common lesions. Most colorectal polyps are either adenomas or hyperplastic polyps. Adenomas are considered to be premalignant. Adenoma-carcinoma sequence is an established theory of carcinogenesis in the large bowel in Western countries. However, adenomas, particularly the smaller ones, are ubiquitous phenomena, and it is questionable whether such small adenomas are actually precancerous. Furthermore, in Japan, small flat carcinomas have been reported as an important precursor of advanced colorectal carcinoma. In this review, the modern management of colorectal polyps will be discussed with regard to the benign nature of small adenomas, and as well as the importance of small flat carcinoma as a precursor of advanced colorectal cancer.

Polyps of the Colon and Rectum and their Malignant Potential: General Aspects

Polyps of the colon and rectum are relatively common lesions, particularly in elderly people. Many researchers have reported on the histopathology of colorectal polyps. Among them, Basil Morson of St Mark's Hospital¹ is the

most well known. He classified colorectal polyps as two main types, neoplastic and non-neoplastic. Neoplastic polyps consist of adenomas and carcinomas in the early stages. The adenomas have a malignant potential with different grades, depending on their size, shape and histological type. Non-neoplastic polyps include hamartomatous, inflammatory and hyperplastic polyps. These non-neoplastic polyps are usually not premalignant; however, under certain special circumstances these non-neoplastic polyps occasionally show malignant potentials. From our experience, the most common types are either adenomas or hyperplastic polyps. Except for uncommon special circumstances, hyperplastic polyps are not considered premalignant. Adenomas are considered to be the most frequent precursor of colorectal carcinomas.

Prevention of Colorectal Carcinoma by Endoscopic Resection of Adenomas

There are two reports on the effect of endoscopic resection of adenomas on the incidence of colorectal carcinomas. In the study by Winawer et al,² 1418 patients who had polypectomy were followed up for an average of 5.9 years. Their study showed a significantly lower incidence of

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colorectal carcinoma in these patients compared to the general population. However, 494 (35%) of the patients had adenomas larger than 1 cm, and 10% of the adenomas removed had severe dysplasia. Murakami et al³ analysed patients with polyps in a colonoscopic series and followed up on patients with and without polypectomy. They reported a lower observed versus expected ratio of cancer occurrence in the polypectomy group versus non-polypectomy group. However, 45% of the polyps removed in the polypectomy group were larger than 1 cm.

Based on the results of these reports, it can be speculated that endoscopic removal of larger adenomas may contribute to a reduction in the incidence of colorectal cancer. However, we do not know if the endoscopic resection of smaller polyps less than 1 cm contributes to a reduction in the development of colorectal cancer.

Prevalence of Small adenomas and their Malignant Potential

In general, the incidence of colorectal adenomas is relatively high, especially in the elderly. According to an extensive autopsy study carried out by Kanazawa et al⁴ in Japan, which included more than 4000 autopsies on the elderly, the incidence of colorectal adenomas was approximately 65% in the those above 60 years of age, and reached 70% in those aged above 70. Most of the adenomas were less than 1 cm in diameter and did not contain a carcinomatous component. Therefore, colorectal adenoma is considered a relatively ubiquitous phenomenon, particularly in the elderly.

Colonoscopic resection of colorectal polyps is routinely performed nowadays without any significant complications. However, in view of the high incidence of colorectal adenomas in the elderly population, endoscopic resection of small adenomas is not considered to have contributed to a reduction in the development of colorectal carcinomas. It is clear that larger adenomas have greater malignant potential. When adenomas are larger than 15 mm in diameter, the chances of having carcinomatous foci (areas with severely dysplastic glands) or invasive carcinoma will increase by about 50%. On the other hand, the incidence of having carcinomatous foci within small adenomas is relatively low. The percentage is usually less than 5% when the adenoma is less than 10 mm, and it is rare to detect a carcinomatous component in adenomas smaller than 5 mm in diameter (Fig. 1).

Prospective Colonoscopic Observation of Small Adenomas

We carried out a prospective observational study of small adenomas in patients who have had colorectal cancer surgery. Because of the possible occurrence of

metachronous colorectal cancer after colorectal cancer surgery, we had been carrying out prospective surveillance colonoscopy every one to two years. In this prospective study, we found a large number of small adenomas during the follow-up period. The cumulative incidence of adenomas was approximately 50% five years after surgery (Fig. 2). Most of the adenomas were smaller than 5 mm in diameter. Between 1997 and 2001, we prospectively observed 208 adenomas found during surveillance colonoscopy after colorectal cancer surgery. When an adenoma was 5 mm or smaller, we did not remove the lesion but tattooed it with India ink so that we could identify it at a later colonoscopy. Of the 208 lesions, 184 were detected in subsequent colonoscopies. The mean follow-up period of the 184 lesions was 23 months. The size of the polyps remained constant in 163 lesions (89%), but increased in 17 polyps (9%). The maximum increase in size was by 4 mm, which was seen in two lesions. There were 4 polyps whose size had decreased. We removed 8 of the 17 lesions that showed an increase in size, and their histology showed adenomas with mild to moderate dysplasia.

In this prospective study, we proved that most small adenomas measuring 5 mm or smaller do not grow larger, and would not have been premalignant. However, we still do not know the characteristics of the small number of tiny adenomas that may grow bigger in future. Based on the results of this prospective observational study, as well as the fact that small adenomas are ubiquitous phenomena with an incidence of 60% to 70% in the elderly population, we consider that it would be probably safe to leave such small adenomas behind, particularly when follow-up examination is periodically performed, such as in patients who have undergone colorectal cancer surgery.

Familial Adenomatous Polyposis

In a special condition of familial adenomatous polyposis (FAP) coli, numerous small adenomas develop in the colon and rectum. If left untreated, the incidence of colorectal carcinomas in FAP is 100%. Bussey⁵ reported that in his series of 151 FAP that underwent surgery, 67 (44.4%) contained multiple colorectal carcinomas in the resected specimens. However, the highest number of carcinoma in any specimen was only 7. Considering the fact that in FAP patients, there are hundreds and thousands of adenomas, or a even higher number of adenoma if microscopic adenomas are taken into account, most of the adenomas in FAP do not develop into carcinomas.

Small Flat Carcinoma

(1) Importance of Small Flat Lesions as a Precursor of Colorectal Cancer

The macroscopic appearance of carcinomas in the early

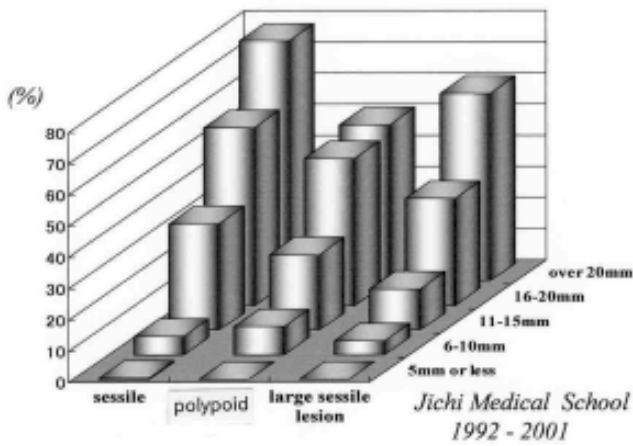


Fig. 1. Malignancy rate of colorectal polyps in relation to the shapes of the lesions. Malignancy was defined as a carcinoma either confined to the mucosa (ca-m, Tis) or having invaded the submucosa (ca-sm, T1).

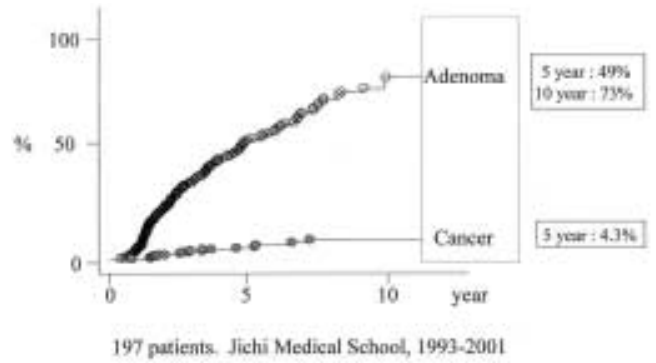


Fig. 2. Cumulative incidence of adenomas and carcinomas in patients who have had colorectal cancer surgery. The data were analysed based on the results of periodic surveillance colonoscopy carried out after surgery in 197 patients who were operated on before 1997.

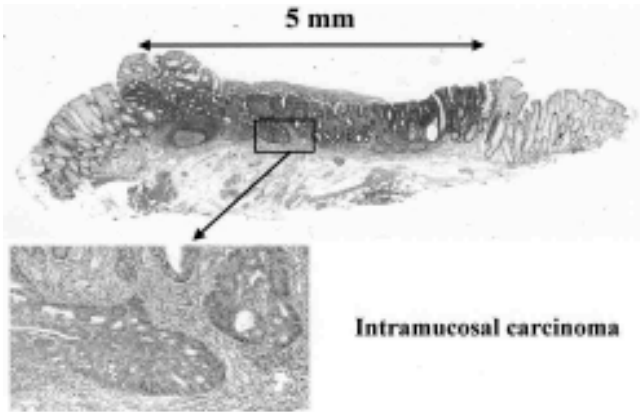


Fig. 3. Small flat carcinoma measuring 5 mm (haematoxylin and eosin staining x9).

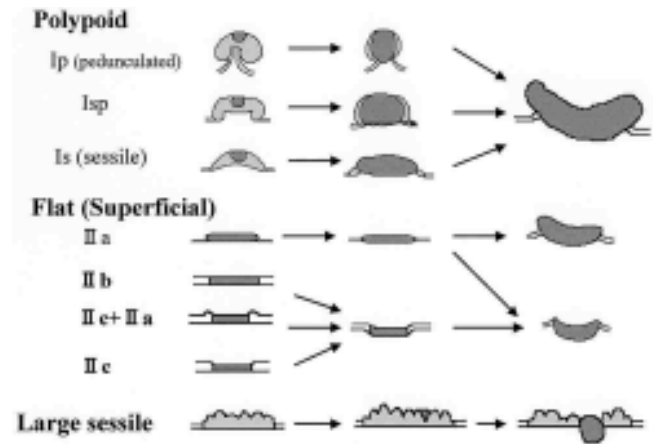


Fig. 4. Different pathways in the evolution of colorectal cancer.

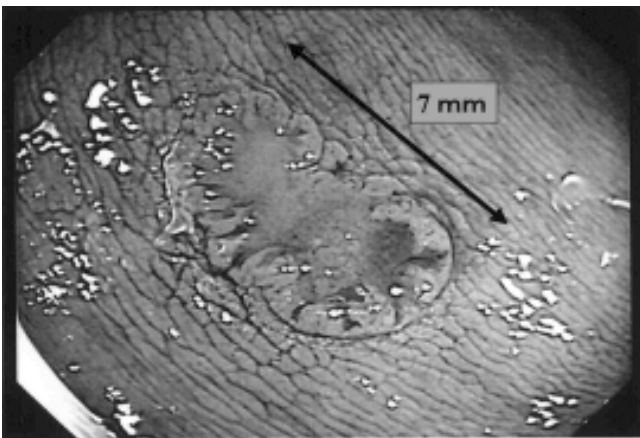


Fig. 5. A small flat and slightly depressed carcinoma measuring 7 mm. The lesion is surrounded by a marginal elevation of non-neoplastic mucosa (indigocarmine dye spray method).

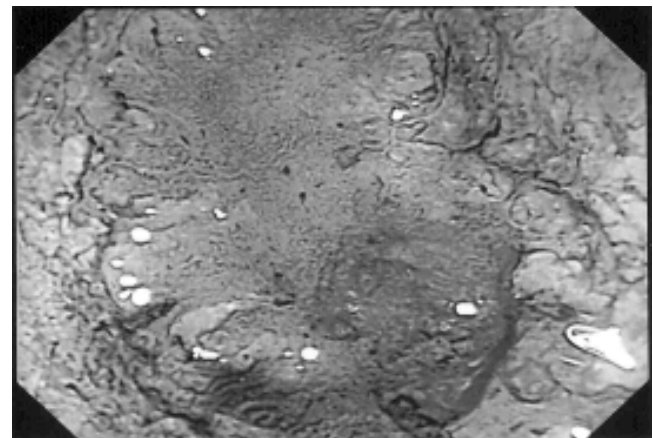


Fig. 6. Magnified colonoscopic view of the lesion in Figure 4. The surface structure was destroyed, suggesting the presence of invasive carcinoma (cresyl violet staining method).

stages is classified into two types, the usual polypoid and flat type. Figure 3 is a good example of a flat-type carcinoma in the early stages. In flat-type carcinomas, the size of the lesion is usually smaller than 10 mm, the surface is entirely flat and the thickness of the lesion is often smaller than that of the normal mucosa. Often, the lesion is completely occupied by a highly dysplastic epithelium that is equivalent to carcinoma on histology. In the West, it is generally considered that the polypoid type is the only precursor of more advanced colorectal carcinoma. On the other hand, in Japan, small flat carcinomas are found in about 20% to 30% of colorectal carcinomas in the early stages. Figure 4 shows different pathways in the development of advanced colorectal carcinoma. Polypoid type is a usual type and the flat type is also important. Though not frequently encountered, large sessile adenomas are also a precursor of more advanced colorectal carcinoma. Some colonoscopic series in the West have shown that flat-type carcinomas were also seen in their population. Therefore, such lesions are not specific to the Japanese population.⁶⁻⁸

(2) Detection of Small Flat Carcinoma

To detect the small flat carcinoma, it is important to pay attention to any slight change in the colour of slight rough areas during colonoscopic observation of the mucosa. When these abnormalities are found, dye spray using 0.2% indigocarmine solution should be performed. Indigocarmine dye spray is essential to the visualization of small flat lesions of the colon and rectum.⁹ Figure 5 is a good example of small flat and slightly depressed carcinoma measuring 7 mm in diameter. Such a small flat carcinoma is usually surrounded by a raised non-neoplastic mucosa. In this case, on magnifying colonoscopy, the surface structure showed a distorted pit pattern suggestive of invasive carcinoma (Fig. 6).¹⁰ Histology of the endoscopic mucosal resection (EMR) specimen of this lesion showed an invasive carcinoma that almost reached the resection line (Fig. 7). A bowel resection was carried out in this case.

(3) Early Studies and the Definition of Flat Lesions

Muto et al,¹¹ who first described flat adenoma, did not provide a clear definition but described that the characteristic features of flat adenoma as having a slight elevation with a reddish surface and a height that is less than twice the thickness surrounding normal mucosa on histological sections. On the other hand, Kuramoto and Oohara¹² proposed that the height of flat early cancer did not exceed 50% of the longer diameter, but their proposal is generally not accepted. Wolber and Owen¹³ advocated a strict definition comprising three points: 1) flat lesions lack an exophytic polypoid configuration; 2) histologically, the dysplastic mucosa is never greater than two times the thickness of the adjacent non-dysplastic mucosal segment;

and 3) flat lesions show radial extension of the dysplastic epithelium in the superficial luminal portion of the mucosa without any vertical extension. Their definition has been well accepted by both Japanese and Western investigators thus far.

(4) Analysis of our Materials

Materials

Colorectal lesions detected colonoscopically at Jichi Medical School Hospital between January 1992 and June 2001, and in Miyashita Hospital between April 1992 and May 1997, were analysed. Using high-resolution video-endoscope, we performed meticulous colonoscopy after bowel preparation with polyethylene glycol lavage solution. All neoplastic lesions were either biopsied or removed by colonoscopic polypectomy, including the EMR technique, or surgical intervention. Gross appearance was determined from both colonoscopic findings and resected specimens, and was classified into flat type, polypoid type or large sessile type. The height of the flat type was less than twice that of the surrounding normal mucosa. Polypoid-type lesions were sub-classified into sessile type or pedunculated type based on the presence or absence of stalk. Flat-type lesions were sub-classified into flat depressed type or flat elevated type from the presence or absence of depression.

Histological examination

We used a standard protocol to examine the resected specimens. Each lesion was fixed in formalin and sections were stained with haematoxylin and eosin. Adenomas, including serrated adenomas and carcinomas confined to the mucosal layer or the submucosal layer, were analysed. Rubio et al¹⁴ defined "intramucosal carcinoma" according to this criteria.

Malignant potential of small flat lesions

Of the 5408 neoplastic lesions, 5035 were adenomas, 249 were carcinomas confined to the mucosa (ca-m or Tis in TNM classification), and 124 were carcinomas invading the submucosa (ca-sm or T1 in TNM classification). The histological definition of early-stage carcinoma in this study followed the Japanese criteria. When severely dysplastic glands equivalent to carcinoma exist within the mucosa, the lesion was diagnosed as a carcinoma limited in the mucosa or intramucosal carcinoma. Such a lesion is commonly diagnosed as adenoma with severe dysplasia or carcinoma in situ in Western classifications.

Figure 8 shows the percentages of the different types in the 373 early-stage carcinomas in this series. Sessile type was the most frequent, followed by pedunculated, large sessile, flat and depressed, and flat and elevated. The flat type made up approximately 20% of all early-stage carcinomas. Regarding the shape, the malignancy rates

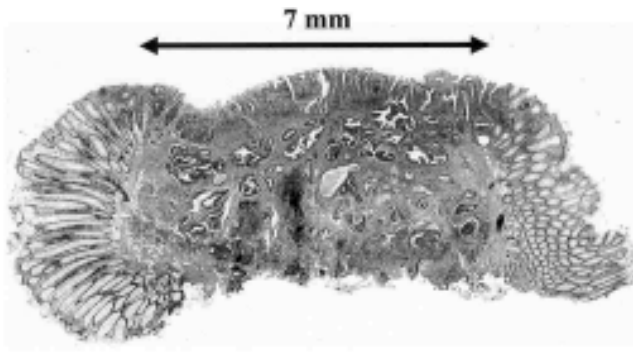


Fig. 7. Low-power view of the histology section showing a flat carcinoma invading the submucosa (haematoxylin and eosin staining x6).

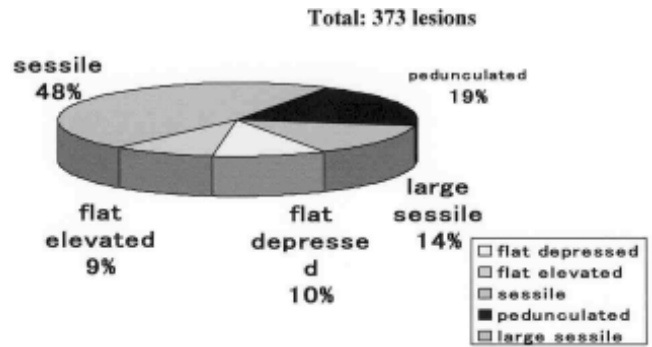


Fig. 8. Types of carcinomas in early-stage carcinomas. Carcinoma was defined as either cancer confined to the mucosa (ca-m, Tis) or had invaded the submucosa (ca-sm, T1).

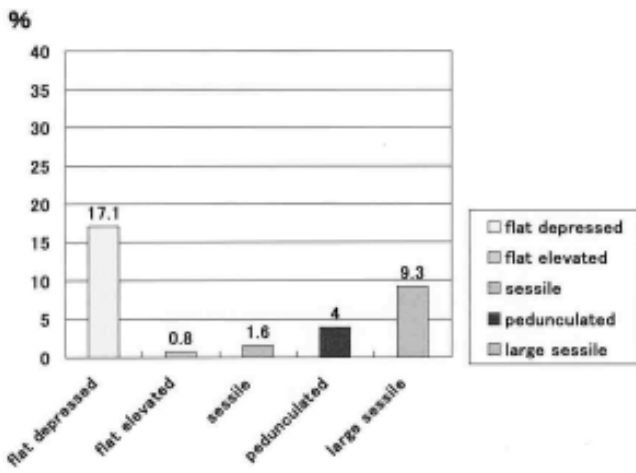


Fig. 9. Malignancy rates of different types of lesions. The malignancy rates of small flat and depressed lesions are the highest.

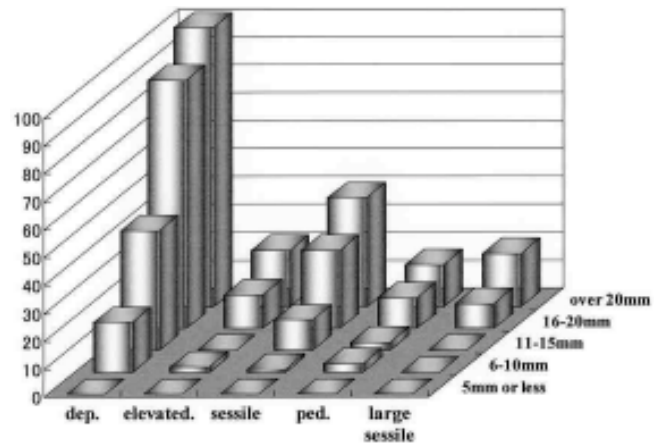


Fig. 10. Malignancy rate in relation to the size and shape of the lesions. The flat and slightly depressed type showed the highest malignancy rates in all the size categories. dep.: flat depressed, elevated.: flat elevated, ped.: pedunculated

(mucosal carcinoma plus submucosal carcinoma) of the flat depressed type and large sessile type are significantly higher than those of any other shapes ($P < 0.05$). When the malignancy rate was defined according to Western criteria (those with invasion in the submucosa), the flat depressed type showed a higher rate than any of the other types, and a significantly higher rate than those of the flat elevated type, sessile type and pedunculated type (Fig. 8; $P < 0.0001$).

The relationship between the percentage of mucosal carcinoma and submucosal carcinoma, shape and size is shown in Figure 9. The malignancy rate of flat depressed type lesion was the highest in every size category. It is noteworthy that the malignancy rates of the depressed type in “6 to 10 mm” and “11 to 15 mm” are the highest among those with other shapes. When carcinoma with invasion in the submucosa was defined as carcinoma in the early stages, the tendency to have the highest malignancy rates

in the flat and depressed type lesions became more pronounced (Fig. 10).

(5) Clinical importance of flat elevated and flat depressed lesions

In early research on flat adenoma, “flat adenoma” had referred to both flat depressed and flat elevated lesions. Flat elevated lesions were thus frequently confused with flat depressed lesions. When flat elevated and flat depressed lesions were classified into the same category as “flat adenoma”, flat lesions were generally considered to have a high malignancy rate. In fact, the malignancy rate of flat elevated lesions was not higher than that of sessile lesions, and flat depressed lesions showed a significantly higher malignancy rate.¹⁵ This suggests that the biological behaviour of flat depressed lesions is quite different from that of flat elevated lesions. Therefore, flat depressed

lesions should be distinguished from flat elevated lesions in general practice, although the former resemble the latter in their colonoscopic appearance when dye spraying is not applied.

(6) Role of small flat lesions in colorectal carcinogenesis

Studies in the West have stated that excision of polypoid adenomas could prevent the development of two-thirds of colorectal cancers. This suggests that the remaining one-third might originate from flat adenomas. Our data on submucosally invasive cancers show that approximately 20% to 30% have a flat appearance. Kudo et al,¹⁶ who detected a large number of flat depressed lesions, also reported a similar distribution of the two different types of lesions in their gross appearance. Therefore, it can be considered that two-thirds of colorectal cancers are derived from polypoid type lesions and one-third from flat lesions. The conventional setting of colonoscopy targeting the polypoid lesions would not be sufficient for detecting the wide range of colorectal cancers in the early stages.

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