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Prognostic significance of high-grade dysplasia in colorectal adenomas.

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Abstract:

Aim Colonoscopy to detect and remove polyps has contributed to a reduction in colorectal carcinoma. Three-year follow up is recommended for patients considered to be at high risk (at least three adenomas, adenoma ‡ 1 cm, villous or high-grade features). Our study focused on patients diagnosed with high-grade dysplasia with regard to initial management and follow up.

Method A search of patients who had had endoscopic removal of a high-grade adenoma was carried out. Patients with the following were excluded: follow up of < 1 year, polyposis syndromes, prior colon cancer and a diagnosis of adenocarcinoma within 6 months following initial diagnosis.

Results Eighty-three patients treated between 1999 and 2007 for high-grade dysplasia (HGD) in a colorectal adenoma were identified. Over a median follow-up period of 4 years, 53 (64%) developed further adenomatous polyps. Among these, 7% had an adenoma with HGD or an adenocarcinoma. In all these patients, the initial high-grade

adenoma was > 1 cm in diameter. Initial follow-up colonoscopy was performed on average 7 months following the initial diagnosis. Ten per cent of patients underwent prophylactic segmental resection, and 6% received argon laser therapy.

Conclusion The study demonstrates that patients who have a colorectal adenoma > 1 cm with HGD may be at high risk of developing further adenomas with HGD or carcinoma. Close follow up is warranted.

Keywords High-grade dysplasia, polyps, adenomas, colon cancer

Introduction

Adenomatous polyps are precursors of adenocarcinoma. Their number, size and histology provide the basis for recommended surveillance intervals [1]. Three-year follow up is recommended for patients with 'advanced' adenomas, including the presence of at least three adenomas, diameter ‡ 1 cm, those with villous morphology and high-grade dysplasia (HGD) [1]. Prospective studies have validated this recommendation, showing that although < 15% of patients fall into this category, metachronous adenoma formation in these cases exceeds 40% at 3 years [2]. Risk factors associated with HGD are similar to those used to define patients recommended for 3-year follow up, as well as other factors, including older age and not taking nonsteroidal anti-inflammatory medication [3].

The clinical response to a diagnosis of adenoma with HGD has not been sufficiently evaluated [3–12]. Our study focused, therefore, on patients diagnosed with HGD with regard to initial management and subsequent follow up.

The reporting of HGD in adenomas has been a topic of ongoing debate. Although current guidelines refer to HGD as a feature of advanced adenomas, no histological criteria have been provided to establish reporting guidelines [1]. Among reference pathology texts, the entity of HGD has not been clearly defined. The World Health Organization book on tumours of the digestive tract makes no mention of criteria for HGD, and the Armed Forces Institute of Pathology states that separations of low-grade dysplasia from HGD are superficial in nature because the two entities are part of a spectrum [13–15].

Histological definitions of HGD are essentially similar to adenomatous change with regard to cytological and architectural atypia, but more pronounced. Histological features including a cribriform glandular architecture have been suggested by some groups to represent intramucosal carcinoma; however, this may still be classified as HGD by other pathologists [13]. The thresholds for diagnosing HGD and intramucosal carcinoma also vary according to country. The Japanese literature focuses on nuclear features, while Western pathologists place more emphasis on invasion through the muscularis mucosae [16]. This may account for the greater incidence of early carcinoma in the Japanese literature [16,17]. Despite diagnostic ambiguity and interobserver variability, HGD continues to be reported and influences patient management. An assessment of the prognosis for these patients is needed. This will help

to define the role of HGD within the category of advanced adenoma to guide the clinical management.

Method

Following approval from the Institutional Review Board of Thomas Jefferson University Hospital, a search of the surgical pathology database was performed to identify cases of colorectal adenoma with a diagnosis of HGD (in our practice, low-grade dysplasia is not reported). The cases comprised a mixture of different polyp morphologies, including tubular and villous types. The percentage of HGD in each polyp was not evaluated, as this is not routinely carried out in pathology practice. Resection of the adenoma was complete in all patients, with no dysplastic mucosa remaining in the patient. Histological examination was performed on a minimum of three (range 3–9) transverse levels.

Larger adenomas were oriented to show complete cross-sections from the apex to the cauterized base. Most of the cases were reviewed or signed out by one of the coauthors (JPP) to minimize interobserver variability. The endoscopic size, rather than gross measurement, was used to determine polyp dimensions. Microscopic features of HGD include enlarged, stratified nuclei with vesicular chromatin and nucleoli. Glandular branching, back-to-back glands and cribriforming are common, with occasional foci of necrosis. Our practice does not utilize the term intramucosal adenocarcinoma in isolation; however, this is sometimes used in conjunction with HGD (for example, patients may be diagnosed as HGD/intramucosal adenocarcinoma). Extension through the muscularis mucosae was used to diagnose invasive adenocarcinoma.

Four hundred consecutive patients with a diagnosis of HGD from 1999 to 2007 were identified from chart and pathology database review. The following exclusion criteria were used: follow up of < 1 year, familial polyposis syndromes, previous history of colon cancer and a diagnosis of adenocarcinoma within 6 months following initial diagnosis (implying the diagnosis was a result of sampling error). After accounting for these, 83 patients qualified for the study. Preanalytic variables, including demographics and polyp location/size, were collected. Initial therapeutic interventions were recorded, as were the colonoscopic intervals and neoplasm recurrence rate. A control population of 100 consecutive patients with a diagnosis of tubular adenoma from 2000 were obtained using the same exclusion criteria, follow-up time and postpolypectomy recurrence markers.

Statistical comparisons were performed using Fisher's exact test for gender and race and Wilcoxon analysis for age. A P-value of < 0.05 was taken as being statistically significant.

Results

The results are summarized in Table 1. No statistically significant differences were identified in adenoma location. Villous architecture was seen in 53% of HGD cases

(either villous or tubulovillous), and serrated features were noted in one case. Sixty-four per cent (53 of 83) of patients in the study group developed a metachronous adenoma at a median follow up of 4 (1.25–10) years. Among patients with a recurrent neoplasm, six (7%) developed an adenoma with HGD or an adenocarcinoma (five HGD, one adenocarcinoma). In all the six patients, the initial adenoma was > 1 cm in diameter.

Follow-up colonoscopy was performed at an average of 7 (1–36) months following the initial diagnosis. The breakdown of the intervals was as follows: £ 6 months 46.2%, 7–12 months 33.3%, 13–24 months 6.4%, and 25–36 months 14.1%. Ten per cent (n = 8) of patients underwent prophylactic segmental resection, 6% (n = 5) had endoscopic ultrasound, and 6% (n = 5) argon laser therapy. The average age of patients undergoing resection was 63.5 years, and argon therapy was 66 years. Three of the five patients having argon treatment chose this in preference to segmental resection. Among the eight patients who underwent segmental resection, three were felt to have an endoscopically unresectable adenoma owing to its large size or sessile morphology. Two cases were clinically regarded to be adenocarcinoma. Pathological examination of the resection specimen showed either residual adenoma or a scar, and none showed invasive adenocarcinoma. Among the control population of patients diagnosed with a tubular adenoma, 18 (18%) developed a metachronous adenoma; however, none showed HGD or adenocarcinoma.

Discussion

A colorectal adenoma with HGD larger than 1 cm in diameter may be a risk factor for metrachronous adenoma with HGD or ca rcinoma. Over a period of 4 years, 7% of patients with a previous adenoma with HGD developed a recurrent adenoma with HGD or a carcinoma, compared with none in the control group. This finding is in agreement with previous studies of HGD [19,20]. Adenomas with HGD did not appear to have a particular endoscopic appearance. They were distributed throughout the colon, and although most were > 1 cm, 17% were < 1 cm. One of the larger studies of the prognostic significance of advanced adenomas included 1905 patients followed over 4 years. Villous histology was the only independent predictor of metrachronous advanced adenoma formation [3]. In the present study, 53% of the cases of adenoma found to have HGD were villous in type.

In addition to focusing on HGD, our experience is the first from a single institution to assess the postpolypectomy management. Although based on consensus guidelines, management will continue to be individually tailored, and our study confirms the validity of this approach. Previous epidemiological studies have focused mainly on short- and long-term outcome, with little emphasis on the initial management. We found the diagnosis of HGD prompted earlier follow-up colonoscopy (mean 7 months) than would have been the case for adenomas not having HGD. There was also a high prevalence of invasive procedures, including argon laser therapy (6%) and prophylactic segmental resection (10%). Interventions during the follow up should also be guided by

nonpathological factors, such as completeness of the polypectomy and the quality of the bowel preparation. Even after accounting for these, the diagnosis of HGD has a direct impact on management.

Despite adherence to postpolypectomy surveillance guidelines, there remains a population of patients who develop colorectal adenocarcinoma during follow up [21]. While some of these may have had an adenoma missed during the initial colonoscopy, there remains a significant population of true 'interval' cancers. Our study attempted to control for lesions missed at the index colonoscopy by excluding patients diagnosed with invasive adenocarcinoma within 6 months following it. Furthermore, we controlled for interobserver variability by using a control population and by having a single specialist pathologist (JPP) review the cases of HGD. While the term 'advanced adenoma' is useful to describe general features which increase the risk of carcinoma, it is difficult to apply in individual cases. High-grade dysplasia identifies a subset of patients falling into the category of advanced adenoma that require close follow up. From the standpoint of pathological reporting, our study confirms that both HGD and villous architecture should continue to be routinely reported. Future research focusing on the identification of molecular markers which may predict recurrence of HGD and the development of adenocarcinoma would greatly assist the gastroenterologist in managing these patients.

A close working relationship between the gastroenterologist and pathologist is needed to ensure that the clinician understands the pathological findings and appreciates the varying threshold for diagnosing HGD.

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Table 1 Demographics and follow-up information for high-grade dysplasia (HGD).

	Study group (n = 83)
Gender, n (%)	
Female	36 (43%)
Male	47 (57%)
Age [years] (Range)	62 (44–87)
> 40, n (%)	83 (100%)
> 50, n (%)	74 (89%)
Race, n (%)	
White	53 (64%)
African-American	15 (18%)
Asian	3 (4%)
Hispanic/other	0 (0%)
Unknown	12 (14%)
Location*, n (%)	
Rectum	20 (24%)
Sigmoid	26 (31%)
Descending colon	14 (17%)
Transverse colon	5 (6%)
Right colon and caecum	17 (20%)
Unknown	1 (1%)
Adenoma size*, n (%)	
< 1 cm	14 (17%)
> 1 to < 5 cm	51 (61%)
> 5 cm	1 (1%)
Unknown	24 (29%)
Median follow up (years)	4
Adenoma recurrence, n (%)	53 (64%)
By size: < 1 cm	11 (79%)
> 1 cm	34 (65%)
Missing/not determinable	8 (47%)
Recurrence with HGD or cancer, n (%)	6 (7%)
Ultrasound, n (%)	5 (6%)
Prophylactic resection, n (%)	8 (10%)
Argon beam, n (%)	5 (6%)
Years to recurrence, median (95% CI)	5 (4, 6)
Months to follow-up colonoscopy, median (min, max)	7 (1, 36)

*Percentages sum to > 100, because some patients had more than one location.