A New Biomarker that Predicts Colonic Neoplasia Outcome in Patients with Hyperplastic Colonic Polyps

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Abstract

The most frequently occurring lesions in the colon are the hyperplastic polyps. Hyperplastic polyps have long been considered as lesions with no malignant potential and colonoscopy for these patients is not recommended. However, recent works suggest that hyperplastic polyps may represent precursor lesions of some sporadic colorectal cancers. Until now, no biomarker allows to identify the subset of hyperplastic polyps that may have a malignant potential. Because the hormone precursor progastrin has been involved in colon carcinogenesis, we investigated whether its expression in hyperplastic polyps predicts the occurrence of colonic neoplasm after resection of hyperplastic polyps. We retrospectively analyzed progastrin expression in hyperplastic polyps from 74 patients without history of colorectal pathology. In our study, 41% of patients presenting an initial hyperplastic polyp subsequently developed adenomatous polyps, recognized as precursor lesions for colorectal adenocarcinomas. Progastrin was overexpressed in the hyperplastic polyps in 40% of the patients. We showed a significant association between progastrin overexpression and shortened neoplasm-free survival (P = 0.001). Patients with high overexpression of progastrin had a 5-year neoplasm-free survival rate of 38% as compared with 100% for the patients with low progastrin expression. In addition, we established a predictive test on the basis of progastrin staining and patients’ age that predicts occurrence of neoplasm after developing a first hyperplastic polyp with a sensitivity of 100% [95% confidence interval (CI), 79%–100%] and a specificity of 74% (51%–90%). We show that progastrin expression evaluation in hyperplastic polyps is an efficient prognostic tool to determine patients with higher risk of metachronous neoplasms who could benefit from an adapted follow-up. Cancer Prev Res; ©2012 AACR.

Introduction

In the general population, the most frequently occurring lesion in the colon is the hyperplastic polyp, with a prevalence of 10% to 35% in Western populations (1). Hyperplastic polyps have long been considered as innocuous lesions with no malignant potential, whereas adenomatous polyps were recognized as neoplastic precursor lesions for colorectal adenocarcinomas. However, large hyperplastic polyps (size > 1 cm) and the presence of multiple hyperplastic polyps (number > 5) in hyperplastic polyposis syndrome have been clearly associated with colorectal adenomas or adenocarcinoma (2–5). In addition to these cases, more recent studies have suggested a link between hyperplastic polyps and sporadic colorectal cancer. Huang and colleagues (6) found that patients with hyperplastic polyps on initial colonoscopic examination have an increased incidence of colorectal adenomas on follow-up colonoscopy. Other groups have proposed the idea that hyperplastic polyps may represent precursors of some sporadic colorectal cancers, particularly in the serrated neoplasia pathway (7–10). Despite these new data, the colonoscopy for patients with hyperplastic polyps is not recommended, except after resection of one large hyperplastic polyp (>1 cm) and/or multiple polyps (n ≥ 5) or if there is a family history of hyperplastic polyps, neither in the guidelines from the French National Agency for Accreditation and Evaluation in Healthcare, nor by the American College of Gastroenterology (11, 12).

Until now, there is no biomarker to identify the subset of hyperplastic polyps that may have a malignant potential. However, data previously enounced strongly suggest that identifying a marker that could predict, with a good
sensitivity and specificity, the occurrence of colonic neoplasms after resection of hyperplastic polyps would be crucial for identifying the subset of patients at risk after hyperplastic polyps who could benefit from a more suitable follow-up strategy.

The hormone precursor progastrin is now recognized as a growth factor playing an important role in colon carcinogenesis. Transgenic mice overexpressing progastrin present an increased proliferative index in colonic mucosa. They also have an increased risk of developing preneoplastic lesions and adenocarcinomas in colonic epithelium when treated with a carcinogen, azaoxymethane (13, 14). The role of progastrin in proliferation, survival, and migration of human colon cancer cells has also been clearly established (15–20). Progastrin growth-promoting effects are mediated through the activation of several key signal transduction pathways (21, 22). In addition, several works including ours showed that depletion of endogenous progastrin produced by colon cancer cells leads to an inhibition of tumor growth (23, 24). Moreover, high concentrations of progastrin are found in colon tumors and in blood of 80% of patients with colorectal cancer. Surgical resection of the tumor induces a dramatic decrease of progastrin levels in the serum, suggesting that the tumor itself is the source of progastrin (25–27). Progastrin is also expressed in adenomatous polyps (26, 28), which represent neoplastic precursors for colorectal adenocarcinomas. In contrast, this hormone precursor is absent from the healthy intestinal epithelium.

All these data and our previous results suggested that progastrin may be a key factor of colon carcinogenesis and that its expression may predict the clinical outcome of early colonic lesions such as hyperplastic polyps. In consequence, we investigated whether progastrin is expressed in hyperplastic polyps and showed whether its expression in hyperplastic polyps is associated with the occurrence of colorectal cancer. We also assessed the performance of a predictive test on the basis of progastrin staining of hyperplastic polyps.

Materials and Methods

Study design

We conducted a single-center historical cohort study.

Sample size, patients, and data collection

The required sample size for the main endpoint of our study, neoplasms-free survival (NFS), was estimated for the log-rank test using the method of Freedman and Schoenfeld, with StATA v11 software (StataCorp). Thirty-eight patients were required. To show an association between progastrin staining and neoplasm occurrence, our sample size was calculated to detect a 4-fold increase in the hazard of the case group (minimum HR of 4) with 80% power. On the basis of our preliminary data, the probability of free neoplasms surviving to the end of the study was set at 0.65 in the control group and prevalence of strong expression of progastrin at 50%.

We reviewed the medical records of all cases of hyperplastic polyps diagnosed in the Pathology department of Rangueil Hospital (Toulouse, France), from January 1, 2000, through December 31, 2001. We excluded cases with a preceding colorectal adenocarcinoma or adenoma, familial colorectal adenocarcinoma history, hyperplastic polyposis, chronic inflammatory bowel disease, insufficient colon site information, or follow-up data. In addition, none of the patients in the cohort showed any evidence of colorectal adenoma at the initial colonoscopy. The final study group included 74 patients. We also selected 14 normal colonic tissues from resected uncomplicated diverticula, 8 adenomas and 6 colorectal adenocarcinomas. Clinical data were collected for all the patients, including colonoscopic data for 39 patients. Follow-up colonoscopies have been conducted for surveillance purpose without particular colorectal pathology (see the exclusion criteria above). Approval of an Institutional Research Ethics Committee was obtained in accordance with the precepts of the Helsinki Declaration.

Immunohistochemistry

For immunohistochemistry on the formaldehyde-fixed, paraffin-embedded tissues, heat-induced epitope retrieval was done in TRIS-EDTA buffer and primary antibodies were applied overnight. Detection was done using the DakoCytomation Envision+ System-HRP. Antiprogastrin antibody (1137; ref. 29) kindly provided by A. Shulkes was used for all the study (dilution used 1:1,000). In additional experiments (when mentioned), antiprogastrin antibody H-90 (Santa Cruz) was used at the dilutions recommended by the provider.

Progastrin staining was measured by the percentage of stained epithelial cells in the whole polyp. All specimens were examined in a double-blinded fashion by 2 pathologists. Because the inter-rater agreement was excellent [intraclass correlation coefficient (ICC) = 0.9], percentages were reported as the average between the 2 readers.

Statistical analysis

Univariate analysis was conducted to compare clinical and immunohistochemical findings between different study groups using the χ² test or Fisher exact test (when required) for categorical variables and Wilcoxon–Mann–Whitney for quantitative variables. We calculated intraclass correlation to determine inter-rater agreement for immunohistochemical staining.

For neoplasms-free survival analysis, only patients with colonoscopic follow-up data were included (39 patients). We conducted Kaplan–Meier and log-rank tests to assess the association of progastrin expression with the occurrence of a new colorectal neoplastic event. The main endpoint was NFS. The time to event was determined as the time interval between the diagnosis of hyperplastic polyps and the occurrence of metachronous colorectal adenomas in the same site (proximal or distal colon) as the first hyperplastic polyp. Progastrin expression was recorded as low, moderate, or high expression with the percentage of positive epithelial cells. The “normality” threshold of progastrin expression (low expression) was determined using the 95th percentile of percentage of stained cells in normal colonic tissue.
(<10%). Moderate expression of progastrin was defined as staining in 10% to 50% of polyp epithelial cells and high expression as staining in more than 50% of cells. When a patient had several polyps, the polyp with the strongest expression of progastrin was retained for evaluation. The log-rank test was also used to assess significance of clinical characteristics. Quantitative variables were recorded into 2-class variables using the median. To show that progastrin was a prognostic factor independent from other clinical factors, Cox proportional hazards model was conducted to test the simultaneous influence on disease-free survival of all covariates with a P value < 0.20 in the univariate analysis. After a backward stepwise selection, only significant variables (P < 0.05) were kept in the final Cox model.

Receiver operating characteristic (ROC) analysis was then conducted to select optimal “diagnostic” threshold for each significant quantitative variable after multivariate analysis. Using the ROC analysis results, we constructed a predictive test on the basis of a composite score with the significant variables, to predict the occurrence of a neoplastic event among patients with hyperplastic polyps. Performance of this test was measured by sensitivity (Se), specificity (Spe), positive predictive value, and negative predictive value. We also constructed a classification tree using the same variables significantly associated with the occurrence of a neoplastic event. To validate the classification tree, a bootstrap validation (refs. 30, 31; with 100 bootstrap samples) was conducted and the misclassification error rate estimated.

In our study, all tests were 2-sided and statistical significance was set at a P value of 0.05. Analyses were conducted with STATA v11 (32) and R (with “tree” and “ipred” packs).

Results

Patient and polyps characteristics

Clinical and pathologic features of patients and their polyps are shown in Table 1. For the whole cohort, the median age of patients was 65 years (SD, 14 years) and 43% of the patients were female. All polyps measured less than 1 cm with an average diameter of 3 mm, and the number of polyps at diagnosis was less than 5 for all the patients. Twenty percent of hyperplastic polyps were localized in the proximal colon and 80% in the distal colon, which is consistent with the previous observations. In our sample, no hyperplastic polyp displayed in normal colon, average percentage of progastrin expression was higher in adenomas and adenocarcinomas than in normal colon (median, 45%; range, 0%–100% vs. 1%; range, 0%–10%; P = 0.002, respectively). All (100%) of the tested adenomas or adenocarcinomas displayed an important expression of progastrin. As previously described (26, 28), progastrin expression in hyperplastic polyps was significantly different from the expression in normal colon (median, 45%; range, 0%–100% vs. 1%; range, 0%–10%; P = 0.002, respectively). The results have been obtained with the commercially available antiprogastrin H-90 antibody. Representative pictures with this antibody are shown in Supplementary Data S1. The percentages of progastrin-positive cells in normal colon, hyperplastic polyps, adenomas, and adenocarcinomas are reported in Fig. 3A. Progastrin expression was higher in adenomas and adenocarcinomas than in normal colon (low-grade dysplasia adenomas, P = 0.001; high-grade dysplasia adenomas, P = 0.0007; adenocarcinomas, P = 0.0005).

In normal colon, average percentage of progastrin staining was 2.6% (SD, 3.7%; range, 0–10). We considered that progastrin staining was low when the percentage of staining was less than the 95th percentile of the normal tissue (<10%). In the whole cohort, weak expression of progastrin (<10%) was found in 26% of the hyperplastic polyps. Expression of the prohormone was moderate (10%–50% of staining) in 34% of the hyperplastic polyps and high (>50% of staining) in 40% of them (Table 1). The results were not significantly different in the patients group with colonoscopic follow-up (weak expression, 18%; moderate expression, 36%; and high expression, 46%; P = 0.26).

Patient NFS

Survival analysis was conducted with data from patients who had at least one colonoscopy during their follow-up. As mentioned above, clinical and immunohistochemical characteristics of these patients did not significantly differ from the other patients of the cohort. The median for the follow-up period was 5 years (range, 2–10). Only occurrence of metachronous adenomas at the same general area of the colon (proximal or distal colon) was found in 41% of the patients. The pathologic type of these metachronous adenomas was tubular adenomas except in one case where a tubulovillous adenoma was observed. Mainly low-grade adenomas (38%) were diagnosed and 3% were high-grade adenomas.
period, the median survival was not reached by patients with a low expression of progastrin, as no recurrence occurred (Table 2, Fig. 3C). The 5-year NFS rate for the patients with weak progastrin expression was 100%, this value decreased to 84% for the patients with moderate expression and to 38% for the patients with high expression. In the same way, age was significantly associated with the occurrence of adenoma ($P < 0.0001$, for patients who were younger than 64 years: 5-year survival rate $= 95%$ and median $= 10$ years vs. 5-year survival rate $= 26%$ and median $= 5$ years for older patients; Table 2).

To show that the association between progastrin staining and NFS was independent from the subject’s age and localization and size of hyperplastic polyps, we conducted multivariate analysis (Table 2). After adjustment, progastrin expression was still highly significantly associated with adenoma occurrences ($P < 0.0001$). Taken together, these results show that progastrin staining in hyperplastic polyp is an independent prognostic factor. As mentioned above, 41% of patients having an initial hyperplastic polyp developed metachronous adenomas (Table 1) with 100% of these adenomas presenting a high staining of progastrin. Interestingly, the surrounding unaffected mucosa of the adenomas was also positive for progastrin. Representative pictures are shown in Supplementary Data S2.

### A predictive test for recurrence

To assess whether a predictive test using progastrin and age can predict the occurrence of a neoplasm after developing a first hyperplastic polyp, we conducted the ROC curve analysis for the percentage of progastrin-positive cells and for age (Fig. 4A and B). The predictive performance of progastrin and age were estimated by the area under the curve (AUC), which were, respectively, 0.81 (95% CI, 0.68–0.94) and 0.86 (95% CI, 0.74–0.98). With the ROC curves, we also determined the best "diagnostic" threshold (i.e., with a 100% sensitivity to detect all the patients at risk to develop an adenoma and an optimal specificity) for each parameter to construct a classification tree. For progastrin staining, we chose the

### Table 1. Clinical and immunohistologic features

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole cohort (N = 74)</th>
<th>Patients with colonoscopic follow-up (N = 39)</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Percentage (95% CI)</td>
<td>Percentage (95% CI)</td>
<td></td>
</tr>
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<td>33–89</td>
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</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>57 (45–68)</td>
<td>59% (42–74)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>43 (32–55)</td>
<td>41% (26–58)</td>
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</tr>
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<td>Number of polyps</td>
<td></td>
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<tr>
<td>1</td>
<td>59 (47–71)</td>
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<tr>
<td>2–4</td>
<td>41 (29–53)</td>
<td>38 (23–55)</td>
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<tr>
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<td>20 (12–31)</td>
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<tr>
<td>Distal colon</td>
<td>80 (69–88)</td>
<td>82 (66–82)</td>
<td></td>
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<tr>
<td>Occurrence of metachronous adenoma</td>
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<td>41 (26–59)</td>
<td></td>
</tr>
<tr>
<td>Loss of expression of MLH1</td>
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<td>0 (0–9)$^a$</td>
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<tr>
<td>Expression of progastrin</td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>No/low expression (&lt;10%)</td>
<td>26 (16–37)</td>
<td>18 (8–34)</td>
<td></td>
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<tr>
<td>Moderate expression (10%–50%)</td>
<td>34 (23–46)</td>
<td>36 (21–53)</td>
<td></td>
</tr>
<tr>
<td>High expression (&gt;50%)</td>
<td>40 (29–53)</td>
<td>46 (30–63)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Progastrin expression was recorded as "No/low moderate or high expression" with the percentage of positive colonic epithelial cells. The "physiological" threshold of progastrin expression was determined using the 95th percentile of percentage of stained cells in normal colonic tissue (10% of positive cells). The $\chi^2$ tests (for categorical variables) and Student t tests (for continuous variables) were conducted to compare clinical and immunohistologic features between patients who had a colonoscopic follow-up and those who had not. 95% CI: Binomial exact 95% CI was calculated for each percentage.

**Abbreviations:** NA, not available; NC, not calculable.

$a$One-sided, 97.5% CI.
40% threshold [Sensitivity (Se) = 100% and specificity (Spe) = 57%] and for age the 54-year-old threshold (Se = 100% and Spe = 48%). The classification tree, calculated with R software, shows that all patients with less than 40% of progastrin-positive hyperplastic polyp cells can be considered "at low risk." Among patients with more than 40% of progastrin staining in hyperplastic polyps, only patients older than 54 years can be considered as...
"at high risk" (Fig. 4C). This composite test had a sensitivity of 100% (95% CI, 79%–100%), a specificity of 74% (95% CI, 51%–90%), a positive predictive value of 73% (95% CI, 50%–89%), and a negative predictive value of 100% (95% CI, 81%–100%). Misclassification error rate was 15% in our study sample. To estimate generalization error of classification, a bootstrap validation was conducted. The out-of-bag misclassification error estimate was 25.6%. Among misclassification errors, no false negative was found and all neoplasm occurrences were detected.

Figure 2. Progastrin staining in colon adenomas and adenocarcinomas. A and B, strong staining in low-grade (A, ×20) and high-grade dysplasia adenoma (B, ×40). C–F, strong progastrin staining in adenocarcinomas at different magnifications (×4, ×20, ×40, and ×100). G, adenocarcinoma-adjacent normal tissue positive for progastrin. Antiprogastrin antibody 1137 (29) was used for all experiments.
Therefore, we established a predictive test on the basis of progastrin staining and patient’s age that predicts occurrence of colonic neoplasm after developing a first hyperplastic polyp.

**Discussion**

We show for the first time the expression of progastrin in hyperplastic polyps. This supports the hypothesis that this hormonal precursor, known to be expressed in human colorectal adenomas and adenocarcinomas, could also play a protumoral role at the very early stage of colonic carcinogenesis.

More importantly, we also showed that patients, whose hyperplastic polyps displayed a strong expression of progastrin, were at a higher risk to develop adenoma. These patients had a 5-year NFS rate of 38% as compared with 100% for the patients with no or weak progastrin expression.

In our study, 41% of patients having hyperplastic polyps developed metachronous adenomas. Only 2 patients showed recurrent hyperplastic polyps at follow-up colonoscopy with a progastrin staining similar to the initial polyp. These results are in accordance with a previous study, which reported a 2-time greater risk for subsequent colon neoplasia in patients with hyperplastic polyps compared with hyperplastic polyp–free patients (6).

It is generally accepted that a subset of hyperplastic polyps, named SSA by Torlakovic and Snover (4) and Torlakovic and colleagues (10), might be preneoplastic lesions. In our study, no hyperplastic polyp displayed characteristics of SSA, such as architectural abnormalities and loss of MLH1 (33). The metachronous adenomas that we observed in our cohort were all tubular or tubulo-villous adenomas and did not display histologic feature of serrated adenoma, nor carcinoma. However, the existence of an association between hyperplastic polyps and classical neoplasms is not surprising as patients with hyperplastic polyposis develop both serrated and classical carcinomas. Furthermore, hyperplastic polyps are known to share the same risk factors as classical colorectal adenocarcinoma. Distinction between the serrated and classical pathway might not be as dichotomic as suggested by the existence of mixed polyps, in which serrated and nonserrated features coexist.

Because the progastrin gene has been previously shown to be a target of the transcriptional complex β-catenin/TCF-4 (34, 35), we analyzed the activation of the β-catenin pathway in the hyperplastic polyps. None of the hyperplastic polyps presented a delocalization of β-catenin from the plasma membrane to the cytoplasm or the nucleus, characteristic of the activation of the pathway (Supplementary Data 3). The Ras/Raf pathway is known to be activated in 50% to 80% of hyperplastic polyps (36, 37) and some authors suggest its involvement in the development of hyperplastic lesions (6). Because several studies have suggested a correlation between the Ras/Raf pathway activation and progastrin gene expression (34, 38), this pathway might be responsible of the progastrin overexpression observed in the hyperplastic polyps.

In our study, patients with hyperplastic polyps presenting a high expression of progastrin were at higher risk to develop metachronous adenomas in the same location. This high expression of progastrin in hyperplastic polyps might reflect an environmental background with greater risk for developing colorectal neoplasia. However, in our cohort, 3 patients developed adenomas in another site than
their original hyperplastic polyp site but progastrin was overexpressed (>50%) in only one of them, whereas progastrin was overexpressed in all hyperplastic polyps with the occurrence at the same site. This result suggests that progastrin overexpression is not only a marker of pejorative background. Indeed, another hypothesis is the presence of molecular abnormality, such as progastrin expression, in these polyps but also in the adjacent colon. Interestingly, adjacent colonic epithelium of all hyperplastic polyps with a high expression of progastrin also showed a strong expression of the hormonal precursor. In contrast, for all the hyperplastic polyps negative for progastrin, the surrounding unaffected mucosa was also negative. Representative pictures are shown in Supplementary Data S4. Similar observations have also been shown on normal colonic epithelium adjacent to adenocarcinomas. This may suggest that the adjacent histologically normal colonic epithelium of both lesions also express early molecular abnormalities. “The molecular security margin” might be lower than the histologic security margin. Therefore, hyperplastic polyp endoscopic excision thus might not be extensive enough to prevent a further neoplastic event. We showed that progastrin staining could be an efficient tool to detect patients with higher risk of metachronous neoplasms. On the basis of our data, a test based on progastrin staining and age would display 100% of sensitivity and 74% of specificity. In our study, there was no false-negative patient (NVP = 0). Thus patient with no progastrin overexpression, whatever their age, would have a low risk to develop metachronous neoplasm, whereas patients in our high progastrin expression group had a 73% risk of developing a neoplasm. Misclassification rate of our composite predictive test was only 15%. In this study, the sample size with colonoscopic follow-up was restricted to 39 patients for several reasons. First, the guidelines from either the French National Agency for Accreditation and Evaluation in Healthcare, or the American College of Gastroenterology do not recommend follow-up colonoscopies for patients with “benign” hyperplastic polyps. Second, to avoid potential bias in our study, we excluded all the cases with a preceding colorectal adenocarcinoma or adenoma, familial colorectal adenocarcinoma history, hyperplastic polyposis, or chronic inflammatory bowel disease, as well as insufficient colon site information or follow-up data. Third, we included only the patients with hyperplastic polyps diagnosed in the Pathology department of Rangueil Hospital, from January 1, 2000, through December 31, 2001, to have up to 10 years of follow-up. Despite the relative small size of our sample, progastrin expression predicts

<table>
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<th>HR (95% CI)</th>
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<td>Proximal colon</td>
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<td>Distal colon</td>
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<td>Expression of progastrin</td>
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<td>No/low expression (&lt;10%)</td>
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<td>100 (NC)</td>
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<td>84 (50–96)</td>
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<td>High expression (&gt;50%)</td>
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<td>1.6e09 (4e09–7e10)</td>
<td>0.799</td>
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</table>

NOTE: NFS among patients with colonic hyperplastic polyps who had a colonoscopic follow-up. Multivariate analysis was conducted using a Cox model including all variables with a P value <0.20 in the univariate analysis. Final model was obtained after backward stepwise selection, keeping variables with a P value <0.05. 95% CI was calculated for all 5-year survival values. Abbreviations: NC, not calculable; NR, Not reached.
the occurrence of neoplasm after developing a first hyperplastic polyp with a high sensitivity and specificity and we obtained a very high and significant difference in NFS between patients with high expression of progastrin (5-year NFS rate of 38%) as compared with patients with no/weak expression (5-year NFS rate of 100%). However, it might be interesting to complete this study by a retrospective multicenter study including more patients or a prospective study.

We conducted a bootstrap cross-validation to estimate misclassification error. The out-of-bag misclassification rate estimate was 26%. Interestingly, none of the patients in our study cohort met the guidelines criteria for endoscopic surveillance, that is, resection of one hyperplastic polyp ≥1 cm and/or multiple polyps (n ≥ 5) or a family history of hyperplastic polyps. Hence, a predictive test based on progastrin staining and age could be useful to select a subset of patients who would benefit from colonoscopic surveillance. In our study, none of the patients developed colorectal adenocarcinoma during their follow-up. Nevertheless, because these patients have benefited from an endoscopic surveillance although current guidelines do not recommend it, they could have been treated at adenoma stage before adenocarcinoma transformation.

We show for the first time that progastrin expression in hyperplastic polyps is a strong independent predictive factor of risk for developing an adenoma and we establish here and propose a classification tree to select the population of patients who need a colonoscopic follow-up. In summary, we have shown that progastrin staining in hyperplastic polyps could be an efficient tool to detect patients with higher risk of metachronous neoplasms.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interests were disclosed.

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Figure 4. A predictive test for recurrence. A, ROC curves for progastrin staining. B, ROC curves for age. I. threshold had a 100% sensitivity and the optimal specificity. PG, percentage of progastrin staining; Se, sensitivity; Spe, specificity; y.o., year old. C, classification tree using variables significantly associated with neoplasm occurrence after multivariate analysis (progastrin staining and age).
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