ORIGINAL PAPERS

Malignant colonic adenomas. Therapeutic criteria. Long-term results of therapy in a series of 42 patients in our healthcare area

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ABSTRACT

Objective: a) to evaluate the appropriateness of histological criteria as proposed by Morson as indicators for surgery; and b) to compare the adequacy of Morson's criteria with Haggitt's levels as indicators for surgery in the case of malignant sessile lesions.

Material and methods: we carried out a prospective, protocolized study of 42 patients with polyps with invasive carcinoma (IC) who underwent colonoscopic polypectomy from 1979 through 2008. We applied the histological criteria proposed by Morson to all the patients included in the series.

Results: we treated 24 polyps with IC and favorable histological criteria (FC) and 18 polyps showing unfavorable histological criteria (UC). All polyps with FC were treated by means of colonoscopic polypectomy. None of the patients showed signs of disease after a mean follow-up period of 9.67 yrs. Patients with polyps with UC were recommended to undergo surgery. The presence of unfavorable histological criteria in the polypectomy sample was clearly associated with an unfavorable patient outcome and showed a 100% sensitivity level, a negative prognostic value (NPV) of 100%, and a false negative (FN) percentage of 0% for the prognosis of the disease. We found 12 sessile polyps (Haggitt's level 4). Colonoscopic polypectomy was the treatment employed in 9 out of 12 cases. All patients are free from disease (mean follow-up 7.3 yrs). If Haggitt's level criteria had been applied, all 12 patients would have undergone surgery. This means 58% more patients than following Morson's criteria.

Conclusions: Morson's criteria are considered an adequate diagnostic tool for the indication of surgery in patients with malignant adenomas. Haggitt's invasion levels do not accurately discriminate the necessity for surgery in case of malignant sessile lesions.

Key words: Malignant adenomas. Adenomas with invasive carcinoma. Morson's histological criteria. Haggitt's levels.

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INTRODUCTION

Malignant adenoma is defined as an adenoma containing a carcinoma that has penetrated into the submucosa. Its incidence ranges from 0.2 to 9% of all adenomas endoscopically removed, and from 9 to 11% of adenomas surgically resected (1).

Incomplete excision through endoscopic polypectomy always requires surgery, but after complete endoscopic removal there is still a risk for residual tumor at the polypectomy site, presence of loco-regional lymph-node metastases or distant metastases with a variable incidence in the various series reported (2-4). Such variability depends on different patient selection criteria and different polyp management in the different studies.

Initially, surgery was indicated for all patients with malignant polyps, but very often neither residual tumor nor lymph nodes metastases were found in the resected specimen. Therefore, several authors began to investigate which histological characteristics could predict the risk of lymph node metastases, and thus be used to consider endoscopic polypectomy as an adequate therapy or otherwise.

Morson in 1972 established endoscopic polypectomy as sufficient therapy when polyps had been completely excised in one piece, the carcinoma was well or moderately well differentiated, and the pathologist identified at

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least a 2 mm of tumor-free margin in the endoscopically resected piece (5-7). Subsequently, other authors added a further histological criterion, namely the absence of tumor infiltration of lymphatic or venous vessels in the submucosa (8-10). Whenever all these "favorable" criteria were met, the risk of lymph-node metastasis in Morson's series and in subsequent series using such criteria was less than 1%. These criteria could be applied both to pedunculated and sessile polyps endoscopically excised in a single piece, and therefore of limited size. Whenever any of these criteria were not met, colonoscopic polypectomy should be followed by subsequent surgery.

Other researchers have used Haggitt's invasion levels to establish when colonoscopic polypectomy alone is curative (11). Haggitt defines 4 levels of carcinoma invasion: a) level 1: carcinoma invading through the muscularis mucosae into the submucosa, but limited to the head of the polyp; b) level 2: carcinoma invading into the neck of the adenoma; c) level 3: carcinoma invading any part of the stalk; and d) level 4: carcinoma invading into the bowel-wall submucosa below the polyp stalk but above the muscularis propria (Fig. 1). In his study, all patients showing a negative outcome had malignant polyps with a level 4 for invasion, and that is why he considered this

level of invasion as the only indication for surgery. All malignant sessile lesions would have therefore an indication of surgery.

The present study was performed in order to evaluate the suitability of Morson and Williams criteria for the indication of the treatment applied to our patients with malignant adenomas, and to compare them with Haggitt's criteria depending on patient outcome at follow-up.

PATIENTS AND METHODS

We carried out a prospective and protocolized study of 343 patients with endoscopically resected colon adenomas who had been referred for follow-up to the colorectal cancer high-risk Unit between January 1983 and August 2008.

Forty-two of these patients (12%) with a mean age of 64.8 yrs (range: 36-80) had adenomas with invasive carcinoma and were included in our study. Mean follow-up was 9.67 yrs, with a median follow-up of 9,00 years (range: 3-25).

All adenomas with invasive carcinoma were endoscopically resected. All polypectomies were performed at the Unit of Digestive Endoscopy, Digestive Diseases De-

Fig. 1. Haggitt levels for tumor invasion (adapted from Haggitt R, et al. Gastroenterology 1985; 89: 328-36).

partment, University Hospital Virgen del Rocío, Sevilla. Before colonoscopies an informed consent was obtained from all patients. An initial colonoscopy was completed and all polyps found were removed. In each case the endoscopist attempted a complete endoscopic polypectomy.

The histological analysis of resected specimens informed about the resection margins of polyps, tumor infiltration of lymphatic or venous vessels in the submucosa, and tumor staging according to the WHO classification (12) (Table I).

Table I. Grade of tumor differentiation according to WHO classification

Grade 1:	Well differentiated
Grade 2:	Moderately differentiated
Grade 3:	Undifferentiated or with signet ring cells

These histological criteria were used to define the risk of residual neoplastic disease after endoscopic treatment, and to stratify patients into low-risk and high-risk categories. Unfavorable histological criteria included tumor-free resection margins smaller than 2 mm; presence of tumor infiltration in lymphatic or venous vessels in the submucosa, and grade-III adenocarcinomas according to WHO classification (13). In the absence of these criteria, an adenoma with invasive carcinoma was considered to have favorable histological criteria.

Whenever favorable criteria were met, colonoscopic polypectomy alone was considered an adequate treatment for the malignant adenoma. In these cases patients were recommended to undergo a subsequent colonoscopy 6 months later, and then every 3 years. Unfavorable histological criteria required surgery and subsequent follow-up according to findings.

Residual disease was defined as the presence of residual tumor in the surgically resected specimen or of regional lymph-node metastases. We considered an "adverse outcome" the presence of residual colonic wall tumor, lymph-node metastases at the time of surgery, and the development of local recurrence or distant metastases during follow-up (1).

Polypectomy samples available at the Department of Pathology, University Hospital Virgen of Rocio were reviewed in order to apply tumor invasion levels as described by Haggitt (Fig. 1) to malignant adenomas in our series. We analyzed the suitability of favorable and unfavorable histological criteria, and levels of tumor invasion as described by Haggitt in predicting adverse outcomes.

The statistical analysis was carried out with the SPSS 15.0 software, and Fisher's exact test was used to establish significant values.

RESULTS

We analyzed 42 endoscopically excised polyps with invasive carcinoma, with an average size of 22.35 mm (range: 5-40).

Nine of these polyps (21.4%) were located in the rectum, 30 (71.6%) in the sigmoid colon, and 3 (7%) in the descending colon. Thirty (71.4%) were pedunculated polyps, 12 (28.6%) were sessile, 14 (33.3%) were tubular adenomas, and 28 (66.6%) had a histological villous component.

In all, 24/42 polyps had favorable histological criteria (57%). None of the patients underwent surgery, and none of them showed signs of disease after a mean follow-up period of 10.8 yrs, and a median of 9.5 years; 18/42 polyps had unfavorable histological criteria (43%), and we indicated surgical treatment for all of these patients; however, three of them refused the procedure. Figure 2 shows surgical findings and patient outcomes.

The most common unfavorable histological criterion observed in our series was the presence of invasive carcinomatous cells at the resection margin or a tumor-free resection margin smaller than 2 mm in 13/42 (31%). We found grade-3 adenocarcinomas in 4 of 42 polyps (9.5%). In all these cases lymphatic or venous infiltration beyond the mucosa was also present. This latter criterion was observed in 6 of 42 patients (14.2%), almost always associated with another unfavorable histological criterion (83.4%) and just in one case was it the only unfavorable criterion (16.6%) (Fig. 1). The only patient with an adverse outcome had a malignant adenoma with lymphatic infiltration and grade-3 adenocarcinoma.

Only 4 of 15 patients (26%) undergoing surgery due to unfavorable histological criteria showed residual disease in the analysis of the resected specimen, and only one of these four patients (25%) had an aggressive local recurrence with fatal consequences. The remaining three patients did not show any signs of disease during follow-up.

No statistically significant differences were found regarding size, morphology and location between adenomas with invasive carcinoma with favorable and with unfavorable criteria. Patient age, size, morphology and location of adenomas with invasive carcinoma were not significantly associated with patient outcome (Table II).

The presence of unfavorable histological criteria in an endoscopically resected specimen was significantly associated with the subsequent development of an adverse patient outcome. All patients with an adverse outcome had polyps with invasive carcinoma and unfavorable histological criteria ($p = 0.02$) (Table II).

The analysis of the statistical validity of unfavorable criteria in predicting a negative outcome showed a sensitivity of 100%, a specificity of 63.2%, a negative post-test probability, and a negative predictive value of 0%.

Table III shows the classification of malignant adenomas in our series according to Haggitt's tumor invasion levels.

Fig. 2. Outcome of patients with polyps with unfavorable criteria.

Table II. Characteristics of patients with polyps with favorable and unfavorable criteria

	Favorable	Unfavorable	p
Age (years)	63.2	66.8	ns
Size (mm)	21.33	23.72	ns
Morphology: sessile	7 (29%)	5 (28%)	ns
pedic.	17 (71%)	13 (72%)	ns
Follow-up: (years)	8.8 a	5.56	ns
Location: rectum	7 (29%)	2 (11%)	ns
sig. + LC	17 (71%)	16 (89%)	ns
Unfavorable outcome	0 (0%)	4 (100%)	0,02

Twelve of the 42 patients in our series (28.5%) had sessile malignant adenomas and therefore level 4 in Haggitt's tumor invasion classification. Only 5 of these 12 patients (42%) showed Morson's and William's unfavorable histological criteria, and only these patients were recommended surgery, which means 58% less patients than if we had used Haggitt's levels for indicating surgery. Two of these patients refused surgery and were treated with endoscopic polypectomy only. The nine patients in this group that were not operated on are free of

Table III. Frequency of Haggitt's invasion levels

Level of invasión	Frequency	Percentage
Level 1	22	52,4%
Level 3	1	2,4%
Level 4	12	28,6%
Indeterminate	7	16,7%
Total	42	100%

disease after an average follow-up of 7.3 yrs and a median of 5.00 years.

Polyps were pedunculated in 30 of 42 patients (71.5%), and 22 of them had a level 1 of invasion; 1 patient had level 3, and in the remaining 7 patients (16.7% of the series) the pathologist could not differentiate between level 2 and the rest of levels described by Haggitt, since in many cases the micro-anatomical orientation of polyp sections was wrong, and because very often the stalk was not or only partially included in the endoscopic resection specimen. In no cases included the resection specimen of pedunculated polyps colonic wall submucosa, so whether there was a level 4 of invasion could not be established. All 12 sessile polyps were level 4 of tumor invasion.

From the data we obtained we may conclude that in our series Haggitt's level 4 showed 0% sensitivity in predicting an adverse outcome, a specificity of 63%, and a positive predictive value of 0%.

DISCUSSION

The endoscopic resection of a polyp with invasive carcinoma implies a necessity to establish whether this therapy alone is adequate or on the contrary the patient will require further radical oncologic surgery. In order to do so, we must be aware of the risk of residual disease after endoscopic polypectomy, and we must also consider the surgical morbidity-mortality for each patient.

Mortality associated with colectomy is around 3% in patients under 70, but reaches 12-13% in older patients (1,14). On the other hand, the risk of residual cancer after endoscopic polypectomy varies greatly in the different studies published so far, and ranges from 55% in the first series to 22% in more recent ones. Such variability is mainly due to the inclusion of polyps non-resectable by means of endoscopic polypectomy in some series, which are resected surgically (15).

Nowadays, endoscopic polypectomy is considered enough if excision is complete, the lesion is removed in a single piece, and certain histological criteria are met (14, 16-18). Piecemeal endoscopic resection hinders the accurate evaluation of such histological criteria and therefore is considered an indication for surgery. The analysis of data from most series found in the literature suggests that the risk of metastases to lymph nodes and/or residual disease in the colonic wall decreases when a colonoscopically resected malignant adenoma fulfills certain histological criteria. This decreased risk is enough to avoid surgery for many patients who are often old and have a much higher surgical risk.

Histological criteria have varied over time according to various authors, but most important criteria include: resection margin involvement, tumor infiltration of lymphatic or venous vessels in the submucosa, and grade of tumor differentiation. Other authors consider polyp morphology and/or Haggitt's tumor invasion levels risk factors for residual disease and adverse outcome after colonoscopic polypectomy.

Morson's initial study (1972) (5) determined that polypectomy alone was an adequate therapy if histological criteria of complete resection were met and the tumor was well or moderately well differentiated. None of the patients in his series who showed these characteristics had an unfavorable evolution. Subsequently, other authors studied the role of lymphatic vessel infiltration as a risk factor related to the presence of lymphatic metastases. In the series by Muller and colleagues 17.6% of patients presented with tumor infiltration of lymphatic or venous vessels in the submucosa, and 83.3% of them had regional lymph-node metastases or

developed local recurrence with a negative prognosis (9). This was not the experience in the St. Mark's Hospital series. Consequently, Geraghty, Williams and Talbot carried out a detailed analysis of venous or lymphatic submucosal vessel infiltration cases in patients with malignant adenomas (8). They found venous infiltration in 37% of patients included in their series, and probable lymphatic infiltration often mistaken for tissue retraction. Only one patient of 21 showing this as their only unfavorable histological criteria died as a result of the tumor. The rest showed a positive evolution throughout a mean follow-up period of 16 yrs.

Tumor infiltration of lymph nodes is a histological factor difficult to evaluate by pathologists, and is often mistaken for different artifacts occurring during sample sectioning and staining. The high frequency of such infiltration as observed in Geraghty's series is probably due to special awareness and training in searching these histological criteria.

In our series, the percentage of lesions showing infiltration of lymph vessels beyond the mucosa was 14.2%, and it was the only unfavorable criterion in one patient who had no residual disease and who evolved favorably throughout a follow-up period of 9 years. Despite the low number of patients included in our series, the results obtained suggest that tumor infiltration of lymphatic vessels beyond the mucosa is very often associated with other unfavorable histological criteria. Such infiltration, as the only criterion indicating surgery, should be weighed against surgical risk for each individual patient, and it would be advisable to consider the opinion of a second pathologist.

In the series by Netzer (1998) (1) the three unfavorable histological criteria mentioned above were considered, and patients were classified as high and low risk depending on whether their lesions met any unfavorable histological criteria or all favorable criteria. The presence of favorable histological criteria in the resected sample was associated with 0% adverse outcomes, whereas 45% of patients with unfavorable criteria showed adverse outcomes.

Our patients were also classified prospectively as high- and low-risk patients, and surgery was indicated according to such classification, considering as well the risk surgery posed for each individual patient. In our series, the validity of this classification to predict a negative outcome and to recommend surgery has been very high, with a sensitivity of 100% and a negative predictive value of 0% for high-risk patients. Even in the case of high-risk patients we observed a negative outcome in 22% of them.

The unfavorable histological criterion most commonly found in our patients was tumor involvement of resection margins. This is in many series the only factor with an independent predictive value of adverse outcome (1,8,16,19). Nevertheless, only 23.3% of our patients with lesions with involved resection margins had residual disease in the surgically resected specimen, and none of

them showed lymph-node metastases or local or distant tumor recurrence. This lack of correlation between resection margin involvement and presence of residual tumor in the colonic wall is probably explained by the destructive effect of diathermy on polyps' cut surface. Although some authors have suggested that in these patients a second biopsy from the area of endoscopic resection could suffice before recommending surgery (7,8,20), in our opinion surgical treatment should be always performed in these patients, as some cases of local recurrence after a second negative biopsy have been described (1).

We must also take into account that an absence of residual tumor or lymph-node metastasis in surgically resected specimens does not imply that there is no risk of unfavorable outcome, as there are at least 7 such cases reported in the literature (1,3,6,21-23) of distant metastases after radical surgery without signs of residual tumor in the resected specimen. This suggests a mechanism of hematogenous tumor dissemination.

Several studies have focused on the association between sessile polyps and risk of lymphatic metastases (15,24,25). In our series we observed no significant association between sessile morphology and risk of unfavorable outcome after polypectomy. All our patients with sessile polyps and favorable histological criteria evolved favorably and are free of disease after a mean follow-up period of 7.3 years.

The results of the last series of patients with polyps with invasive carcinoma published in the literature (16), and those of the recent meta-analysis by Hassan and colleagues (15), confirm the validity of Morson's histological criteria. These results confirm that after endoscopic polypectomy we must evaluate all 3 histological risk criteria and classify patients into high- and low-risk categories in order to decide whether surgery is the most adequate option, as has been the case in our series.

However, other authors consider Haggitt's levels of tumor invasion as histological risk criteria. In the study carried out by Nivatongs (26) all patients with lymphatic metastases had level 4 of invasion, so they considered that this level had a predictive value for predicting the risk of lymphatic metastases. Both this series and that of Haggitt have the selection bias of mixing up polyps endoscopically resected with polyps resected by surgery. Often polyps resected by surgery are larger, and the specimens obtained for histological study are different from those obtained by endoscopic polypectomy. Kyzer (23) applied Haggitt's levels of invasion as risk criteria to a series of endoscopically resected malignant adenomas, and found that in 14% of pedunculated adenomas the level of invasion could not be determined due to problems with the orientation of histological sections.

In our opinion, Haggitt's levels of invasion are difficult to apply to specimens obtained by endoscopic polypectomy due to the following reasons: a) the complex orientation of the microscopic section obtained; b) in most instances the stalk of pedunculated polyps is not

completely included in the sample; and c) almost always the sample does not include the submucosa of the colonic wall.

On the other hand, Haggitt classifies all sessile lesions into level 4 of invasion, and therefore all of them should be treated by surgery. In our study, 58% of patients with sessile polyps had favorable histological criteria, all of them were treated by endoscopic polypectomy alone, and all are free of disease after a mean follow-up period of 7.3 years. In view of our results and those obtained in other series (16,24), an important number of patients with sessile polyps can be cured by endoscopic polypectomy alone if they meet favorable histological criteria. As a result we consider that Haggitt's levels of invasion cannot be applied to sessile adenomas with invasive carcinoma, as their application entails a significant number of surgical interventions that patient outcomes have proven unnecessary.

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