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ORIGINAL PAPERS

Factors associated with complete endoscopic resection of an invasive adenocarcinoma in a colorectal adenoma

Paola Quintas[1], Joaquín Cubiella[1], Ignacio Couto[2], Luis Bujanda[3], Carol Cobian[3], Inés Castro[1] and Javier Fernández-Seara[1]

[1]Department of Gastroenterology. Complexo Hospitalario Universitario de Ourense. Ourense, Spain. [2]Department of Gastroenterology. Complexo Hospitalario Universitario de A Coruña. A Coruña, Spain. [3]Hospital Donostia. Instituto Biodonostia. Universidad del País Vasco (UPV/EHU). CIBERehd. San Sebastián, Guipúzkoa. Spain

ABSTRACT

Background and objective: endoscopic polypectomy may allow curative resection of invasive adenocarcinoma on colorectal adenoma. Our goal was to determine the factors associated with complete endoscopic resection of invasive adenocarcinoma.

Methods: retrospective observational study. We included 151 patients with invasive adenocarcinoma on adenomas endoscopically resected between 1999 and 2009. We determined those variables independently related to incomplete resection by a logistic regression. Relation was expressed as Odds Ratio (OR) and its 95% confidence interval (95% CI).

Results: patients were predominantly male (66.2%) and their mean age was 68.03 ± 10.65 years. Colonoscopy was complete in 84% of the patients and 60.3% had synchronous adenomas. Invasive adenocarcinoma was mainly located in distal colon (90.7%) and morphology was pedunculated in 75.5%. The endoscopic average size was 22.61 ± 10.86 mm. Submucosal injection was required in 32.5%. Finally, the resection was in one piece in 73.5% and incomplete in 8.6% of the adenocarcinomas. Factors independently associated with incomplete endoscopic resection were size (mm) (OR 1.08, 95% CI 1.03-1.14, p = 0.002), sessile or flat morphology (OR 8.78, 95% CI 2.24-34.38, p = 0.002) and incomplete colonoscopy (OR 4.73, 95% CI 1.15-19.34, p = 0.03).

Conclusions: endoscopic polypectomy allows complete resection of 91.4% of invasive adenocarcinomas on colorrectal adenoma in our series. Factors associated with incomplete resection were the size of the lesion, sessile or flat morphology and incomplete colonoscopy.

Key words: Colorectal cancer. Adenoma. Endoscopic resection.

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Correspondence: Joaquín Cubiella Fernández. Departmen of Gastroenterology. Complexo Hospitalario de Ourense. C/ Ramón Puga 52-54. 32005 Ourense, Spain
e-mail: joaquin.cubiella.fernandez@sergas.es

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INTRODUCTION

Colorectal adenoma is the primary precursor lesion of colorectal cancer (CRC). For this reason, endoscopic resection of adenoma is performed to prevent progression to CRC (1). In 1-2% of endoscopic polypectomies, the adenocarcinoma is observed to be invading the submucosa indicating a malignant polyp (2). This finding, usually unexpected, is associated with an 8.7% risk of residual disease and 3% risk of recurrence (3). Given this, the management of colorectal adenoma with invasive adenocarcinoma with an initial endoscopic polypectomy is controversial. There are criteria for low risk of residual disease or recurrence after endoscopic resection: well-differentiated adenocarcinoma, absence of vascular or lymphatic invasion, disease-free margin resection, and limited depth of tumour invasion measured using the Haggitt and Kikuchi classifications (3-8). When these criteria are met, endoscopic treatment as an intention-to-cure treatment can be considered, given that the risk of residual disease or recurrence after resection is similar to the risk associated with surgical treatment (2).

Although malignant polyps are uncommon, population-based screening programmes are increasing the number of cases of CRC diagnosed in the initial stages of the disease (9,10). In this context, as many as 27% of CRC cases detected are candidates for endoscopic treatment (11). In relation to this, we need accurate diagnostic criteria for assessing which cases of invasive adenocarcinoma arising in adenoma can be exclusively treated by endoscopic resection (2). A recently published retrospective study identifies factors that are independently associated with the risk of residual disease or recur-

rence after endoscopic resection: histological high-risk features and incomplete endoscopic resection (12).

For this reason, we decided to analyse a retrospective cohort of patients with endoscopically resected invasive adenocarcinoma arising in adenoma in order to identify factors associated with an incomplete endoscopic resection.

PATIENTS AND METHODS

Study design

This was a retrospective observational study based on data on cases of invasive colon adenocarcinoma, defined as carcinoma with submucosal invasion, initially treated by endoscopic polypectomy in three Spanish university hospitals in Ourense, A Coruña, and Donostia between 1999 and 2009. We only excluded patients with intraepithelial or intramucosal adenocarcinoma, that is, cases of carcinoma without submucosal invasion; and patients with invasive adenocarcinoma arising in adenomas initially resected surgically. The cases were selected from the pathology department registries (SNOMED-CT code: M-82103).

Clinical and endoscopic data collected

For each patient the following information was collected: demographic data (age and sex) and relevant medical history, including any previous diagnosis of cancer or adenoma of the colon. In all cases, endoscopic examinations was carried out by expert endoscopists: more than 2 years of specialist experience in gastroenterology including performing more than 200 colonoscopies per year. Regarding the endoscopic examination, we reviewed whether it had been possible to perform a complete colonoscopy and the presence of synchronous lesions. With respect to the adenoma with invasive adenocarcinoma, we recorded size, location of the lesion, morphology based on the Paris endoscopic classification (13), if submucosal saline injection was required and how resection was performed: complete or incomplete; en bloc or fragmented. The assessment of whether the endoscopic resection had been complete was based on the endoscopist's description. In addition, we checked whether there had been complications after endoscopic resection. Finally, to determine whether there had been a change in the rate of complete endoscopic resection during the study, two time periods were established arbitrarily: before and since 2005.

Statistical analysis

The data were entered in a dedicated database. The continuous variables were described using the mean and standard deviation, while categorical variables were described by the number of cases per category and percentages. Comparisons to identify significant differences were made with the Student's t-test for quantitative variables, and Fisher's exact test for categorical variables. Finally, the variables related to polyp characteristics and the endoscopic examination found to be statistically significant were included in a logistic regression model, to assess whether they were independently associated with the presence of residual disease. Any such associations were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). We considered results to be statistically significant when $p < 0.05$. The statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL).

Ethical considerations

The study was approved by the Clinical Research Ethics Committee of Galicia (ref. 2008/250, 9 December 2008). To gain access to patient medical records for research purposes, we followed the protocols established by the Health Information Management Departments of the hospitals.

RESULTS

Baseline characteristics

We analysed 151 patients diagnosed with invasive adenocarcinoma in adenoma. The mean age of patients was 68.03 ± 10.65 years, mainly men (66.3%). Sixteen patients had a previous diagnosis of cancer, including four cases of CRC. The baseline characteristics are reported in table I.

Endoscopic findings

The endoscopic findings are summarised in table II. Notably, colonoscopy was complete in 84% of the patients and, overall, synchronous adenomas were found in 60.3% (91) patients. The most advanced histological features of the synchronous adenomas were villous histology in almost half the cohort (43 cases, 47.3%) and high-grade dysplasia in 17 patients (18.7%). Synchronous adenomas were found in the following locations: rectum, 22 cases; sigmoid colon, 48; descending colon, 30; transverse colon, 24 and ascending colon, 33.

As for the invasive adenocarcinoma in the adenoma, the most common location was distal to the splenic flexure (rectum, 26 cases; sigmoid colon, 93; descending colon, 18; transverse colon, 6; and ascending colon, 8), as illustrated in figure 1. The mean diameter of malignant polyps was 22.61 ± 10.86 mm, with 114, 35 and 2 being classified as pedunculated, sessile and elevated, respectively (Fig. 2). Saline was injected into the submucosa prior to resection in 49 patients and resections were piecemeal in 40 patients, 13 of these being incomplete. Only 5 patients (3.3%) had

Table I. Baseline characteristics of patients and variables associated with complete resection

	Total	*Complete resection*		*p*
		No (13)	*Yes (138)*	
Age (years)	68.03 ± 10.65	69.78 ± 10.22	67.86 ± 10.71	0.53
Sex (woman)	51 (33.7%)	4 (38.4%)	47 (33.3%)	0.76
Diabetes (yes)	21 (13.9%)	3 (23%)	3 (13%)	0.39
High blood pressure (yes)	57 (37.7%)	5 (38.5%)	52 (37.7%)	1
Heart disease (yes)	38 (25.2%)	1 (7.7%)	37 (26.8%)	0.18
Lung disease (yes)	32 (21.2%)	3 (23%)	29 (21%)	0.36
Nephropathy (yes)	11 (7.3%)	0 (0%)	11 (7.9%)	0.61
History of cancer (yes)	16 (10.6%)	2 (16.7%)	14 (10.1%)	0.61
History of adenoma (yes)	4 (2.6%)	1 (8.3%)	3 (2.2%)	0.28

Data are expressed as absolute values and percentages of the total for qualitative variables, and as means and standard deviations for quantitative variables. Differences were assessed with the Fisher's exact test and Student's t-test for qualitative and quantitative variables respectively, and considered statistically significant if $p < 0.05$.

complications after the endoscopic procedure in the form of self-limiting haemorrhage. In the period prior to 2005, 12% of the endoscopic resections were incomplete while since 2005 only 2.9% of these resections have been incomplete, but the difference was not statistically significant, as can be observed in table II.

Variables associated with incomplete resection

The factors found to be associated with incomplete endoscopic resection in the univariate study were: incomplete colonoscopy ($p = 0.036$), a sessile or flat morphology ($p = 0.003$), polyp diameter (mm) ($p = 0.002$), and fragmented resection ($p < 0.001$). Including these variables in the logistic regression model, the factors found to be independently associated with incomplete endoscopic resection were polyp diameter (mm) (OR 1.08, 95% CI: 1.03-1.14; $p = 0.002$), non-pedunculated morphology (OR 8.78, 95% CI: 2.24-34.38; $p = 0.002$) and incomplete colonoscopy (OR 4.73, 95% CI 1.15-19.34; $p = 0.03$).

DISCUSSION

In our series, the rate of complete endoscopic resection in invasive adenocarcinoma arising in adenoma was high and has increased with time. In piecemeal resections there is a greater risk of incomplete resection than when *en bloc* resection is performed. Finally, the diameter and morphology of the lesion, as well as the quality of colonoscopy are independently associated with complete resection of invasive adenocarcinoma.

The diameter and morphology of the lesion have been associated not only with the risk of incomplete endoscopic resection (14-16), but also with the probability of the ade-

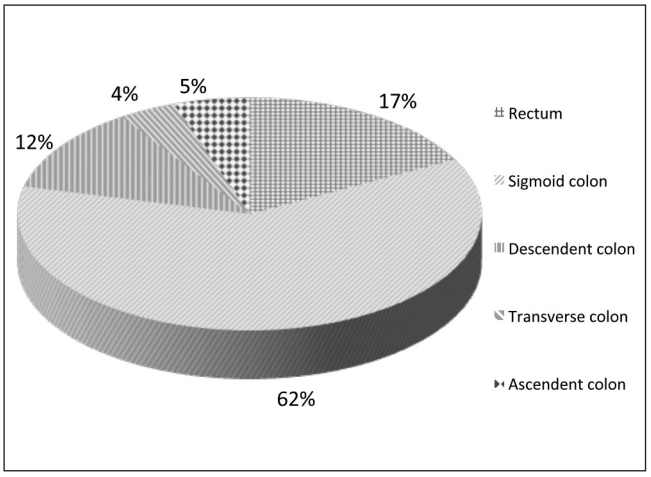

Fig. 1. Location of endoscopically resected invasive adenocarcinoma in adenoma of the colon. The values are expressed as percentages of the total.

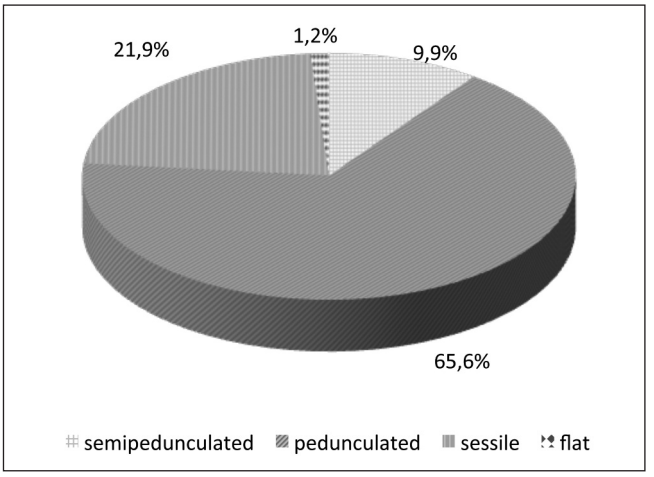

Fig. 2. Morphological descriptions of endoscopically resected invasive adenocarcinoma in adenoma, based on the Paris endoscopic classification. The values are expressed as percentages of the total.

Table II. Endoscopic findings and variables associated with complete resection

	Total	*Complete resection*		*p*
		No (13)	*Yes (138)*	
Complete colonoscopy (yes)	126 (84%)	8 (61.5%)	10 (85.5%)	0.036
Year resection was performed (2005-9)	68 (45%)	2 (16.7%)	66 (47.5%)	0.06
Synchronous adenomas (yes)	91 (60.3%)	7 (53.8%)	84 (60.8%)	0.76
No. of synchronous adenomas	3.93 ± 24.74	1.08 ± 1.32	4.2 ± 25.87	0.665
Location of adenocarcinoma (distal)	137 (90.7%)	10 (76.9%)	127 (92%)	0.1
Location of adenocarcinoma (rectal)	26 (17.2%)	4 (30.7%)	22 (15.9%)	0.24
Diameter (mm)	22.61 ± 10.86	31.15 ± 10.23	21.8 ± 10.6	0.003
Morphology (pedunculated)	114 (75.5%)	5 (38.4%)	109 (79%)	0.003
Submucosal saline injection (yes)	49 (32.5%)	3 (23%)	46 (33%)	0.54
Piecemeal resection (yes)	40 (26.5%)	13 (100%)	17 (19.6%)	< 0.001

Data are expressed as absolute values and percentages of the total for qualitative variables, and as means and standard deviations for quantitative variables. Differences were assessed with the Fisher's exact test and Student's t-test for qualitative and quantitative variables respectively, and considered statistically significant if $p < 0.05$.

noma transforming into invasive adenocarcinoma (17). In many cases, this is an incidental finding on histological analysis. On the other hand, only complete en bloc resection makes possible to assess whether the surgical margins are disease free or not, and to measure the depth of the tumour invasion (6,10,18). In our series, we have previously found a statistically significant relationship between incomplete resection and the risk of residual disease or recurrence (12). These relationships highlight the need for using complex endoscopic techniques that achieve complete endoscopic resection in advanced adenomas. Both endoscopic mucosectomy and endoscopic submucosal dissection allow the complete en bloc resection of large colonic cancerous lesions with flat or sessile morphologies (19). In this way, we can achieve a complete resection and a proper histological assessment of the risk of residual disease or recurrence.

Another key finding of our study is the relationship between the performance of incomplete colonoscopies and incomplete endoscopic resection. We should note that the rate of complete colonoscopies in our series is lower than the recommended by the quality practice guidelines on colonoscopy (20). It is, however, comparable to other reports of the rates currently described in our setting (21). This finding could be related to the technical skills of endoscopists. For this reason, lesions detected by colonoscopy that are candidates for endoscopic resection should be treated by endoscopists with sufficient experience to perform complex resections. This is of particular importance in screening programmes for CRC based on quantitative immunochemical tests for faecal occult blood. In this context, it is possible to detect advanced adenomas in more than 50% of colonoscopies (22). On the other hand, it is known that referral of patients with adenomas to specialised units when resection is likely to be difficult avoids surgical treatment in 32% to 90% of cases (23-25). In this way, it is possible to reduce both morbidity and healthcare costs associated with the treatment of adenomas (24).

Our study does, however, have some limitations in particular due to the nature of the research. As this was a retrospective study, looking backwards over a considerable period of time, we were not able to collect data on variables associated with the risks of submucosal infiltration (the non-lifting sign) (26) or of detecting invasive adenocarcinoma in adenoma (Kudo classification) (27). Indeed, though non-significant, we observed difference in the rate of complete endoscopic resection in adenocarcinomas resected before and since 2005. This methodological problem is, however, common to all studies analysing the risk factors associated with the natural history of invasive adenocarcinoma arising in adenoma. As this is a relatively uncommon condition, long periods of time are required to collect sufficiently large sample sizes to produce statistically significant results. On the other hand, we did not collect information either on polypoid lesions that were not considered candidates for endoscopic resection or on those endoscopically resected but with no signs of malignancy or with *in situ* adenocarcinoma in the same period of time. The lack of these data could limit the conclusions in our study, since information to confirm the diagnosis of invasive adenocarcinoma is only obtained from histological analysis of the polyp.

Identifying factors associated with the risk of residual disease after endoscopic resection was not the objective of this analysis. It is nevertheless interesting to note that a recently published study found two factors to be associated with the risk of residual disease or recurrence: incomplete endoscopic resection and histological high-risk features (3,12). Currently, two types of criteria are used to determine the risk of recurrence: histological high risk features (3) and the extent of submucosal invasion (6,7,18). The latter is useful for determining the risk of residual disease in invasive adenocarcionma in sessile protruding or flat elevated lesions (7,18).

In conclusion, endoscopic resection of invasive adenocarcinoma completely removes a high percentage of colonic

lesions. The rate of complete endoscopic resection has progressively increased in recent years. Further, the risk of incomplete endoscopic resection was found to be independently associated with the polyp diameter, non-pedunculated morphology, and caecal intubation.

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