

MALIGNANCY IN LARGE COLORECTAL LESIONS

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ABSTRACT - Context - The size of colorectal lesions, besides a risk factor for malignancy, is a predictor for deeper invasion. **Objective** - To evaluate the malignancy of colorectal lesions ≥ 20 mm. **Methods** - Between 2007 and 2011, 76 neoplasms ≥ 20 mm in 70 patients were analyzed. **Results** - The mean age of the patients was 67.4 years, and 41 were women. Mean lesion size was 24.7 mm \pm 6.2 mm (range: 20 to 50 mm). Half of the neoplasms were polypoid and the other half were non-polypoid. Forty-two (55.3%) lesions were located in the left colon, and 34 in the right colon. There was a high prevalence of III L (39.5%) and IV (53.9%) pit patterns. There were 72 adenomas and 4 adenocarcinomas. Malignancy was observed in 5.3% of the lesions. Thirty-three lesions presented advanced histology (adenomas with high-grade dysplasia or early adenocarcinoma), with no difference in morphology and site. Only one lesion (1.3%) invaded the submucosa. Lesions larger than 30 mm had advanced histology ($P = 0.001$). The primary treatment was endoscopic resection, and invasive carcinoma was referred to surgery. Recurrence rate was 10.6%. **Conclusions** - Large colorectal neoplasms showed a low rate of malignancy. Endoscopic treatment is an effective therapy for these lesions.

HEADINGS - Colonic polyps. Colorectal neoplasms. Gastrointestinal endoscopy.

INTRODUCTION

Colorectal cancer (CRC) is a major cause of cancer-related morbidity and mortality. It affects mainly people older than 50 years and its development can be explained either by the adenoma-carcinoma sequence⁽²²⁾, the pathway of the *de novo* cancer^(19, 27), or, more recently, the serrated pathway⁽²⁴⁾.

The removal of precursor colorectal lesions has enabled a significant reduction in the incidence of cancer, and early detection of CRC reduces mortality⁽³³⁾. The characteristics of the removed lesions and histopathology determine colonoscopic surveillance. A recent guidelines⁽⁸⁾ indicates shorter intervals for advanced neoplasms (adenomas ≥ 10 mm, villous histology or high-grade dysplasia, and cancer). Besides these criteria, the presence of three or more adenomas and serrated polyps ≥ 10 mm fulfill the requirements for the high-risk group. Thus, large lesions (≥ 2.0 cm) are considered high risk neoplasms, with potential for malignancy, submucosal invasion and lymphatic involvement. These lesions may be polypoid (sessile, pedunculated and subpedunculated) and non-polypoid (flat lesions and laterally spreading tumors/LST).

Techniques for resection of these large lesions can use a diathermy loop for pedunculated or subpedunculated lesions, and the method of endoscopic

mucosal resection or submucosal dissection for sessile and non-polypoid lesions^(11, 30).

This study aimed to analyze the characteristics and malignancy rate of large neoplastic colorectal lesions (> 20 mm).

METHODS

Between January 2007 and December 2011, 76 neoplastic lesions ≥ 20 mm were diagnosed in 70 patients, corresponding to 3.7% of neoplasms found during this period at our Endoscopy Unit. This study prospectively analyzed the characteristics (age, sex, size, morphology, site, pit pattern, histology, grade of dysplasia, recurrence) and the malignancy of these lesions. Lesions are called superficial when their appearance at endoscopy suggests that depth is limited to the mucosa or submucosa. All colonoscopies were performed by the same experienced endoscopist (CEOS). Bowel preparation was performed with a day of clear liquid diet, and a 10% mannitol solution on the day of the exam. Conscious sedation (intravenous midazolam and meperidine or fentanyl) was administered and a high resolution colonoscopy was performed (Fujinon 490ZW5 and 590ZW5, Fujifilm Corp., Saitama, Japan) with progression to the cecum/terminal ileum. The processor used was EPX4400.

Declared conflict of interest of all authors: none

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Exclusion criteria were: inadequate bowel preparation, incomplete colonoscopy, coagulopathy, history or presence of inflammatory bowel disease, polypoid syndromes, presence of advanced cancer, previous surgical colorectal resection, non-neoplastic lesions and lesions smaller than 2.0 cm.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Hospital Santa Casa de Caridade de Bagé. All patients signed an informed consent prior to colonoscopy. The Paris classification determined the morphology of the lesions⁽³¹⁾. Lesion size was estimated by open biopsy forceps with an opening of 8 mm between its claws (FB 24U-1, Olympus Medical Systems Corp., Tokyo, Japan) and, when possible, after its removal. The site was estimated according to the anatomical landmarks. The Kudo classification was chosen as reference standard for the study of pits^(12, 13), and indigo carmine was the dye for chromoendoscopy (CE). All lesions were removed in a single session. Pedunculated and subpedunculated lesions were removed by polypectomy snare and non-sessile polypoid lesions were resected by endoscopic mucosal resection (EMR), en bloc (lesions = 20 mm) or piecemeal (lesions >20 mm), and all the material removed was placed in 10% formalin and stained with hematoxylin and eosin for histopathological analysis. Histological diagnosis was defined according to the guidelines of the World Health Organization⁽⁷⁾. Advanced histology was defined as presence of high-grade dysplasia or early cancer⁽²⁶⁾. The cancer was considered advanced when invading the submucosa, and these cases were excluded from the study. In the case of multiple lesions, each lesion was placed in a separate flask. Local recurrence was defined as the presence of neoplastic tissue in the area of previous resection at the control colonoscopy. Follow-up was conducted every 6 months, with a total follow-up of 24 months for lesions underwent endoscopic mucosal resection. Recurrent lesions were removed with a new endoscopic mucosal resection and were identified by the EMR scar. Recurrent lesions were removed with a new endoscopic mucosal resection.

Statistical analysis

Numerical variables were expressed as mean \pm standard deviation, and categorical variables were expressed as percentages. Fisher's exact test was used for comparison between means. The significance level for all the statistical tests was 5%.

RESULTS

The mean age of patients was 67.4 years (\pm 13.3 years), with 41 women and 29 men. Mean lesion size was 24.7 mm (\pm 6.2 mm), ranging between 20 and 50 mm. Thirty-eight (50%) lesions were polypoid (10 type 0-Is, 8 type 0-Isp and 20 type 0-Ip) and 38 (50%) lesions were non-polypoid (1 type 0-IIc and 37 laterally spreading tumor/LST). Regarding site, 42 (55.3%) were located in the left colon (15 in the rectum, 22 in the sigmoid and 5 in the descending) and 34 (44.7%)

were located in the right colon (4 in the transverse, 19 in the ascending and 11 in the cecum).

Polypoid lesions were more frequent in the left colon (31/38) and non-polypoid lesions were more commonly found in the right colon (27/38). Analyzing the pit patterns, 1 (1.3%) lesion was type II, 29 (38.2%) were type III L, 41 (53.9%) were type IV and 5 (6.6%) were type V. Therefore, 75 (98.7%) lesions \geq 20 mm presented a pit pattern compatible with neoplasms (III - V), according to the Kudo classification^(12, 13), with a predominance of the villous histologic subtype. The neoplastic lesion with a type II pit pattern, suggestive of a non-neoplastic lesion, was a non-granular LST of the smooth subtype, measuring 25 mm, located in the cecum, and histology showed that it was a sessile serrated adenoma. Among the five type V lesions, however, four lesions were adenocarcinomas and one was an adenoma with high-grade dysplasia. The relationship between pit patterns and histology is shown in Table 1.

TABLE 1. Relationship between pit pattern and histopathology of colorectal neoplasms

Pits	Ca / HGD	TA, TVA, VA, SA / LGD	TOTAL
II	0	1	1
III L	7	22	29
IV	21	20	41
V	5	0	5

$P = 0.002$. Ca: adenocarcinoma; HGD: high-grade dysplasia; TA: tubular adenoma; TVA: tubulo-villous adenoma; VA: villous adenoma; SA: serrated adenoma; LGD: low-grade dysplasia

Histology revealed 72 adenomas (20 tubular, 42 tubulo-villous, 8 villous, and 2 serrated adenomas) and 4 adenocarcinomas (3 intramucosal carcinomas and 1 invasive). Among the adenomas, 29 (40.3%) of the lesions presented high-grade dysplasia. The relationship between the morphological appearance and histology is shown in Table 2. All lesions in this study were superficial lesions. Thirty-three lesions presented advanced histology (adenomas with high-grade dysplasia or adenocarcinoma), affecting three patients under 50 years of age and 28 patients aged 50 years or more. There was no difference in the morphology (15 polypoid versus 18 non-polypoid, $P = 0.644$) and site (20 in the left colon versus 13 in the right colon, $P = 0.358$) for these lesions. However, 100%⁽¹⁵⁾ of the

TABLE 2. Relationship between the morphology and histopathology of colorectal neoplasms

Morphology	Ca / HGD	TA, TVA, VA, SA / LGD	TOTAL
Is	5	5	10
Isp	3	5	8
Ip	7	13	20
IIc	1	0	1
LST	17	20	37

$P = 0.841$. LST: Laterally Spreading Tumor; Ca: adenocarcinoma; HGD: high-grade dysplasia; TA: tubular adenoma; TVA: tubulo-villous adenoma; VA: villous adenoma; SA: serrated adenoma; LGD: low-grade dysplasia

polypoid neoplasms with advanced histology were located in the left colon, whereas 72.2% (13/18) of the non-polypoid neoplasms with advanced histology were in the right colon.

Neoplasms were still divided into two groups according to their size: 20-30 mm and >30 mm. All lesions >30 mm were adenomas with high-grade dysplasia or cancer, while 25 (36.7%) of the remaining 68 lesions with size between 20 and 30 mm presented with advanced histology ($P < 0.001$).

The only invasive cancer in our study was a non-polypoid, depressed superficial type 0-IIc lesion measuring 25 mm, with type V pit pattern, located in the sigmoid colon and massively invading the submucosa, which was later referred for surgical resection. The remaining 75 neoplastic lesions underwent only endoscopic treatment. Forty-seven lesions were treated by endoscopic mucosal resection: 24 (51%) lesions were resected en bloc and 23 (49%) lesions were removed using the piecemeal technique.

Resection was considered incomplete when there was evidence of malignancy in lateral or deep margins, which was only found in one lesion. No deaths were associated with endoscopic treatment. Recurrence was observed in five lesions (10.6%), all LST type, without significant difference between en bloc and piecemeal techniques (4.2 vs 17.4%, $P = 0.188$). Recurrence was observed in five (10.6%) lesions, all LST type removed by the technique of endoscopic mucosal resection and diagnosed at the first control colonoscopy, 6 months after resection. The recurrent lesions were treated with new endoscopic mucosal resection, with complete removal. No new or recurrent lesions were found for the remainder of the follow-up. We had 94 lesions with morphology advanced cancer who were referred to surgery and histopathology demonstrated muscular propria invasion or more, with all these lesions excluded from the study.

DISCUSSION

Colorectal neoplasms ≥ 20 mm are considered advanced neoplasms and, therefore, present high risk for progression to cancer. Thus, the interval recommended for colonoscopy surveillance is reduced to 3 years after the first colonoscopy⁽⁸⁾. In the group of high-risk lesions (≥ 10 mm, villous histology or high-grade dysplasia, >2 adenomas and serrated polyps ≥ 10 mm), an increased risk of advanced adenoma and metachronous CRC at the follow-up colonoscopy was observed. Chung et al.⁽³⁾ have shown a 6-fold higher incidence of metachronous advanced neoplasms for patients in the high-risk group, when compared to individuals without adenomas at the index colonoscopy, considering that the size ≥ 10 mm is an independent predictor.

Martinez et al.⁽¹⁶⁾ have observed a 15.5% risk of advanced neoplasm during follow-up in the high-risk group and of 6.9% in the low risk group. The risk of invasive cancer was 1.2% in patients who had adenomas ≥ 20 mm at the index colonoscopy and 1.3% in patients who presented lesions with high-grade dysplasia. Compared to patients with adenomas ≥ 20 mm at the baseline colonoscopy, the adjusted probability for advanced neoplasm was 2.99.

Studies have shown a strong correlation between lesion size and its potential for malignancy^(2, 4, 32), and these lesions are considered to be at higher risk for submucosal invasion and lymph node involvement⁽⁹⁾. A greater malignant potential for lesions >10 mm ($P < 0.0001$) was observed by Reinhart et al.⁽²³⁾, regardless of morphology. However, there have been series showing that small, non-polypoid lesions are more likely to contain carcinoma and a deeper infiltration of the submucosa, when compared to larger, polypoid lesions^(14, 20, 29). Kurisu et al.⁽¹⁴⁾ have investigated the development and progression of early CRC, and observed that non-polypoid lesions were significantly smaller than polypoid lesions and presented with deeper invasion of the submucosa. Soetikno et al.⁽²⁹⁾ have also found that non-polypoid lesions were more likely to contain carcinoma (OR = 9.78) than polypoid lesions, regardless of their size. Matsuda et al.⁽²⁰⁾ have shown a similar aggressiveness and malignant potential when comparing smaller and larger lesions.

In our study, we found four (5.3%) adenocarcinomas among the 76 neoplasms ≥ 20 mm, and 29 (38.2%) adenomas with high-grade dysplasia. Therefore, 43.4% presented with advanced histology. All adenocarcinomas were located in the left colon, but only one lesion had massively invaded the submucosa (1.3%). In the study by Ahlawat et al.⁽¹⁾, 183 lesions of the colon and rectum ≥ 20 mm, most of them sessile, were removed endoscopically, and the rate of invasive carcinoma was 10%.

When comparing our polypoid and non-polypoid lesions, no difference was observed in relation to advanced histology. Luigiano et al.⁽¹⁵⁾ have shown increased malignancy in sessile polypoid lesions when compared to non-polypoid, superficial lesions (21.6% versus 6%, $P = 0.0013$). Another series has examined the risk of lymph node metastases in patients with invasive pedunculated polypoid type CRC. Among the patients that were treated surgically, the incidence of lymph node metastases was 3.5% (8/230); however, the incidence was 0% (0/101) in patients with invasion at the polyp head and 6.2% (8/129) when the invasion occurred at the pedicle of the polyp⁽¹⁸⁾. Caputi et al.⁽²⁾ have reported malignancy in 9.3% of lesions ≥ 20 mm, with 3.3% of invasive carcinomas.

There was no statistical difference when comparing the site of the neoplasms with the occurrence of advanced histology, but all 15 polypoid tumors with advanced histology were located in the left colon, whereas 72.2% (13/18) of non-polypoid neoplasms were in the right colon. This was corroborated by Rondagh et al.⁽²⁶⁾, who found that proximal neoplasms with advanced histology were more likely to be non-polypoid (OR 4.68, $P = 0.006$).

In our study, lesions >30 mm were adenomas with high-grade dysplasia or cancer. We have used image magnification for 15 years, and commonly use real or digital chromoscopy. The endoscopic diagnosis of the pit patterns showed good results in terms of sensitivity, specificity and accuracy in the diagnosis of neoplasms, including the case of invasive cancer^(17, 21). In previous studies^(5, 28), for discriminating between neoplastic and non-neoplastic lesions, we had sensitivity of 97%-97.6%, specificity of 88.9%-93.9%, accuracy of 94.9%-

96.8%, positive predictive value of 96.1%-98.4%, and negative predictive value of 91.2%-91.4%.

In this study, only one lesion (1.3%) presented a type II pit pattern, suggestive of a non-neoplastic lesion, however, after endoscopic resection, it was revealed to be a sessile serrated adenoma, a lesion that could be mistaken for a hyperplastic lesion at colonoscopy⁽¹⁰⁾. Among the five lesions with type V pit pattern, histology showed one adenoma with high-grade dysplasia, three intramucosal carcinomas and one invasive carcinoma, which was surgically treated later.

We found a recurrence rate of 10.6%, all of them for non-polypoid LST-type lesions, which underwent endoscopic mucosal resection. In a previous study of colorectal endoscopic mucosal resection, we found a low recurrence

rate (4.1%), with a significant association with larger lesion sizes ($P < 0.01$)⁽⁶⁾. The screening and the complete removal of colorectal neoplasms is of paramount importance. Robertson et al.⁽²⁵⁾ have observed 11 cases of CRC in colonoscopic surveillance, possibly associated with incomplete resection of the lesions.

CONCLUSION

Once analysing our colorectal neoplasms ≥ 20 mm, 43.4% had advanced histology, but with a low rate of malignancy (5.3%), either for polypoid or non-polypoid lesions, and invasive carcinoma (1.3%). Therefore, endoscopic treatment is an effective therapy for large colorectal neoplasms.

Santos CEO, Malaman D, Carvalho TS, Lopes CV, Pereira-Lima JC. Malignidade em grandes lesões colorretais. Arq Gastroenterol. 2014;51(3):235-9.

RESUMO - Contexto - O tamanho em lesões colorretais, além de risco para malignidade, é preditor para invasão profunda. **Objetivo** - Avaliar a presença de malignidade em lesões colorretais ≥ 20 mm. **Método** - Entre 2007 e 2011, 76 neoplasias colônicas ≥ 20 mm em 70 pacientes foram analisadas. **Resultados** - A idade média foi de 67,4 anos, e 41 eram mulheres. O tamanho médio das lesões foi de 24,7 mm \pm 6,2 mm, com variação de 20 a 50 mm. Metade das neoplasias foram polipoides e a outra metade, não polipoides. O cólon esquerdo apresentou 42 (55,3%) neoplasias e o direito, 34. Houve alta prevalência de lesões com criptas padrão III L (39,5%) e IV (53,9%). Houve 72 adenomas e 4 adenocarcinomas. Malignidade foi detectada em 5,3% dos casos. Histologia avançada (adenoma com displasia de alto grau ou adenocarcinoma precoce) foi diagnosticada em 33 lesões, sem diferença quanto à morfologia e local da lesão. Apenas uma lesão (1,3%) invadiu a submucosa. Lesões maiores de 30 mm apresentaram histologia avançada ($P = 0,001$). A ressecção endoscópica foi a terapêutica primária, e carcinoma invasivo foi encaminhado para cirurgia. Recorrência foi de 10,6%. **Conclusão** - Grandes neoplasias colorretais demonstram uma baixa taxa de malignidade. A ressecção endoscópica é terapêutica adequada para estas lesões. **DESCRITORES** - Pólipos do colo. Neoplasias colorretais. Endoscopia gastrointestinal.

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