Complete endoscopic mucosal resection of malignant colonic sessile polyps and clinical outcome of 51 cases

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Abstract	**Background** Meta-analyses and guidelines recommend that deep submucosal invasion (>1 mm) of malignant sessile colonic polyps is an important risk factor for lymph node metastasis. However, existing data are based on small retrospective studies with marked heterogeneity. We herein aimed to investigate the long-term outcomes of patients who underwent complete endoscopic mucosal resection (EMR) of malignant colonic sessile polyps invading the submucosal layer.

Methods Endoscopy records for the period 2000-2016 were reviewed retrospectively. All enrolled patients exhibited an endoscopically resected malignant colonic sessile polyp. All patients were advised to undergo surgery, but some opted for conservative treatment and endoscopic follow up.

Results Fifty-one patients with confirmed infiltrative submucosal adenocarcinoma in sessile colonic polyps that had undergone complete EMR were detected. A total of 32 (62.7%) patients opted for surgery after EMR and 19 (37.3%) chose endoscopic follow up. In 44 (86.3%) patients the submucosal invasion was >1 mm. Residual malignant disease was identified in the surgical pathological specimen of only 1 patient. During a median follow up of 23.41 months (interquartile range 33.45, range 1.84-144.92), no local recurrences or lymph node metastasis were identified. Forty-nine patients are alive without evidence of disease and 2 died of other causes (without evidence of local or metastatic disease at last follow up).

Conclusion Our data suggest that complete EMR of cancerous colonic sessile polyps, even in cases of submucosal invasion >1 mm carries a low risk of recurrence and therefore may need further evaluation as an alternative strategy to surgical resection.

Keywords Malignant polyp, endoscopic mucosal resection, submucosal invasion

Ann Gastroenterol 2019; 32 (2): 174-177

Introduction

The term "malignant polyp" refers to an adenoma with a benign endoscopic appearance [1] and a histology report that suggests malignancy invading into the submucosa [1-3]. A malignant polyp is therefore classified as an early carcinoma.

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Conflict of Interest: None

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These account for 0.75-5.6% of large bowel polyps removed in screening colonoscopies [1].

The management of a malignant polyp following endoscopic removal is controversial, because of the supposed increased risk of residual malignant cells within the bowel wall and the increased rate of lymph node metastasis (LNM) [4,5]. The most commonly identified risk factors for LNM are submucosal invasion depth, lymphovascular invasion, poor tumor differentiation, presence of tumor budding (the presence of isolated single cells or small clusters of fewer than 5 cells scattered at the leading edge of the invasion [6,7]) and positive resection margin status (dysplastic cells to distance ≤1 mm from polyp excision margins) [3-5]. In low-risk patients, with none of the aforementioned factors and submucosal invasion <1 mm from *muscularis mucosae*, the risk of LNM in malignant polyps has been reported to be insignificant (0-1.2%); thus, endoscopic resection alone seems to be an adequate treatment [8-10]. Meta-analyses and guidelines recommend that deep submucosal invasion (>1 mm) in

malignant colonic polyps is an important risk factor for residual malignant disease and LNM (8-25%) [4,5,8,11]. However, existing data are based on small retrospective studies with marked heterogeneity [3-5,12,13].

The primary aim of this study was to investigate the long-term outcome of patients who underwent complete endoscopic mucosal resection (EMR) of malignant colonic sessile polyps invading the submucosal layer of the bowel wall. Secondary outcomes included the evaluation of other polyp parameters, such as lymphovascular invasion, tumor differentiation, resection margin status, and the presence of tumor budding in the long-term outcome of those patients.

Patients and methods

From January 2000 to December 2016 a retrospective review of the endoscopy records was conducted in Venizeleion General Hospital, which is a tertiary referral center in Crete, Greece. The study was approved by the Institutional Ethics Review Board of our Hospital. All enrolled patients exhibited a malignant colonic sessile polyp, completely endoscopically resected. Patient's age, sex, polyp size (estimated by visual comparison to the opening width of biopsy forceps) and location (right colon was defined the part proximal to the splenic flexure) were recorded. According to the Paris classification all polyps were classified as Is [14]. Complete polyp resection was endoscopically confirmed after the completion of polypectomy. Lesions with incomplete resection were excluded. Piecemeal resection was performed in large lesions when *en bloc* resection could not be applied. Experienced endoscopists, each of them with more than 3000 colonoscopies, performed all procedures. A variety of snares were used, including the Snare Master snare (Olympus) and the Captivator-II snare (Boston Scientific), with sizes ranging between 10 and 30 mm. For EMR a methylene blue-tinted normal saline solution was injected into the submucosal space, underneath the lesion, using a 25-G needle. Cautery was applied with monopolar coagulation current, using the ERBE ICC200 or the ERBE VIO200D in the fractionated cutting mode ENDO CUT Q.

Histological features of the polyps were also recorded. This included the depth of submucosal invasion (less or more than 1 mm) (Fig. 1), the presence of lymphovascular invasion, tumor differentiation according to the World Health Organization's classification (well-, moderately-, or poorly-differentiated) [15], tumor budding, and resection margin status.

Computed tomography (CT) or magnetic resonance imaging (MRI) scanning was performed as a regular workup in all patients before any decision on further management. All patients were informed about their condition and surgery was advised. Some of them opted for further surgical treatment and others preferred conservative management with repeat colonoscopies at 3-6 and 12 months, oncologic consultation and further follow-up CT and/or MRI studies. In most cases, oncologist suggested imaging at 6 months after resection and every year after that for 5 years, combined with oncologic consultation over the same period. In recent years, a tattoo was placed next to the polypectomy site, according to current guidelines [1].
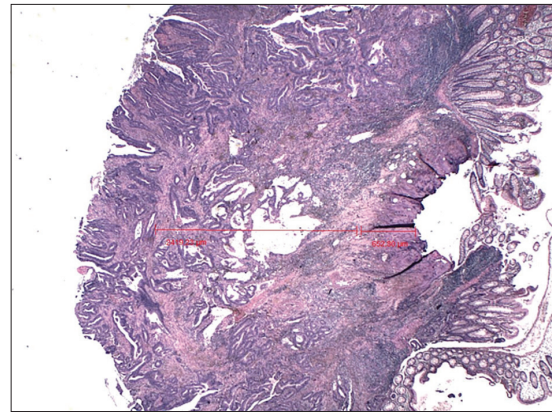

Figure 1 Submucosal invasion >1 mm in a patient who chose endoscopic follow up

Table 1 Demographic characteristics of the 51 patients and histological characteristics of the sessile malignant polyps

Characteristic	Value
Age (years), Median (IQR, range)	70 (17, 38-88)
Sex (%)	
Male	28 (54.9)
Female	23 (45.1)
Tumor size	
>20 mm	30 (58.8)
≤20 mm	21 (41.2)
Location	
Rectum	15 (29.4)
Left colon	29 (56.9)
Right colon	7 (13.7)
Resection method	
En bloc	21 (41.2)
Piecemeal	30 (58.8)
Submucosal invasion	
≤1 mm	7 (13.7)
>1 mm	44 (86.3)
Resection margin status (mm) Median (IQR, range)	1 (1.7, 0-7)
Lymphovascular invasion	7 (13.7)
Tumor differentiation	
Well-differentiated	14 (27.5)
Moderately-differentiated	28 (54.9)
Poorly-differentiated	9 (17.6)
Tumor budding	9 (17.6)

IQR, interquartile range

Statistical analysis

Medians with interquartile range (IQR) were calculated for continuous data and percentages were computed for discrete data. The Kolmogorov-Smirnov test was used to evaluate distribution normality. Continuous variables were compared using Student's *t* or Mann-Whitney tests as appropriate. Statistical significance was defined as P≤0.05.

Table 2 Characteristics of the EMR only and EMR+surgery groups and histological characteristics of the sessile malignant polyps

Variable	EMR only (n=19), n (%)	EMR+surgery (n=32), n (%)
Age (years), Median (IQR, range)	72 (15, 53-88)	69 (21, 38-87)
Sex (%)		
Male	7 (36.8)	21 (65.6)
Female	12 (63.2)	11 (34.4)
Tumor size		
>20 mm	11 (57.9)	19 (59.4)
≤20 mm	8 (42.1)	13 (40.6)
Location		
Rectum	10 (52.6)	5 (15.6)
Left colon	9 (47.4)	20 (62.5)
Right colon	-	7 (21.9)
Resection method		
En bloc	3 (15.8)	18 (56.3)
Piecemeal	16 (84.2)	14 (43.8)
Submucosal invasion		
≤1 mm	2 (10.5)	5 (15.6)
>1 mm	17 (89.5)	27 (84.4)
Resection margin status (mm) Median (IQR, range)	1 (1.3, 0-4)	0,65 (1.1, 0-7)
Lymphovascular invasion	0	7 (21.9)
Tumor differentiation		
Well-differentiated	7 (36.8)	7 (21.9)
Moderately-differentiated	9 (47.4)	19 (59.4)
Poorly-differentiated	3 (15.8)	6 (18.8)
Tumor budding	4 (21.1)	5 (15.6)

EMR, endoscopic mucosal resection; IQR, interquartile range

Results

Fifty-one patients with confirmed infiltrative adenocarcinoma in sessile colonic polyps who had undergone EMR were retrospectively identified and included in the study. The demographic and clinical characteristics of the patients are summarized in Table 1. A total of 32 (62.7%) patients underwent surgery after EMR, and 19 (37.3%) chose endoscopic follow up. All patients with lymphovascular invasion underwent surgery. None of the patients in the EMR group had lymphovascular invasion. The characteristics of the two groups are shown in Table 2.

In 44 (86.3%) patients the submucosal invasion was >1 mm. After surgery, residual malignant disease was identified in the surgical pathological specimen of only 1 patient. This sessile polyp, located in the left colon, was less than 10 mm in size, moderately differentiated with a submucosal invasion >1 mm, and with no evidence of tumor budding or lymphovascular invasion. With a median follow up of 23.41 months (IQR 33.4, range 1.84-144.92), no local recurrences or LNM were identified. Forty-nine patients are alive without evidence of disease and 2 died from other causes (without evidence of disease at last follow up).

Discussion

This study suggests that, even in cases of malignant colonic sessile polyps with submucosal invasion >1 mm and the presence of other high-risk features (lymphovascular invasion, tumor budding), complete EMR might be a sufficient treatment. This finding, if confirmed by larger studies, can be of vital importance, especially in high-risk groups of patients, such as the elderly, and in those with polyps located in the lower rectum, where surgery is not always a favorable option.

Recently, the European Society of Gastrointestinal Endoscopy published polypectomy guidelines suggesting the need for measurement of the submucosal invasion depth, in addition to other histological risk factors—without, however, clearly stating the exact invasion depth beyond which patients need to undergo additional surgery [3]. Results from studies show mixed results regarding the long-term safety of the invasion depth. According to Oka *et al* [16], a systemic review [5] and a meta-analysis from the United Kingdom [4], submucosal invasion <1 mm is a reliable histopathological criterion associated with a negligible risk of LNM or recurrence. On the other hand, Nakadoi *et al* [9] extended the safe submucosal invasion depth to 1.8 mm and Han *et al* [17] to 1.9 mm as an independent factor for LNM. Although invasion depth represents the most frequent indication for subsequent surgery, there are studies that suggest other polyp features (tumor differentiation, budding and resection margin status) might be more important predictors than submucosal invasion regarding the necessity for subsequent surgery [9,17,18]. Our data support the extension of the submucosal invasion depth of >1 mm for patients who require additional surgery. Furthermore, since residual malignant disease was identified in only 1 surgical specimen, it is rather difficult to evaluate the role of the other parameters in terms of residual disease and risk of recurrence. In addition, another important factor to evaluate is the location of the malignant sessile polyp. A study from Japan points out that high-risk submucosal rectal cancer should be surgically resected, given its higher risk for recurrence [19], but since no recurrence was identified in our patients (N=15) we are unable to further evaluate this factor.

A systemic review by Bosch *et al* pointed out that lymphatic invasion was the most powerful predictor of LNM (relative risk [RR] 5.2, 95% confidence interval [CI] 4.0-6.8), vascular invasion was a much weaker predictor of LNM (RR 2.2, 95%CI 1.4-3.2), whereas lymphovascular invasion had an intermediate relative risk (RR 3.9, 95%CI 2.7-5.6) [5]. It is important to point out that in our study none of the endoscopically treated patients had lymphovascular invasion; this might be an explanation of the favorable results of this group.

Novel endoscopic methods that provide complete *en bloc* resection, such as endoscopic submucosal dissection and full thickness resection, can lower the rate of unnecessary additional surgery [20,21], but these were not applicable in our department, especially in the early years of the study period. Moreover, a recently published study from Japan proposed the use of a new artificial intelligence model as a predictor of LNM after endoscopic resection of T1 colorectal cancers [22].

Our study had certain limitations. First, it was a retrospective study conducted in a single tertiary institute with a limited

number of cases. Second, there was some heterogeneity in the polypectomy techniques and technology utilized over all these years. New polypectomy guidelines have recently been established, based on newly evolving endoscopic technology and more advanced EMR techniques, developed and used throughout that period. Third, the follow-up period is still rather short to assess both late disease recurrence events and, in particular, LNM.

In conclusion, even in cases with submucosal invasion >1 mm and the presence of other high-risk features (lymphovascular invasion, tumor budding), complete EMR may be an adequate treatment for malignant invasive colonic sessile polyps. However, because of the risk of LNM, surgical resection is still the gold standard for patients with malignant invasive colonic sessile polyps and endoscopic resection alone should only be considered for patients who are unfit for surgery or refuse it. Our data require further validation from larger, prospective, multicenter studies, which will examine in more detail the features of resected malignant polyps in order to possibly redefine criteria for preventing unnecessary colectomies without compromising oncological safety.

Summary Box

What is already known:

- Malignant sessile polyps have an increased rate of lymph node metastases (LNM)
- Deep submucosal invasion (>1 mm) in malignant polyps is an important risk factor for residual malignant disease and LNM

What the new findings are:

- Malignant sessile polyps with submucosal invasion >1 mm can be treated endoscopically
- If confirmed by larger prospective studies, this might influence the treatment strategy, particularly in patients with significant comorbidities

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