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SURGICAL MANAGEMENT OF ENDOSCOPICALLY UNRESECTABLE COLORECTAL POLYPS

ENDOSKOPİK OLARAK ÇIKARILAMAYAN KOLOREKTAL POLİPLERE CERRAHİ YAKLAŞIM

Burak İLHAN[1], Enver KUNDUZ[2], Özge PASİN[3], Derya SALİM UYMAZ[4], Emre BALIK[4]

[1]Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, Istanbul, Turkiye
[2]Bezmialem University, Faculty of Medicine, Department of General Surgery, Istanbul, Turkiye
[3]Bezmialem University, Faculty of Medicine, Department of Biostatistics, Istanbul, Turkiye
[4]Koç University, Faculty of Medicine, Department of General Surgery, Istanbul, Turkiye

ORCID IDs of the authors: B.İ. 0000-0002-7538-7399; E.K. 0000-0002-7686-2809; Ö.P. 0000-0001-6530-0942; D.S.U. 0000-0002-2590-5872; E.B. 0000-0001-5751-1133

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ABSTRACT

Objective: To define the management of colorectal polyps that were technically unsuitable for endoscopic removal.

Materials and Methods: Between May 2010 and January 2019, 4886 polyps from 3822 of 16,996 colorectal endoscopies were analyzed. Of the total colorectal polyps, 135 (2.8%) were identified as endoscopically unresectable single polyps and examined in detail.

Result: The rate of invasive colorectal cancer (CRC) in unresectable and resectable polyps was 26.7% and 1.7%, respectively (p<0.001). Unresectable polyps were more common in the ascending colon and cecum (p<0.001), but the potential to contain invasive CRC was greater in the sigmoid colon and rectum-located polyps (p=0.001). In addition, advancing age (p=0.014), increased polyp size (p=0.012), deep submucosal invasion (p<0.001), and the presence of lymphovascular invasion (p<0.001) were associated with the development of CRC. Unresectable polyps requiring surgery after non-curative endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) were found to have a significantly higher risk of containing CRC compared with polyps that underwent surgical resection primarily (p=0.002). In the multivariate model, advancing age (p=0.010) and detected deep submucosal invasion (p=0.002) were more associated with the development of CRC.

Conclusion: The study suggests that oncologic surgery for polyps with deep submucosal invasion (particularly by EMR or ESD) that cannot be endoscopically resected in older patients should be considered carefully and, perhaps, without delay,

ÖZET

Amaç: Bu çalışma, endoskopik olarak çıkarılması teknik olarak uygun olmayan kolorektal poliplerin tedavisini tanımlamayı amaçladı.

Gereç ve Yöntem: Mayıs 2010 ile Ocak 2019 tarihleri arasında 16,996 kolorektal endoskopiden 3,822'sinde 4,886 polip analiz edildi. Total kolorektal poliplerin 135'i (%2,8) endoskopik olarak çıkarılamayan tekli polip olarak tanımlandı ve detaylı olarak incelendi.

Bulgular: Rezeke edilemeyen bir polipte invaziv kolorektal kanser (KRK) oranı %26,7 iken, rezeke edilebilir bir polipte bu oran %1,7 idi (p<0,001). Rezeke edilemeyen polipler çıkan kolon ve çekumda daha yaygındı (p<0,001), ancak invaziv KRK içerme potansiyeli sigmoid kolon ve rektum yerleşimli poliplerde daha fazlaydı (p=0,001). Ayrıca ilerleyen yaş (p=0,014), artmış polip boyutu (p=0,012), derin submukozal invazyon (p<0,001) ve lenfovasküler invazyon varlığı (p<0,001) KRK gelişimi ile ilişkiliydi. Küratif olmayan endoskopik mukozal rezeksiyon (EMR) veya endoskopik submukozal diseksiyon (ESD) sonrası ameliyat gerektiren rezeke edilemeyen poliplerin, primer olarak cerrahi rezeksiyon uygulanan poliplere kıyasla anlamlı derecede daha yüksek KRK içerme riskine sahip olduğu bulundu (p=0,002). Çok değişkenli modelde ilerleyen yaş (p=0,010) ve saptanan derin submukozal invazyon (p=0,002) KRK gelişimi ile daha fazla ilişkiliydi.

Sonuç: Çalışma, yaşlı hastalarda endoskopik olarak rezeke edilemeyen derin submukozal invazyonlu (özellikle EMR veya ESD ile) polipler için onkolojik cerrahinin dikkatli bir şekilde düşünülmesi gerektiğini ve belki de gecikmeden, öncelikle tekrarlanan

Corresponding author/İletişim kurulacak yazar: Burak İLHAN – burakmd@yahoo.com

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primarily by abandoning repeated endoscopic resection attempts.

Keywords: Colorectal neoplasms, polyps, endoscopy, endoscopic mucosal resection, endoscopic submucosal dissection

endoskopik rezeksiyon girişimlerinden vazgeçilmesi gerektiğini önermektedir.

Anahtar Kelimeler: Kolorektal neoplaziler, polipler, endoskopi, endoskopik mukozal rezeksiyon, endoskopik submukozal diseksiyon

INTRODUCTION

Colorectal cancer (CRC) is the third most common and the second leading cause of cancer-related deaths worldwide (1). Colorectal polyps are well-known precursor lesions of invasive carcinomas. Successful removal of these polyps through screening programs provided reduced incidence of CRCs (2,3). Screening colonoscopy identifies benign adenomatous polyps in approximately 20% of individuals, advanced adenomatous polyps in approximately 6%, and colorectal cancer in just over 1% (4).

Prediction of the presence of carcinoma in a polyp and the carcinoma invasion depth is challenging in endoscopy. Risk modeling can be performed according to pathologic examination or/and endoscopic appearance. The Haggitt level system and Kikuchi classification have been based on pathologic features to reveal the carcinoma invasion depth into colonic layers. The endoscopic appearance of an unresectable polyp can vary from benign appearance to high suspicion of malignancy. The Kudo pit pattern and Paris classifications are based on the endoscopic view in predicting carcinoma invasion depth, supported with dye assistance or image-enhanced methods, according to morphologic features (5). Likewise, assessments of surface and vascular patterns can be used to predict lesion histology and, in particular, assess for areas of early invasion (6).

Furthermore, difficult access, the presence of scarring, and location close to the dentate line, appendical orifice, ileocaecal valve, or diverticula can make resection very challenging, and resection of these difficult polyps requires techniques beyond simple polypectomy and also poses new risks of complications. Irrespective of the experience of the endoscopist, up to 15% of polyps cannot be resected completely due to polyp size, location, features, and patient-specific conditions and it requires surgical resection (7-9).

The present study aimed to investigate colorectal polyps that were technically unsuitable for endoscopic removal, reveal potential risk factors to predict invasive CRC and define the management of these unresectable polyps.

MATERIAL and METHODS

Study design and study population

This retrospective case-control study of patients with polyps was conducted at Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, Surgical Endoscopy Unit between May 2010 and January 2019. Four thousand eight hundred eighty-six polyps from 3822 of 16,996 colorectal endoscopies were analyzed.

The evaluation of polyps was performed according to the following methods:

- Polyp size
- Polyp morphology
  - Paris classification (protruding, flat elevated, flat lesions)
  - Lateral spreading (granular, non-granular)
- Polyp surface pattern (Kudo neoplastic polyp classification)
- Non-lifting sign
- Endosonography (EUS)

The above methods were preferred based on the endoscopists' decision; not all were used in the evaluation of the same polyp. EUS was used to examine the polypectomy margin of suspicious polypectomies in the assessment of invasion depth in incompletely resected pedunculated or sessile polyps. In addition, EUS was used to evaluate the invasion depth of flat lesions with suspicious other lesion features, especially in the distal colon and rectum.

Histopathologically, the Japan NBI Expert Team (JNET) classification, which has a range from carcinoma-free or intramucosal neoplasia to carcinoma with deep submucosal invasion, and which also examines vessel patterns, was used to evaluate polyps.

Submucosal invasion was evaluated according to EUS findings, and through histopathologic examinations, if possible, in incomplete polypectomy specimens of pedunculated or sessile lesions, or non-curative endoscopic mucosal resection/endoscopic submucosal dissection (EMR/ESD) specimens (1,2).

After the initial evaluation, standard polypectomy procedures were performed in line with the surgical endoscopy unit algorithm of our center, including hot biopsy for polyps ≤5 mm, and snare polypectomy for polyps >5 mm. Snare polypectomy was performed with additional submucosal injections for large and sessile polyps.

EMR has been preferred for <30 mm pedicle polyps, <20 mm non-granular/non-depressed flat lesions, or granular lesions since 2012. Generally, EMR was skipped in the ulcerated, depressed, or deep submucosa-infiltrated (by EUS) lesions. ESD has been initiated to be performed as of 2015, in cases where polyps have these features above-mentioned that would not be preferred for EMR and also if the polyp sizes are relatively larger.

Although based on physicians' experience, surgical resection was considered primarily because of the following characteristics of a polyp;

- for laterally (around) more than two-thirds of the intestine covering polyps,
- laterally (around) more than two-thirds of the intestine covering polyps,
- polyps extending longitudinally on two consecutive haustral folds,
- polyps extending to the appendix, diverticulum, through the ileocecal valve,
- lifting-sign negative polyps,
- polyps highly suspected of invasive CRC based on their morphological features of surface pattern,
- according to EUS findings, polyps with deep submucosal invasion especially located in the distal colon and rectum.

In addition, histopathologically, surgical resection was performed under the following conditions;

- cancer at the polypectomy resection margin of <2mm,
- if deep submucosal invasion is present in polyps that cannot be completely resected by polypectomy,
- if deep submucosal invasion is present in non-curative EMR/ESD specimen.

The flow chart of the approach to colorectal polyps is summarized in Figure 1.

In the study, endoscopically resectable (n=4751) and unresectable single polyps (n=135) that could be surgically resected were examined separately. Unresectable polyps were evaluated in two groups. In the first group, some polyps could not be curatively resected through EMR or ESD (n=47). The second group consisted of polyps that were incompletely resected with standard polypectomy that were decided to undergo surgical resection, and polyps that were determined to be unsuitable for any endoscopic removal by endoscopic evaluation and were decided for surgical resection (n=88).

Invasive CRC (T1-T2) was defined as residual T1-T2 cancer in the surgical resection specimens of patients who underwent surgical resection after incomplete polypectomy or non-curative EMR/ESD, or T1-T2 cancer in the surgical resection specimens of patients who underwent surgery primarily.

All patients were informed about the diagnostic and therapeutic procedures, and written informed consent was obtained. The study protocol was approved by the Istanbul Faculty of Medicine Ethics Committee (Date: 17.12.2010, No: 09).

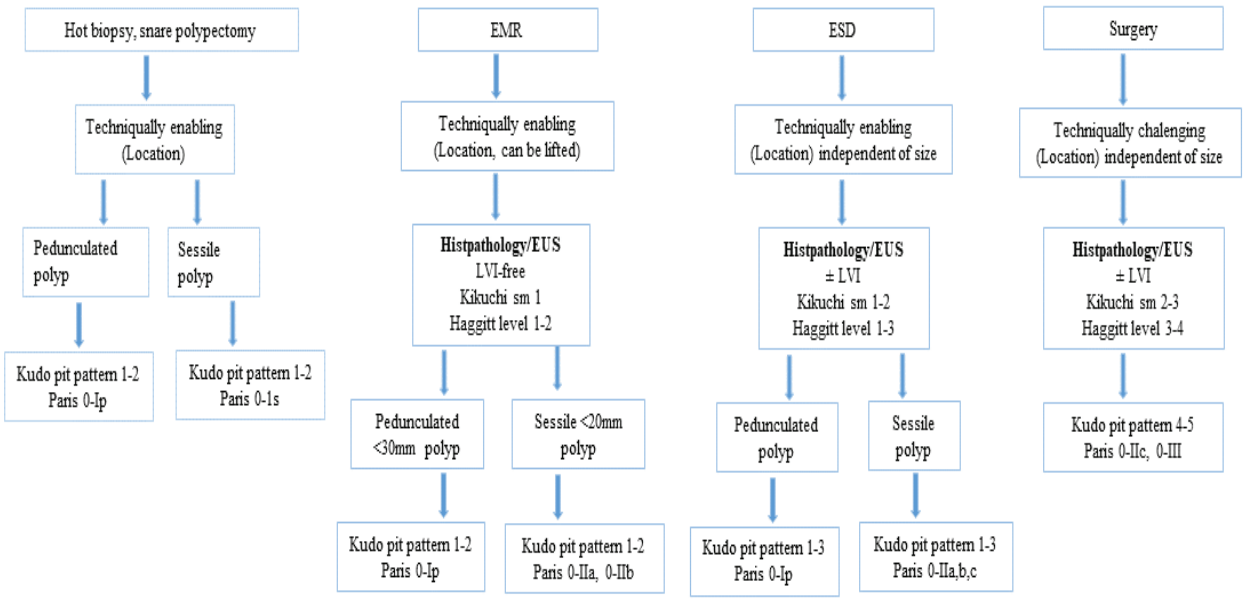

Figure 1: Flow-chart of the study.
EMR: Endoscopic mucosal resection, ESD: Endoscopic submucosal dissection, EUS: Endosonography, LVI: Lymphovascular invasion

Statistics

Descriptive statistics of the quantitative variables in the study are given as numbers and percentages. Pearson's Chi-square test was used for comparisons between groups in terms of the incidence of categories of the relevant qualitative variable. The conformity of the numerical variables to normal distribution was examined using the Shapiro-Wilk test. Student's t-test (independent sample t-test) was used to compare the mean values of two independent groups, and the Mann-Whitney U test was used to compare the median values of two independent groups. Variables that were significant as a result of univariate analyses were included in multivariate analyses, and binary logistic regression analysis was performed. Model explanatory power was examined using the Nagelkerke R square value, and the fit of the model was examined using the Hosmer and Lemeshow test. The agreement between the predicted values obtained as a result of binary logistic regression, and the observed values was examined using the kappa coefficient and accuracy rates were obtained. The statistical significance level was taken as 0.05. The SPSS (version 28) package program was used in the calculations.

RESULTS

Unresectable polyps were usually larger than resectable polyps (p<0.001). Localization of colorectal polyps in the ascending colon and the cecum made endoscopic resection more complicated than in the other parts of the colon (p<0.001). The resectability was independent of the presence of villous features in a polyp (p=0.315). Dysplasia (low/high-grade) was detected in preoperative biopsies with a higher frequency in unresectable polyps than in resectable polyps (p<0.001). Invasive cancer rates of unresectable and resectable polyps were 26.7% and 1.7%, respectively (p<0.001). Table 1 presents the factors affecting the resectability of colorectal polyps and the detected in-situ invasive cancer rates in colorectal polyps.

The frequency of invasive CRC in unresectable colorectal polyps increased with the increase of the age of patients (p=0.014), but it was independent of the patient's sex (p=0.846). The mean size of invasive CRC-infiltrated polyps was significantly larger than invasive cancer-free polyps (p=0.012). The potential to contain invasive CRC was greater in the sigmoid colon and rectum-located polyps (p=0.001). Underlying villous features (p=0.331) and dysplasia (p=0.057) were not effective in developing invasive CRC. Deep submucosal invasion was detected in the pathologic examinations of incomplete polypectomy specimens of two patients and non-curative EMR or ESD specimens of 14 patients. In addition, deep submucosal invasion was demonstrated in EUS examinations of eight patients with distal colon and rectum-located polyps. Deep submucosal invasion (p<0.001) and current LVI (p<0.001) were predictive factors for invasive CRC involvement. Unresectable polyps requiring surgery after non-curative EMR or ESD were found to have a significantly higher risk of invasive CRC involvement compared with polyps that underwent surgical resection primarily (p=0.002). Lymph node spread was detected in the surgical specimens of 6 of all unresectable polyps. Two of these were polyps with cancer invading the deep submucosa, but in which the cancer invasion was limited in the submucosa. Factors associated with invasive CRC involvement are given in Table 2.

The significant associations and potential risk factors in predicting invasive CRC are summarized in Table 3. Overall, polyp size, location, the presence of lymphovascular invasion, and management path were not associated with the development of invasive CRC. However, advancing age (p=0.010) and deep submu-

Table 1: Technical and histological factors affecting resectability and detected cancer frequency

Total=4886		**Resectable polyps n (%)=4751**	**Unresectable polyps n (%)=135**	**p**
Size, mm (mean, std. deviation) *		18.8 (6.3)	50.2 (6.7)	<0.001
Location of the polyp	Rectum, sigmoid colon	1963 (42.3)	30 (22.2)	<0.001
	Descending, transverse colon	1481 (31.2)	36 (26.7)	
	Ascending colon, cecum	1307 (27.5)	69 (51.1)	
Underlying villous features	Absence	3757 (79.1)	104 (77.0)	0.315
	Presence	994 (20.9)	31 (23.0)	
Dysplasia		661 (13.9)	97 (71.9)	<0.001
Invasive cancer-free		4499 (94.7)	99 (73.3)	<0.001
T1-2		82 (1.7)	36 (26.7)	

* Mann Whitney U test, Chi-square test (Pearson Chi-square, continuity correction, Fisher's exact test)

Table 2: Preoperative potential risk factors to predict invasive cancer in an unresectable colorectal polyp

		Invasive cancer-free n (%)=99	T1-2 n (%)=36	p
Age (mean, std. deviation) *		52.1 (7.0)	55.7 (7.9)	0.014
Female, n (%)		50 (50.5)	17 (47.2)	0.846
Male, n (%)		49 (49.5)	19 (52.8)	
Size mm (mean, std. deviation) **		49.0 (7.6)	53.3 (10.7)	0.012
Polyp location	Rectum, sigmoid colon	18 (18.2)	18 (50.0)	0.001
	Descending, transverse colon	32 (32.3)	8 (22.2)	
	Ascending colon, cecum	49 (49.5)	10 (27.8)	
Underlying villous features	Absence	52 (52.5)	15 (41.7)	0.331
	Presence	47 (47.5)	21 (58.3)	
Dysplasia	No	32 (32.3)	6 (16.7)	0.057
	Low-grade	38 (38.4)	12 (33.3)	
	High-grade	29 (29.3)	18 (50.0)	
Deep submucosal invasion		2 (2.0)	22 (61.1)	<0.001
LVI		9 (9.1)	17 (47.2)	<0.001
Non-curative EMR/ESD > SR		27 (27.3)	20 (55.6)	0.002
Primary surgery		72 (72.7)	16 (44.4)	

* Independent sample t-test, ** Mann Whitney U test, Chi-square test (Pearson chi-square, continuity correction, Fisher's exact test), LVI: Lymphovascular invasion, SR: Surgical resection

Table 3: Multivariate logistic regression analysis

	OR	Signature	95% C.I. for EXP(B)	
			Lower	Upper
Age	6.68	0.010	1.03	12.5
Size	0.87	0.722	0.82	1.12
Polyp location	0.78	0.676		
Polyp location *	0.80	0.841	0.74	0.96
Polyp location **	0.49	0.483	0.045	0.88
Deep submucosal invasion (1)	9.68	0.002	4.37	66.78
LVI (1)	2.08	0.149	1.86	2.19
Primary surgery (1)	0.57	0.447	0.396	0.82
Nagelkerke R Square		0.643		
Hosmer and Lemeshow Test		0.944		

* Rectum, sigmoid colon and descending, transverse colon, ** Descending, transverse colon and ascending colon, cecum, LVI: Lymphovascular invasion

cosal invasion (p=0.002) were significantly associated with invasive CRC. It was determined that the established binary logistics model had a good fit (p=0.944) for Hosmer and Lemeshow, and the model was determined to be significant according to Nagelkerke R square (p=0.643). The accuracy rate of the model was 89.6% ((97+24)/135). The kappa coefficient value for the agreement between the predicted value and the observed values was calculated as 0.71.

DISCUSSION

Colonoscopy is the current standard procedure in the screening of possible premalignant lesions located in the

colon and rectum. Colonoscopy could allow diagnosis of these colorectal lesions with a biopsy as well as total excision of suspicious lesions. Although total excision of large polyps is possible through colonoscopy, removal of sessile polyps with lateral extension, very large polyps, or polyps located in the right colon may be more complicated. (10,11).

In previous literature, CRC frequency has been estimated to range from 4.6% for polyps larger than 1 cm, and up to 56% for polyps larger than 2 cm (12). Muto et al. reported that 17% of total polyps were larger than 2 cm, and CRC was detected in 46% of these polyps in their study. The study concluded that large polyp size, polyps containing villous histology, and cellular atypia were effective in developing invasive CRC (13).

Another study from Shinya et al. reported a 10.8% CRC frequency in excised large polyps. This study also revealed similar risk factors for CRC involvement in polyps larger than 2 cm. In addition, they determined that polyps located in the distal colon were associated with an increased risk of CRC (14). These opinions are supported by our similar findings of increased CRC risk with large polyp size and with distal colon polyp location; however, they conflict with the increased risk of malignancy with the presence of villous formation. McDonald et al. examined the cancer risk in 100 surgically-removed endoscopically unresectable colorectal polyps, and again, large polyp size was associated with CRC, which is in line with our present study (15).

Alder et al. reported a CRC frequency of 16%. In their study, they found that unresectable polyps were more often located in the right colon, but localization in the distal colon might probably increase the risk of CRC in a polyp. However, as a counter-opinion to our study, they claimed that polyp size was an independent factor in the occurrence of CRC (16). Despite the known relationship between left-sided lesions and increased CRC rate, our overall low rate of cancer might be explained by the fact that more than 75% of unresectable polyps were in the other parts of the colon.

In light of these reported different invasive cancer frequencies, in our study, the rate of invasive CRC in unresectable polyps was estimated as 36/135 (26.7%). Ninety-seven (97.7%) polyps were identified as containing dysplasia and 24 (17.8%) had deep submucosal invasion identified in preoperative evaluations. As is known, the malignancy risk of CRC increases with increased age, and, in line with this, the risk of malignancy in an unresectable polyp also increases with increased age. Possible factors that may predict the development of CRC in an unresectable polyp were also examined in the study. Accordingly, villous features and dysplasia were found not to be effective in CRC development in unresectable polyps, and deep submucosal invasion was determined as an independent risk factor.

Worldwide, EMR/ESD has become the recent standard practice in managing early-stage CRC. Although EMR is easier and more reliable, it may cause more recurrence or provide less en-bloc or curative resection when compared with ESD. Many studies reported that these endoscopic advanced polyp removal methods were feasible, and reported endoscopic resection results with less morbidity when compared with surgical resection (17). The present study also aimed to investigate the potential of residual invasive CRC after unsuccessful endoscopic resections. CRC was detected more frequently in surgical resection specimens after non-curative advanced endoscopic resection attempts than in specimens of patients who underwent surgery primarily. This finding has been interpreted in a way that avoiding further next endoscopic resection attempts would be a more appropriate approach in this issue.

LVI describes the detection of tumor cells in the lymphatic system within the tissue. Al-Sukhni et al. and Huh et al. reported that LVI was significantly associated with the depth of cancer invasion (18-20). Several studies tried to determine the role of the presence of LVI or perineural invasion in adjuvant therapy (21,22). The present study revealed that LVI had an important role in predicting invasive carcinoma in unresectable polyps; however, although the study did not aim to investigate the effect of LVI in adjuvant therapy, it still revealed a significant association with the prediction of CRC.

It has long been thought that infiltration of tumor cells into the lower third of the submucosa is associated with an increased risk of a lymphatic spread rather than only mild penetration (23). According to evidence from previous patient series, a lymph node metastasis rate of up to 23% has been reported in polyps with deep submucosal invasion by cancer (24). In this study, lymph node spread was detected in the surgical specimens of 6 of all unresectable polyps. Two of these were polyps with cancer invading the deep submucosa, but in which the cancer invasion was limited in the submucosa. Although 2 lymph node spread was detected in the histopathologic examination of cancers with submucosa-limited invasion, no significant association between submucosal invasion and lymph node metastasis was revealed.

The presence of a stalk and the location of the polyp are the main determinants of a successful polypectomy. The polyp location should be tattooed according to the local protocol with a specific reagent containing carbon particles if surgery is considered (25). If a polyp is unsuitable for polypectomy, a biopsy provides no scientific value to the endoscopist. Of note, biopsy results may lead to suboptimal management in 8% of patients (26).

There are some limitations in the study that should be addressed. First, due to being a retrospective case-control study, it does not offer exact prospective standardized criteria for further treatment, but only recommendations. For example, right-sided polyps can be considered technically more difficult to remove, leading to a change in selection criteria. In addition, the differences between the size of the polyp determined by the endoscopic appearance and the size in the definitive pathologic examination may cause confusing interpretations in predicting invasive carcinoma. Furthermore, the level of experience in interventional endoscopy may differ in all institutions. Also, more advanced endoscopic or microinvasive techniques that have been used in the clinic have not been included in the study due to the relatively small number of applications. As another limitation of the study, the rate of colorectal cancer in complex colon polyps has been found as 10-15% in the literature, but there are no polyps that can be resected with advanced endoscopic techniques in these studies (27,28). In our study, the rate of invasive CRC was found in unresectable polyps with a high rate of 26.7%. However, in our study, analyses of polyps that could be resected with advanced techniques were not included, and when these outcomes were added, CRC rates in complex polyps were determined to be similar to the ones in the literature.

CONCLUSION

It may be extrapolated that EMR/ESD is a safe and feasible method to remove early-stage CRC-containing polyps or for resection of benign polyps that have been decided to be endoscopically unresectable. However, after non-curative EMR/ESD procedures, more attention should be paid due to the relatively high risk of CRC.

Unresectable polyps are more prone to CRC involvement than resectable polyps. The presence of LVI and deep submucosal invasion should be considered carefully to predict CRC. However, more importantly, oncologic surgery for polyps with deep submucosal invasion (particularly by EMR or ESD) that cannot be endoscopically resected in older patients should be considered carefully and, perhaps, without delay, primarily by abandoning repeated endoscopic resection attempts.

Ethics Committee Approval: This study was approved by Istanbul University, Istanbul Faculty of medicine Clinical Research Ethics Committee (Date: 17.12.2010, No: 09).

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