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Original Article

New Classification of Benign Epithelial Tumors: Colorectal Polyps and Synchronous Neoplasms: An Update and Critical Assessment: An Analysis of 678 Consecutive Cases and 1137 Polyps

Benign Epitel Tümörlerin Yeni Sınıflandırması: Kolorektal Polipler ve Senkron Neoplazmlar: Bir Güncelleme ve Kritik Değerlendirme: 678 Ardışık Olgu ve 1137 Polip Analizi

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ABSTRACT

Objective: We aimed to evaluate of colorectal high-risk polyps and synchronized neoplasms and carcinomas with anatomical localization and demographic characteristics.

Methods: Between July 1, 2018 and July 1, 2022, 1137 polypectomy materials of 678 consecutive patients who were diagnosed in the pathology department and underwent total colonoscopy were included in the study. All epithelial polyps were re-classified according to the World Health Organization classification of digestive system tumors-2019, 5th edition.

Results: The cases of 60.5% were male and 39.5% were female. The mean age of patients with polyps was 61.1 (±11.1) years. There was a statistically significant difference between the presence of gender and all epithelial polyps (p=0.044). Epithelial polyps were more common in men than in women (ratio; male/female 1.58:1). While the average size of the polyps was 5.2 (±5.08) millimeters (mm), 86.6% of all polyps were smaller than 10 mm. Solitary polyps were observed in 62.5% of all polyps, and multiple polyps were observed in 37.5%. Epithelial polyps constituted 96% of all polyps, and conventional tubular adenoma (69%) was the most common type of polyp. Advanced adenomas (intramucosal adenocarcinomas, polyp cancer) and synchronous adenocarcinomas were found to be 1.4% (16 polyps) and 0.9% (6 patients) respectively. Polyps were most frequently observed in the sigmoid colon, with a rate of 22.8%, followed by the descending colon and rectum most frequently. There was a significant association between epithelial polyps and anatomical locations (p<0.001).

Conclusions: In conventional colorectal adenomas, the frequency of co-occurrence of synchronous neoplasms is higher than in other polyp types.

Keywords: Adenoma, dysplasia, intramucosal carcinomas, tubular

ÖZ

Amaç: Kolorektal yüksek riskli poliplerin ve senkronize neoplazm ve karsinomların anatomik lokalizasyonu ve demografik özellikleri ile değerlendirilmesi amaçlanmıştır.

Yöntemler: 1 Temmuz 2018 ile 1 Temmuz 2022 tarihleri arasında patoloji bölümünde tanı konulan ve total kolonoskopisi yapılan 678 ardışık olguya ait 1137 polipektomi materyali çalışmaya dahil edildi. Tüm epitelyal polipler Dünya Sağlık Örgütü sindirim sistemi tümörleri sınıflandırması-2019, 5. baskıya göre yeniden sınıflandırıldı.

Bulgular: Çalışmada 678 olgunun %60,5'i erkek, %39,5'i kadındı. Polipli hastaların ortalama yaşı 61,1 idi. Cinsiyet ile tüm epitelyal poliplerin varlığı arasında istatistiksel olarak anlamlı bir fark vardı (p=0,044). Epitelyal polipler erkeklerde kadınlardan daha yaygındı (oran; erkek/kadın 1,58:1). Poliplerin ortalama boyutu 5,2 milimetre (mm) iken, tüm poliplerin %86,6'sı 10 mm'den küçüktü. Tüm poliplerin %62,5'inde soliter polipler, %37,5'inde ise multipl polipler gözlendi. Epitelyal polipler tüm poliplerin %96'sını oluşturuyordu ve konvansiyonel tübüler adenom (%69) en yaygın polip tipiydi. İlerlemiş adenomlar (intramukozal adenokarsinomlar, polip kanseri) ve senkron adenokarsinomlar sırasıyla %1,4 (16 polip) ve %0,9 (6 hasta) olarak saptandı. Polipler en sık %22,8 oranıyla sigmoid kolonda görüldü ve bunu en sık inen kolon ile rektum izledi. Epitelyal polipler ile anatomik lokalizasyonlar arasında anlamlı bir ilişki saptandı (p<0,001).

Sonuçlar: Konvansiyonel kolorektal adenomlarda premalign ve malign değişiklikler ile senkronize neoplazmların oranı yüksektir.

Anahtar kelimeler: Adenom, displazi, intramukozal karsinomlar, tübüler

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INTRODUCTION

Colorectal cancer (CRC) remains a major public health and surgical problem despite current screening programs. CRC is the third most common cancer in Western countries and the second leading cause of cancer-related death. If diagnosed early, the prognosis improved significantly. For a long time, CRC was thought to develop from benign colorectal polyps. It was found that approximately 17% of cancers detected in a CRC screening program were polyp cancers. A colorectal polyp or adenoma progression to cancer is directly related to several factors such as characteristics, histological morphology, degree of dysplasia, and size of the polyp[1,2]. The development of flexible sigmoidoscopy and colonoscopy has brought great relief, especially in the removal of polypous lesions, which are detected and removed endoscopically. However, the incidence of colorectal polyps may vary by country or region. The incidence of adenomas in asymptomatic cases is about 10% with sigmoidoscopy and 25% with colonoscopy[3]. Colon polyps are now reclassified with the new updated edition of the World Health Organization (WHO) Classification of Tumors; Tumors of the Digestive System, 5-2019. Accordingly, they have been classified as inflammatory polyps, hamartomatous polyps, benign epithelial tumors and precursors, mesenchymal polyps, and miscellaneous polypoid lesions. Specifically for epithelial neoplastic polyps, concepts such as benign epithelial tumors and precursors, sessile serrated lesion (SSL), and an advanced adenoma (also available in WHO-2010, more detailed in this issue) were developed[4-6].The uneven use of histological criteria and uncertainty in clinician follow-up or patient care are results of ongoing terminological changes. In this study, we sought to determine the prevalence of adenomatous polyps among sporadic CRCs via the adenoma-carcinoma pathway or the risk of synchronous adenocarcinoma, as well as the demographic characteristics of the patients and the histological lineage of the polyps, the localization of these polyps in the colon, and their interrelationships. With the release of the WHO tumor classification 5th edition, the development of tumors or lesions of the digestive system will be updated and critically evaluated (Table 1).

MATERIALS and METHODS

Case Selection and Histologic Evaluation

In a study involving human participants, all necessary procedures were performed by ethical standards, with University of Health Sciences Turkey, Umraniye Training and Research Hospital Clinical Research Ethics Committee approval (decision no: 203, date: 23.06.2022), and covering the 1964 Declaration of Helsinki and subsequent amendments. This study excludes any experiments on animals. Available hematoxylin and eosin preparations and immunohistochemistry slides (if available) of 1137 colorectal polyps from 678 patients who underwent colonoscopic polypectomy between July 1, 2018, and July 1, 2022, at the Department of Pathology, University of Health Sciences Turkey, Umraniye Training and Research Hospital, Istanbul were retrospectively reviewed. Epithelial polyps or lesions were divided into two main categories as benign epithelial tumors and precursors and malignant epithelial tumors, considering the WHO classification of digestive system tumors-2019, 5th edition. Polyps associated with inflammatory bowel disease, familial adenomatous polyposis, patients under 18 years of age, and polyps incidentally detected in the colon and rectal resection specimens were excluded from the study. Other detected polyps; It was classified as inflammatory polyps (inflammatory pseudopolyp, mucosal prolapse changes/polyps, inflammatory cap polyp, etc.) and mesenchymal polyps (leiomyoma of the muscularis mucosae, lipoma, etc.).

Statistical Analysis

These histopathological groups were statistically analyzed based on the WHO diagnostic criteria. Analysis using the McNemar test to determine whether the type,

Table 1. World Health Organization classification of tumours of the colon and rectum-2019.

A. Benign epithelial tumours and precursors
A.1. Colorectal serrated lesions and polyps
Hyperplastic polyp; Hyperplastic polyp, microvesicular type Hyperplastic polyp, goblet cell-rich type
Sessile serrated lesion; Sessile serrated lesion with dysplasia
Traditional serrated adenoma
Serrated adenoma, unclassified
A.2. Conventional colorectal adenoma
Tubular adenoma, low grade Tubular adenoma, high grade
Villous adenoma, low grade Villous adenoma, high grade
Tubulovillous adenoma, low grade Tubulovillous adenoma, high grade
Advanced adenoma
B. Malignant epithelial tumours
B.1. Adenocarcinoma
B.2. Neuroendocrine neoplasms

number, size, and localization (distal or proximal) of polyps detected in each person differed, the Pearson χ^2 or the Fisher's Exact test for the relationship of polyps with sex, and patient age was analyzed using Student's t-test as a continuous variable. SPSS version 22 was used for statistical analysis (SPSS Statistics for Windows; IBM, Armonk, New York, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

Histologic, Demographic, and Anatomic Distribution Data of Colonic Polyps

In 678 patients studied between July 1, 2018, and July 1, 2022, 1137 polypectomy materials were evaluated in the benign epithelial tumors and precursor morphology and coexistence with polyps. Of the 678 cases included in our study, 60.5% (410/678 cases) were men and the remaining 39.5% (268/678 cases) were women. This resulted in a male-to-female ratio of approximately 1.5:1. The age of the patients ranged from 26 to 89 years with a mean age of 61.15±11.12 years. The group with the lowest incidence of polyps in patients aged 40 years and younger with 4.7% (32/678). While the mean age of SSLs was 59.8 (±10.9) years, the mean age of conventional colorectal tubular adenomas (TAs) was 61.4, and the mean age of malignant lesions was 64.5. There was a statistically significant relationship between gender and epithelial polyps (p=0.044).

Table 2. Demographic and clinicopathologic features colorectal polyps.

Age (year, mean ± SD)	61.15	±11.12
Gender, n (%)		
Male	410	60.5
Female	268	39.5
Polyp size (mm, mean ± SD)	5.2	±5.08
A. Benign epithelial tumours and precursors (WHO-2019)	n	%
	1091	96
A.1. Colorectal serrated lesions and polyps		
Hyperplastic polyp;	197	17.3
Sessile serrated lesion; Sessile serrated lesion with dysplasia	24	2.1
Traditional serrated adenoma	7	0.6
Serrated adenoma, unclassified	1	0.1
A.2. Conventional colorectal adenoma		
Tubular adenoma, low grade	785	69
Tubulovillous adenoma, low grade	54	4.7
Villous adenoma, low grade	7	0.6
Advanced adenoma (intramucosal adenocarcinoma)	16	1.4
B. Other polyps or lesions		
Inflammatory polyps	33	2.9
Inflammatory pseudopolyp	29	2.55
Prolapse-type inflammatory polyp	2	0.17
Inflammatory cap polyp	2	0.17
Mesenchymal polyps	13	1.14
Lipoma	4	0.35
Leiomyoma of the muscularis mucosae	6	0.52
Fibrolipoma	2	0.17
Angiolipofibroma	1	0.08
Total	1137	100

WHO: World Health Organization, SD: Standard deviation

Polyp sizes ranged from 0.5 millimeters (mm) to 52 mm, with an average polyp size of 5.2 mm. The size of 86.6% of all polyps was less than 10 mm, 72.4% of polyps were 5 mm or less (diminutive), 14.2% were between 6 and 9 mm (small), 13.4% of polyps of them were 10 mm, and larger (large). Of the 1137 colorectal polyps, 62.5% (n=424 patients) were solitary, and remaining 37.5% (n=254 patients, an average of 2.8 polyps) were multiple. Ninety-six percent of polyps were epithelial; inflammatory polyps accounted for 2.9%, and mesenchymal polyps accounted for 1.1% (Table 2).

The distribution of all epithelial polyps was as follows: TA was the most common epithelial polyp observed, accounting for 69% (785 polyps) (Figure 1, 2, 3); the second most common polyp was a hyperplastic polyp, accounting for 17.3% (197 polyps); the rate of advanced adenomas (intramucosal adenocarcinomas) was 1.4% (16 polyps), and the rate of synchronous adenocarcinomas was 0.9% (6 patients). Polyps were most frequently detected in the sigmoid colon, with a rate of 22.8% (259 polyps), 16.5% (188 polyps) in the descending colon, and 16% (182 polyps) in the rectum (Table 3). There was a significant association between epithelial polyps and anatomical locations (p<0.001).

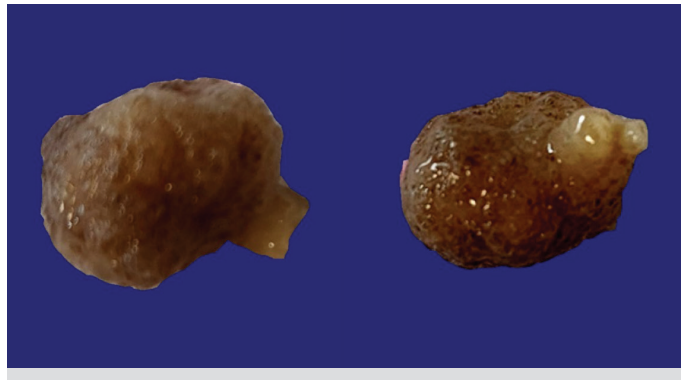

Figure 1. Gross appearance of a pedunculated villous adenoma with head and stalk.

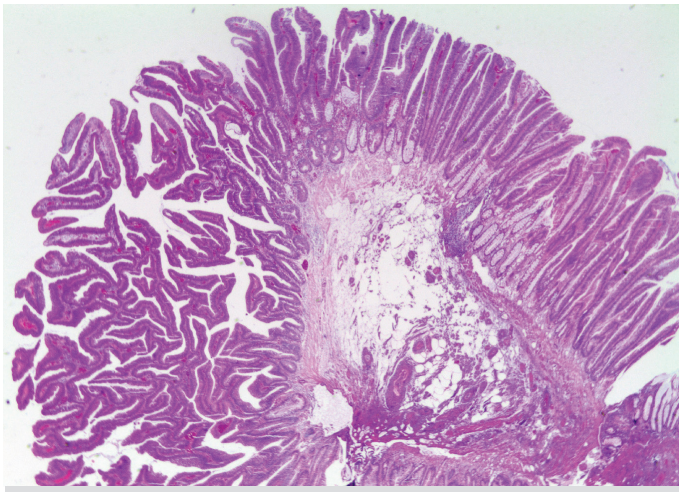

Figure 2. Microscopic appearance of the villous adenoma;consists of finger-like fronds, usually nonbranched, into the lumen of the colon parallel to the muscularis mucosa (H&E).

H&E: Hematoxylin and eosin

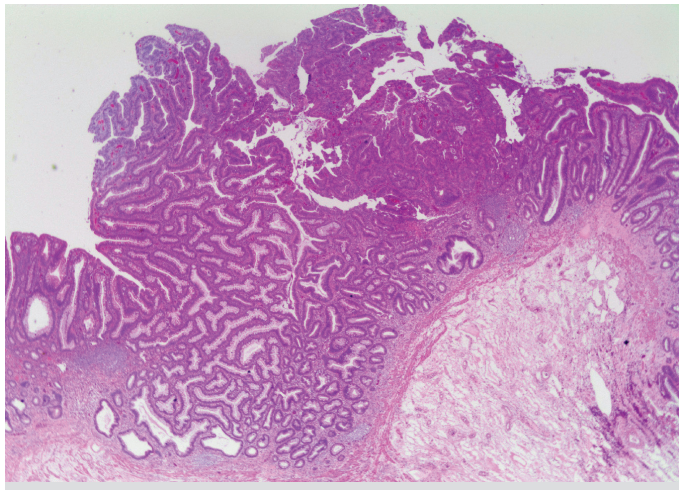

Figure 3. Microscopic appearance of the advanced adenomas (intramucosal adenocarcinomas, polyp cancer); adenomas that invade (but not beyond) the mucosa or muscularis mucosa (H&E).

H&E: Hematoxylin and eosin

DISCUSSION

In the United States, it is estimated that 106,180 individuals will be diagnosed with colon cancer in 2022, 44,850 people will have rectal cancer, and 52,580 people will pass away from the disease (USA). While 20-53% of the general population may have colon adenomas, advanced histological characteristics are between 3.4% and 7.6% of cases, and adenocarcinomas are predicted to be between 0.2 percent and 0.6 percent, around 15% of individuals with colon cancer are seen before the age of 50. The incidence has been observed to reduced by around 2% per year in persons aged 50 and over because of widespread screening program; however, in younger people, the incidence grows by 1.5 percent per year, despite the lifetime risk in the USA being estimated to be 5%[7,8]. Especially elderly people are at risk for both adenomas and carcinomas. However, the rate of newly diagnosed CRC in the population under the age of 50 has increased by approximately 15%. In an autopsy study, it was reported that the prevalence of adenoma increased to approximately 3.59% in the fifth decade compared to other young decades, and the rate of large polyps and advanced adenomas was between 2% and 5.6% at the age of 40 to 49 years[8,9]. It has been reported that the prevalence of adenoma and the relationship with cancer show geographical-cultural changes, differ in studies conducted in the past years and varied from 1.6% to 62%[10-12]. In a study standardized by age and gender in the literature, it was reported that the prevalence of adenoma is approximately 15% between the ages of 13-89, it is seen more in men than in women, and the rate of adenoma increases with age[12]. As mentioned earlier, adenoma development is age-related but also associated with the male gender. Especially, men develop adenomas more frequently than women, and the mean age at diagnosis has been reported as 62. It increased by 21%, especially in the sixth and eighth decades[13]. Among the cases included in our study, the mean age of SSLs was 63.6, and the mean age of conventional TAs was 61.6. Our findings is consistent with the literature. We found that approximately 86.7%

Table 3. The anatomical distribution of polyps/lesions in colon and rectum.

Polyps/lesions site in the colon	n	%
Proximal colon	455	40.1
Distal colon	682	59.9
Total	1137	100
Cecum	59	5.2
Ileocecal valve	2	0.2
Ascending colon	158	13.9
Hepatic flexure	59	5.2
Transverse colon	177	15.6
Splenic flexure	33	2.9
Descending colon	188	16.5
Sigmoid colon	259	22.8
Rectosigmoid region	20	1.8
Rectum	182	16.0
Total	1137	100

(52 cases) of epithelial polyps observed between the ages of 40 and 49 were composed of conventional adenomas, whereas the incidence of intramucosal adenocarcinoma was 5% (3 cases) in this age range. Our findings are consistent with the literature due to both the mean age at diagnosis of adenomas and male predominance. At the beginning of the basic principles of risk, guidelines are to place the cases in risk classification according to their initial findings. Since this surveillance scheme considers the possibility of progressive malignancy; low-risk adenomas are cases smaller than 10 mm, with 1-2 TAs, high-risk adenomas are advanced adenoma [≥10 mm, tubulovillous or villous architecture, and/or high-grade dysplasia (HGD)] or intramucosal adenocarcinoma) and cases with 3 or more adenomas[4,14]. Polyp size has been found to be closely related to malignant change, but an invasive malignancy can be detected in polyps smaller than 1 cm[15]. The incidence of advanced adenomas is higher in cases with multiple adenomas, and observational findings have been reported that adenomas smaller than 1 cm grow consistently over a 3-year interval[16]. In a study, approximately 4.4% of diminutive adenomas showed high-risk histological features, while this risk was found to be 15.6% in small adenomas between 6 and 10 mm, and the cancer rate in both groups was 0.1% and 0.2%, respectively[17]. Our findings are closely related to the results in the literature. In addition to low-grade dysplasia findings in approximately 4.4% of all cases, HGD in focal foci, pure HGD in one case, and advanced adenoma findings in 1.5% of all epithelial polyps were observed. We found 50% of our cases with intramucosal adenocarcinoma (IMAC) ≥10 mm in size, and IMAC were observed in approximately 1.3% of all diminutive polyps. While studies have revealed that sporadic adenomas are mostly seen in the rectosigmoid region, in the follow-up of these patients, the frequency increases in the right or proximal colon, but the frequency of adenoma in the proximal colon increases with age. Polyps of the left colon are more common in young patients and polyps of the right colon in patients over 65 years of age[13,18]. In an autopsy study, it was reported that half of all adenomas were localized in the rectum and sigmoid colon until the age of 69, and solitary adenomas and multiple polyps in the left colon showed an equal distribution in all colon segments[12]. In our study, most of the epithelial polyps (59.9%) were observed in the distal colon. The incidence of epithelial polyps in patients aged 60 and over was 40.1%. The incidence of the cases in our study in the distal colon or left colon is higher with age, which differs from the literature. It has been reported that synchronous adenomas are observed in approximately 40%-50% of the cases with adenoma. However, some autopsy and colonoscopic studies have reported that colorectal neoplasms develop at rates ranging from 20% to 61% of patients. In the study of Tripp et al.[19], it was shown that synchronous adenoma was detected in 75 cases (47%) and synchronous invasive carcinoma was detected in 8 patients (5%)[18]. In our study, the number of cases with at least two synchronous polyps was 254 (37.4%), the number of cases with at least two synchronous polyps were 108 (15.2%), and we found synchronous invasive carcinoma in 6 (0.9%) of all cases. Our findings are consistent with the results in the literature. SSLs account for 1-2% of all colorectal adenomas, the average age at diagnosis is 63, and lesions larger than 10 mm often appear in the right colon. Apparently, certain serrated lesions have isolated foci of HGD, and even 11% of them progress to intramucosal carcinoma[13]. In our study, the incidence of SSLs was 2% among all colorectal polyps, and the mean age at diagnosis was 63, and half of it was observed in the right colon, which is compatible with the literature. Among all serrated lesions, one accompanying synchronous carcinoma (0.6%) and one intramucosal adenocarcinoma (0.6%) case were detected. The adenoma-carcinoma sequence (molecular evidence of cancer development from adenomas) identified for colon polyps forms the basis for our understanding of progression from normal colonic mucosa to adenomas of any size and even cancer. It has been accepted that colorectal adenomas are the precursor lesions of almost all CRCs. However, although it is difficult to predict which type of polyp will directly progress to carcinoma, removing all polyps detected in colonoscopies will eliminate this risk. In particular, the detection of more than one polyp in some cases has increased the importance of surveillance colonoscopies. Family history, particularly the presence of polyps larger than 10 mm, those with three or more adenomas, and the presence of microscopic HGD are important risk factors. In such cases, the colonoscopic follow-up period can be kept shorter. As we found in our study, there are lesions with histopathologically invasive cancer areas after polypectomy, which is an early detected form of CRC, "so-called polyp cancer," and macroscopically benign in colonoscopy. With the increase in population scans, the recognition and detection of such lesions have increased. Because cases with polyp cancer can be removed endoscopically and are considered curative, their prognosis is excellent[2,20].

There are several limitations in our current study. First, our study was not intended to cover the entire general population, but only included patients who applied to a tertiary care hospital during randomized screenings and without ethnic discrimination. For this reason, care should be taken by considering this situation while making

general judgments about the research. Another limitation was the periodical difference between the colonoscopy times of the patients since it was a retrospective study. The third limitation was that each endoscopist did not know the polyp or adenoma detection rate, sensitivity, and withdrawal times.

CONCLUSION

Premalignant and malignant changes are more prevalent in male patients, conventional colorectal TAs, and polyps larger than 10 mm. Although polyp size, which has long been considered a factor, is particularly important in IMACs (polyp cancer), we also detected carcinomas in polyps smaller than 10 mm in our study. We both recommend and support the establishment of planned surveillance programs for the detection and colonoscopic removal of colorectal polyps as one of the best ways to reduce the incidence of CRC. If there are advanced adenoma findings and 3 to 10 adenomas are detected in cases whose initial evaluation is adenoma, guidelines for surveillance recommend that follow-up colonoscopy be performed every 3 years.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, Umraniye Training and Research Hospital Clinical Research Ethics Committee approval (decision no: 203, date: 23.06.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: A.K., Concept: A.K., Design: A.K., Data Collection and/or Processing: A.K., Analysis and/or Interpretation: A.K., T.Z., Literature Search: A.K., T.Z., Writing: A.K.

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