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ABSTRACT
of the dissertation for the degree of Doctor of Sciences

THE CLINICAL SIGNIFICANCE OF STEM CELLS IN COLORECTAL POLYPS

Speciality: 3213.01 – Surgery
Field of science: Medicine

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MAIN CONTENT OF THE DISSERTATION

Relevancy of the research. Although colorectal polyps are benign tumors that develop from the glandular epithelium of the mucous membrane of the large intestine, they are more likely to develop into malignant tumors. Colonic intestinal polyps can be observed in all age groups, are less common in patients under 40 years of age and more common in patients over 50 years of age estimated in 90% of cases, being one of the most common types of cancer in the developed world [1]. Patients between the ages of 60 and 70 are more likely to develop adenomatous polyps[2]. The risk of developing polyps and tumors increases with age. Colorectal polyps are higher in men compared to women. The association of dysplasia with gender differentiation in colorectal polyps is widely studied. Odds ratio (OR) accounts for 1.20; 95%, confidence interval constitutes (CI) 0.83-1.61[3]. The recent scientific studies suggest that taking non-aspirin nonsteroidal anti-inflammatory drugs (eg, ibuprofen) after resection of colonic polyps may reduce the risk of recurrence[4].

Due to the shape of colorectal polyps, they consist of "pedunculated" and "flat" types. They are divided into the following groups according to their size: diminutive (1-5 mm in diameter), small (6-9 mm) large (> 10 mm), and giant polyps. Giant polyps are larger than 3 cm. As the size of adenomatous polyps increases, so does the risk of cancer. Adenomas 10 mm in diameter and larger are already considered progressive, and those smaller than 10 mm are considered

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[2]Pommergaard HC, Burcharth J, Rosenberg J, Raskov H. Advanced age is a risk factor for proximal adenoma recurrence following colonoscopy and polypectomy. Br J Surg 2016;103:e100-e105

[3]Safiyeva, A.K. Gender disparities in colorectal polyps // Klinicheskaia Khirurgiia, - 2021. v. 88, no 1-2, - p. 57-60. https://doi.org/10.26779/2522-1396.2021.1-2.57

[4]Zhang, Y. A meta-analysis of the correlation between non-steroidal anti-inflammatory drugs and recurrent colorectal adenomatous polyps / Y. Zhang, L. Chen, H. Chen // Am J Transl Res., - 2021. v. 13, no 4, - p. 2432-2438.

highly dysplastic if the villous tissue is more than 25% [5]. Their transition to malignant neoplasms varies depending on the degree of dysplasia, the type of polyp (villous adenoma), and its size. Tubular adenoma constitutes 0-25% villous tissue, 5% risk of cancer, tubulo villous adenoma makes up for 25-75% risk of villous tissue, 20% risk of cancer, villous adenoma is about 75-100% risk of villous tissue, and 40% risk of cancer. According to the size of the polyp: <1 cm = <1% risk of cancer; 1cm = 10% risk of cancer; 2 cm = 35% risk of cancer[6].

65-80% of adenomatous polyps are tubular, 25% are tubulo villous, and 5-10% are villous adenoma. The high-grade dysplasia and its transformation into cancer are directly proportional to the size of the polyp, its villous component, the number of polyps, and the patient's age over 60 when the polyp was detected. It was found that 15% of all derivatives with a size of >1 cm are likely to become malignant within 10 years[7].

Recent studies have actively discussed the important role of cancer stem cells in the transformation of adenomatous polyps into colorectal cancer. Preliminary data on the presence of cancer stem cells in derivatives belong to Mackillop (1983)[8]. The large intestinal epithelium is histologically divided into four separate layers. Enterocytes in the upper part of the crypt, goblet, endocrine cells, and panet cells. They are formed from multipotent stem cells. During asymmetric division, these multipotent stem cells renew themselves and migrate to the base of the crypt, creating a difference. According to this theory, abnormal differentiation of crypts in the basal branch

[5] Stewart N Bonnington and Matthew D Rutter Surveillance of colonic polyps: Are we getting it right? / N.B.Stewart, D.R. Matthew // World J Gastroenterol. – 2016, v. 22, no 6, p. 1925–1934.

[6]Marks J. Colon Polyps: Symptoms, Causes, Cancer Risk, Treatment, and Prevention"/ J.W. Marks, B.Anand // Colon polyps center. MedicineNet, - 2020. r.18, - online

[7]Abu-Freha, N. Post-polypectomy surveillance colonoscopy: Comparison of the updated guidelines / N. Abu-Freha, L.H. Katz, R. Kariv [et al.] // United European Gastroenterol J, - 2021. v. 9, no 6, - p. 681-687

[8]Martinez-Climent, J.A. Somatic stem cells and the origin of cancer / J.A. Martinez-Climent, E.J. Andreu, F. Prosper // Clin.Trans Oncology, - 2006. v. 8, no 9, - p. 647-63

leads to the development of colorectal cancer[9].

To accurately determine the presence of cancer stem cells, it is necessary to find a marker that is sensitive to it. CD 133 or prominin-1 is considered a sensitive marker for colorectal adenomas and cancer[10].

There is a lack of information in the published scientific literature on the specific marker of CD 133 marker in colon polyps. The role of the CD 133 marker in the colon and rectal polyps and the emergence of a new direction in its treatment have clinical importance. The study mainly focuses on the cancer stem cells in large intestinal polyps and their susceptibility to CD 133, and the prognostic and diagnostic significance of CD 133 expression in colorectal polyps.

Object and subject of research. In the study, 118 patients with endoscopic removal of colon polyps were examined in the surgery department of the Central Customs Hospital from 2011 to 2016 as a result of clinical and anamnestic examinations and colonoscopy for search purposes. The study consisted of two stages, clinical and pathohistological.

The purpose of the study. To reveal the presence of stem cells in colorectal polyps, to study their correlation with the number, histological type, size, localization, and dysplasia of polyps, to reveal their clinical significance.

Research objectives:

1. To determine the clinical significance of colorectal polyps by finding a sensitive marker for existing cancer stem cells;
2. The investigation of the number and frequency of cancer stem cells in colorectal polyps, depending on their histological type (non-neoplastic, tubular adenoma, tubulovillous, villous adenoma);
3. The determination of the number and incidence of cancer stem cells in colorectal polyps relies on the size of the polyps;
4. Evaluate the clinical significance of the results by determining

[9]Tsai, H.C. Cancer epigenetics: linking basic biology to clinical medicine / H.C. Tsai, S.B. Baylin // Cell Res., - 2011. v. 21, - p. 502–517.

[10]Kazama, S. Expression of the stem cell marker CD133 is related to tumor development in colorectal carcinogenesis / S. Kazama, J. Kishikawa, T. Kiyomatsu [et al.] // Asian J Surg., - 2018. v. 41, no 3, - p. 274-278

the number and incidence of cancer stem cells present in colorectal polyps with and without dysplasia;

5. Comparative analysis of the results obtained by determining the number and density of cancer stem cells in colorectal polyps, depending on their localization;

6. To study the dependence of cancer stem cells in colorectal polyps on the age group of patients and their gender differentiation;

7. To assess its prognostic role in malignancy of the polyps by studying the number and frequency of cancer stem cells in polyps belonging to the high-risk group;

8. To find the cut-off point to determine dysplasia and malignancy depending on the number and density of cancer stem cells in colorectal polyps and to assess its prognostic role.

Core Research methods:

- Laboratory tests
- Methods of radiological examination
- Colonoscopy
- Pathohistological examinations
- Statistical analysis

The main provisions of the defense:

- Colonoscopy is the most useful method of examination in the detection of colorectal polyps, endoscopic polypectomies and their subsequent follow-up procedure.
- Cancer stem cells are found in all polyps of the large intestine, regardless of size, number, localization, and its histological type.
- There is a link between CD133 expression and the development of colorectal cancer. The study confirmed a statistically strong relationship between the increase in CD133 expression and the size, histological type, localization, and dysplasia of colorectal polyps.
- Increased size, dysplasia, and the complications of colorectal polyps are accompanied by an increase in the number and density of cancer stem cells.
- The number and frequency of cancer stem cells in colorectal polyps do not depend on the age, sex, or localization of the polyp
- Expression of cancer stem cells in colorectal polyps with the CD

133 marker is a suitable method for determining the prognosis of dysplasia and malignancy in polyps.

– Expression of cancer stem cells to the CD133 marker in colorectal polyps may be of important clinical importance as a diagnostic and prognostic factor in the carcinogenesis of polyps.

Scientific innovation of the research.

– The number of cancer stem cells in colorectal polyps and their frequency of occurrence are highly dependent on polyp size, histology, dysplasia, and complications.

– The CD133 expression of cancer stem cells was used to calculate the cut-off point in colorectal polyps with and without dysplasia.

– There was no significant difference in the number of cancer stem cells and the incidence of colorectal polyps in patients based on their age, gender, or localization

– The cut-off point of expression of cancer stem cells to the CD 133 marker was studied on the histological type and size of colorectal polyps.

– The number and incidence of cancer stem cells in colorectal polyps from the high-risk group were studied, and the cut-off point for polyp malignancy was determined.

– The cut-off point for predicting the risk of colorectal polyp carcinogenesis was estimated by studying the number and frequency of cancer stem cells in colorectal polyps. Based on this new method of examination, a new algorithm for determining cancer stem cells in colorectal polyps has been developed.

The practical significance of the research.

– The study of cancer stem cell expression in colorectal polyps provides information about their dysplasia, malignancy, and aggravation.

– Whether the expression of cancer stem cells in colorectal polyps affects the risk and prognosis of dysplasia, malignancy**,** and complications in clinical practice.

– It was determined that stem cells in colorectal polyps have clinical significance.

– Recommendations on the study of stem cells in colorectal polyps were made.

Application of the research. The obtained results are mainly applied during the teaching-clinical process at the Department of Surgical Diseases I and the Teaching Surgery Clinic of AMU.

Approbation of the research. The following scientific conferences were held on the topic of the dissertation: 1st Congress of APIMSF (Azerbaijan, Baku, 2018), "Actual problems of military surgery" dedicated to the 100th anniversary of the Popular Front, and the 95th anniversary of Heydar Aliyev 2018, Baku, Azerbaijan, 1st International Conference Baku. (Azerbaijan, Baku, Khazar University, 2018), Monthly meeting of the Union of Surgeons of Azerbaijan (Azerbaijan, Baku, March 30, 2018), II Azerbaijan-Turkey Days of Colorectal Surgery (Azerbaijan, Baku, May 5, 2018), 5 International Medical Congress 1, November 2 (Azerbaijan, Baku.2018), MWIA 100. Medical Women Ambassadors of change in a challenging Global World (United States, New York, 25-28 July. 2019). The finished dissertation is approved for the open defense at the scientific seminar of the I Department of Surgery of the Azerbaijan Medical University (12.11.2021, protocol N-3) and at the Scientific Seminar of the Dissertation Council ED 2.06 of Azerbaijan Medical University 28.12.2021 (protocol N-9).

Published scientific works. 21 scientific articles and 8 theses were published in conjunction with the dissertation topic, along with 10 articles and 4 theses and one book chapter issued abroad.

Volume and structure of the dissertation. The dissertation consists of 245 pages – 365.700 characters, introduction (17.600 characters), literature review (77.200 characters), 4 chapters reflecting the results of the research (30.500 + 82.300 + 24.900 + 70.000 characters), conclusion, results, practical recommendations (63.200 characters), list of used literature. The dissertation is illustrated with 27 pictures, 22 graphics, and 18 tables. The bibliography consists of sources from 156 authors from local and foreign databases.

MATERIALS AND METHODS

The research was carried out between 2011 and 2016 within the scientific program of the Department of Surgical Diseases I of AMU, the Central Customs Hospital, and the Meram Medical Faculty of Erbakan University of the Republic of Turkey.

Clinical characteristics of patients. In the study, 118 patients aged 18 to 81 years were examined in the surgery department of the Central Customs Hospital from 2011 to 2016 as a result of clinical and anamnestic examinations and endoscopic removal of colon polyps. The study consisted of two stages, clinical and pathohistological where the patients consisted of 74 males and 44 females. The second stage of the work was divided into two and a half stages.

In the first phase of the study, 118 patients were admitted to the surgery department of the Central Customs Hospital with abdominal pain, bleeding during defecation, polyps of the colon, or family history of colorectal polyps and malignancies.

The criteria for inclusion in the study were abdominal pain, bloating, bleeding during defecation, the presence of mucous secretions, as well as a group of patients undergoing a routine colonoscopy for search purposes only.

Criteria for exclusion from the study are: patients with incomplete colonoscopy, patients with insufficient bowel cleansing, inability to fully assess the mucous membrane of the large intestine, patients with malignant tumors of the large intestine.

During the clinical and anamnestic examination, a complete anamnesis of the disease, previous illnesses, history of surgical operations, bowel disorders, bleeding during defecation, and mucous secretions were studied.

All patients undergoing colonoscopy were given a bowel cleanse in writing and scheduled for examination the day before.

Registration of patients in the research work, conducting the applied examinations was carried out following the internal rules of the Hospital and using the "AKGUN" program, the outpatient card was entered into the database of the Central Customs Hospital through "AKGÜN".

Examination methods. The following are included in the methods of laboratory and instrumental examination of patients in the study group. General clinical examinations, hemostasis indicators, blood biochemical parameters, immunological-serological examinations. No routine laboratory examinations are performed before colonoscopy in patients who applied to the clinic for research purposes, the patients with clinical complaints underwent laboratory and instrumental examinations.

All patients with cardiovascular disease and those receiving the regular anticoagulants underwent cardiology, general blood analysis, ECC, EchoECG, and coagulograma in some patients, and a colonoscopy after the cardiologist's opinion. Patients with a history of functional thyroid disease, hypothyroidism, hyperthyroidism were consulted by an endocrinologist, TSH, T3, T4 (free) hormonal tests were checked. The study included functional lung spirometry in patients with upper respiratory disease, regular smokers, patients with a history of bronchial asthma, and patients with persistent cough and shortness of breath. In the study, a cardiologist is consulted to assess the anesthetic risk in high-risk patients (those with cardiovascular disease, those undergoing ACB surgery, those receiving regular blood thinners, and those over 60 years of age).

Colonoscopy. To achieve this goal, patients in the study group underwent colonoscopy under intravenous anesthesia. Colonoscopy examination was performed in the surgical department of the Central Customs Hospital with Olympus ExeraII CLV 180 device. Polypectomies were performed with two techniques: Biopsy compression polypectomies and compression snare polypectomies.

Radiological examination methods. The computed tomography was involved in the study group as the most sensitive method for radiological evaluation of patients with suspected perforation after polypectomy after colonoscopy.

Pathohistological characteristics of polyps. The second stage of the study was the pathohistological assessment of endoscopically removed polyps detected during a colonoscopy, the results were statistically analyzed and compared. Pathohistological and immunohistochemical analysis of colon polyps was performed in 118

patients included in the study.

Methodology for the use of Ki-67 and CD 133 markers in colorectal polyps. In 9 out of 118 patients who underwent pathohistological evaluation with HE staining, the Ki-67 index was examined to assess proliferative activity. At the final stage of the pathohistological phase of the study, HE stained materials were re-evaluated for examination and identification of cancer stem cells. This stage was held at the Department of Pathohistology, Meram Medical Faculty at Erbakan University in Konya, Turkey. Thus, in the study, CD 133, a cancer stem cell marker, was used for this purpose.

Clemex Vision Image Analysis Software. To accurately calculate and quantify cancer stem cells, CD-133-stained preparations were analyzed with a Nikon Eclipse E400 light microscope, using the Nikon Coolpix 5000 camera, which selected as many areas as possible for each preparation and then combined under a microscope drawn. All images for the identification and counting of cancer stem cells are transferred to a computer environment and selected by high-level image analysis, which can accurately track the characteristics of microstructures, particle size, surface roughness, percentage of the field of view as the most powerful automated image analysis system. was analyzed using the Clemex Vision Lite 3.5 Image Analysis program (Longueuil, Canada), which allows us to go beyond the methods.

Methods of statistical analysis. The statistical analysis encompasses the variation (U-Mann-Whitney, H-Kruskal-Wallis), variance (ANOVA test - F-Fisher, Fisher-Snedecor), discriminant (chi-square Pearson), correlation (rho-Spearman), and ROC-analysis (+ cut of point), which was performed in IBM Statistics SPSS-26 package program.

ENDOSCOPIC TREATMENT AND MORPHOLOGICAL FEATURES OF COLORECTAL POLYPS

Clinical and laboratory characteristics of patients. The clinical part of the study was the analysis of endoscopic polypectomy

performed on 118 patients aged 18 to 81 years in the Endoscopy Division of the Surgery Department at the Central Customs Hospital between 2011 and 2016 and their pathohistological classification, evaluation by age groups, sex, and size of the removed polyps.

All patients included in the study group were evaluated for their clinical and objective complaints before the examination, indications, and contraindications for colonoscopy. They were identified, and patients with contraindications were excluded from the group. The polypectomy procedure was performed on 118 patients and the pathohistological classification of polyps was removed from them, their correlation in terms of age, size, and number were studied. Patients in the study group were grouped into 3 age groups. The highest number of patients was among patients aged 41 to 60 years, constituting 56.8% of the total number of patients. The lowest number of patients was in the group of patients aged 19-40 years (14.4%).

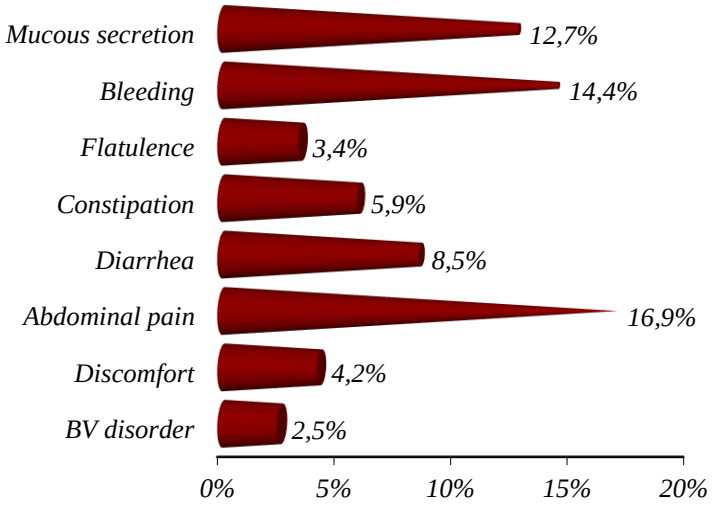
Gender differentiation of polyps was observed in patients. Therefore, several parameters have been studied. Thus, the localization of polyps in the large intestine ($p_p = 0.441$), the size of the polyp found ($p_p = 0.288$), the pathohistological structure of polyps ($p_p = 0.690$), the risk of dysplasia ($p_p = 0.728$), the inclusion of the risk group ($p_p = 0.852$), the relationship between the occurrence of complications ($p_p = 0.990$), and the number of polyps ($p_p = 0.580$) with the sexual characteristics of patients was deeply studied. There is neither gender differentiation of the criteria listed by the Pearson criterion nor a statistically significant difference.

However, during the analysis between the groups, it was released that as the patient gets much older, the polyps found in them become more at risk. Although 14 (50.0%) of the polyps observed in patients over 60 years of age and 11 (20.0%) of the polyps between 41-60 years of age are included in the group of high-risk polyps, only 1 patient (5,9%) was included in this group between the ages of 19 to 40 (pp = 0.002; pH = 0.002).

A correlation was observed between the age group of the patients and the size of the polyps. Thus, polyps 1-3 cm and 3 cm in size were detected in patients older than 41 years. In 9 (13.4%) patients aged between 41 and 60 years and in 10 (29.4%) patients over 60 years of

age, polyps were found between 1 to 3 cm, and 3 cm large polyps were found in 3 (8.8%) patients over 60 years of age. (p_p = 0.011; p_H = 0.006). A statistically significant difference was determined between the age group and polyp size. Thus, dysplasia was observed in only 3 (17.6%) patients aged 19-40 years, in 26 (38.8%) patients aged 41-60 years, and in 19 (55.9%) patients over 60 years of age. correlates as (p_p = 0.007; p_H = 0.030). Thereby, with the age, the symptoms of dysplasia increase, and the results are statistically accurate. Complications also varied by age group. Hence, the complications were detected in patients over 40 years of age. 9.1% of complications were found in patients aged 41-60 years, and 10.7% in patients over 60 years. However, no statistically significant difference was found between these indicators (p_p = 0.397; p_H = 0.401).

We classified the patients in the study group into two groups according to the nature of the application. 55.1% of these patients had relevant intestinal complaints and were admitted to the clinic. The other 53 patients (44.9%) are a group of patients who visit the clinic only for follow-up examinations (Graph 1).



Graph 1. Patient complaints.

In the statistical evaluation of patients with age group and intestinal complaints, it was detected that there was a correlation between the age group and the patient's complaints, and a statistically significant difference was determined (p_p <0.001; p_H <0.001). Results of colonoscopy examination. In the study, 110 (93.2%) patients underwent the procedure without complications during endoscopic polypectomies, and 8 patients underwent complications (three early hemorrhages (2.5%), two late hemorrhages (1.7%), the perforation was observed in one patient (0.8%) and post polypectomy syndrome in two patients (1.7%). The severity is only 6.8%. Surgery was recommended and performed on two patients with colonoscopy for giant polyps.

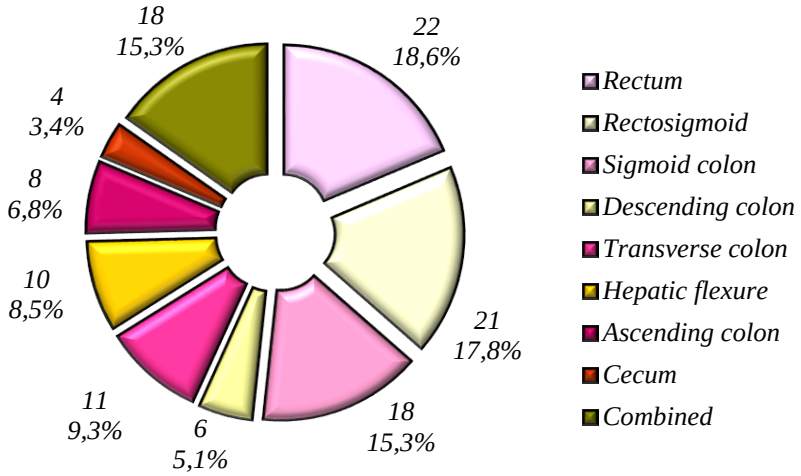
The statistical relationship between the complications that occurred during the examination of polyp removal techniques was studied. The complications were found in none of the 63 (100%) patients removed with the biopsy clamp, but 47 (85.5%) of the polyps removed with the polypectomy ring had no complications, although 8 (14.5%) patients did. Statistically, a clear difference between polyp removal technique and their complications was determined (p_p = 0.002; p_H = 0.001).

All removed polyps were sent for pathohistological examination. The vast majority of polyps removed by biopsy clamps are 29 (46%) tubular, and 14 are hyperplastic (22.2%) and inflammatory (22.2%) polyps. Thus, out of 55 (46.6%) polyps removed by polypectomy ring, 24 (43.6%) are tubulovillous polyps and 23 (41.8%) are tubular polyps. Dysplasia was not observed in 43 (68.3%) of polyps removed by biopsy, and signs of dysplasia were observed in 20 (31.7%). However, in polyps removed with a polypectomy ring, no signs of dysplasia were observed in 28 patients (50.9%) and 27 patients (49.1%). The polyp removal technique was considered statistically significant with signs of dysplasia in polyps and is accurate (p_p = 0.035; p_H = 0.035).

The two (1.7%) serrated polyps in the study group were both polyps smaller than 1 cm. 1 (5.9%) of the patients was in the group of patients aged 19-40 years, and the other was in the group of patients aged 41-60 years. Serrated polyps are located in the left half of the

large intestine and were removed with a biopsy clamp due to their small size. The distribution was the same between women and men. Despite their small size, one of the removed polyps (2.1%) showed signs of dysplasia.

In detected patients, one or more polyps located in the same or different segments were classified based on their localization (Graph 2).



Graph 2. The localization of polyps.

In 18 (15.2%) patients, the polyps were located in different segments of the intestine. The localization of colonic polyps was evaluated for several parameters. The frequency of polyps in the left segment of the large intestine was the same in both groups. However, polyps with combined localization (83.3%) are more common in male patients than in female patients (16.7%) (p_P = 0.441; p_H = 0.842). Statistical analysis of patients by age group (p_P = 0.407), polyp size (p_P = 0.372), pathohistological type (p_P = 0.217), dysplasia (p_P = 0.396), risk group (p_P = 0.340), complications (p_P = 0.136) no clear distinction was made. Effect of polyp localization on dysplasia factor EIF = 7.11%; 95% CI: 0.00-20.91; p_F = 0.409 was calculated. As a result, we could say that the localization of polyps is not directly proportional to the elements of their dysplasia and not considered

statistically significant.

The size of the polyps removed during the examination was 1.57±0.12. They were classified into 3 groups: Polyps up to 1 cm - n = 94 (79.7%); Polyps between 1-3 cm - n = 21 (17.8%); Polyps larger than 3 cm - n = 3 (2.5%)

The pathohistological division of the removed polyps by their size was also investigated according to several statistical criteria. The most common polyps up to 1 cm are tubular n = 46 (48.9%), tubulovillous n = 13 (13.8%), inflammatory n = 18 (19.1%), hyperplastic n = 15 (16%), serrated adenoma n = 2 (2.1%). 1 to 3 cm polyps also belonged to the group of adenomatous polyps, as 12 (57.1%) were tubulovillous and 6 (28.6%) were tubular polyps. The other 3 polyps are inflammatory 2 (9.5%) and hyperplastic 1 (4.8%). Thus, the pathohistological structure of polyps above 3 cm is tubulovillous 2 (66.7%) and villous 1 (33.3%). As the size of the polyp increases, so does their pathohistological severity. Therefore, there is a statistically significant difference between the size of the polyp and their pathohistological type (p_p <0.001; p_H <0.001).

During the colonoscopy, of the polyps removed from patients, 100 (84.7%) were polyps localized in one intestinal segment, and 18 (15.3%) were polyps localized in several intestinal segments. The size of the removed polyps and whether they were single or multiple were also examined. Thus, 82 (87.2%) of polyps small in 1 cm are localized in a single segment, 16 (76.2%), polyps between 1-3 cm are localized in a single segment, and two (66.7%) polyps 3 cm in height are localized in a single segment. The number of polyps up to 1 cm localized in several segments was 12 (12.8%), 1-3 cm in size, the patient with polyps localized in separate segments 5 (23.8%), the patient with polyps larger than 3 cm, the polyps localized in separate segments the number was 1 (33.3%). There was no statistically significant difference between the size of the polyps and their number (p_p = 0.327; p_H = 0.305).

Besides, the relationship between the size of the polyp and their removal technique was investigated. In 61 (64.9%) patients with polyps up to 1 cm, the biopsy was performed with a clamp, in 21 (100%) patients with polyps between 1 to 3 cm and 1 (33.3%) patients

with polyps up to 3 cm, polyps with a compression ring cut of. A statistically significant difference was detected between the size of the polyps and the technique of their removal (p_p <0.001; p_H <0.001) the statistically significant difference was determined.

At the same time, a statistical relationship between the number of polyps localization in the same or different segments was studied. The number of polyps is considered large and their localization is different. Thus, the number of patients with two polyps in the same localization was 10 (10%), the number of patients with two polyps in different segments was 5 (27.8%). In 7 (7.0%) patients with 3 polyps, they were located in the same segment, and in 7 (38.9%) patients, were placed in different segments. In 3 (3.0%) patients with more than 3 polyps, the polyps were localized in the same segment and 6 (33.3%) patients in different segments. A statistically significant difference between the number of polyps and their localization was determined (p_p <0.001).

However, no statistically essential difference was detected between the localization of polyps in either one segment or different segments and dysplasia (p_P = 0.163). The effect of dysplasia factor on one segment or different localization of polyps: EIF = 1.65; 95% CI: 0.00-4.98; p_F = 0.166. The presence of dysplasia is not statistically significant with the localization of polyps in one segment or different segments. At the same time, statistically significant differences in the severity of polyps (p_P = 0.427), pathohistological type (p_P = 0.270), age groups (p_P = 0.503) were not determined by the localization of polyps in one segment or in different segments. In the study, we classified patients into four main groups according to the number of polyps found in patients undergoing colonoscopy: patients with 1 polyp of the large intestine - n = 80 (67.8%); patients with two polyps - n = 15 (12.7%); patients with three polyps - n = 14 (11.9%); patients with ≥3 polyps above - n = 9 (7.6%)

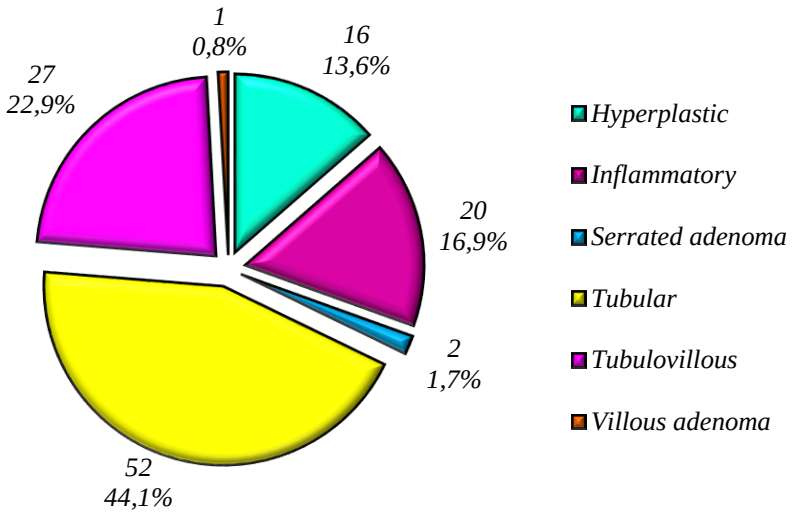
In the study, polyps were found in two different segments in 4 of patients with two polyps and polyps in two and three segments of the intestine in 13 out of the 23 patients with three or more polyps. A statistical assessment of the impact of the increase in the number of polyps on the pathohistological outcome of their localization, the

symptoms of dysplasia was conducted. Although the number of polyps was statistically significant with their localization (p_P <0.001) and risk (p_p = 0.006), its pathohistological results (p_P = 0.537), signs of dysplasia (p_P = 0.425; p_H = 0.429), and with complication (p_P = 0.590) is not considered statistically significant. So that if the number of polyps in the large intestine is considered high, they are more likely to be included in the risk group, but the high number of polyps does not mean that they have an increase in the elements of dysplasia (p_F = 0.434). During the investigation, dysplasia was detected in 48 (40.7%) patients, and no dysplasia was observed in 70 (59.3%) patients. It turned out that as the size of the polyp increases, so do the symptoms. Thus, dysplasia was 34% in polyps up to 1 cm, 61.9% in polyps between 1-3 cm, and 100% in polyps up to 3 cm. There was a direct correlation between the size of the removed polyps and their pathohistological results, dysplasia, as the size of the polyp increased, the symptoms of dysplasia (p_P = 0.007; p_H = 0.007), and the number of polyps with villous component (p_P <0.001; p_H <0.001). Briefly, the influence of polyp size on dysplasia factor: EIF = 8.48; 95% CI: 3.5-13.38; pF = 0.006, ie dysplasia is strongly significant with the size of the polyp.

Pathohistological classification and characterization of colorectal polyps. During the colonoscopy, its pathohistological relationship with the size of all endoscopically removed polyps was examined, and the correlation of the size of polyps with their oncological risk was investigated. The removed polyps were classified based on their histopathological structure, referring to the goals and objectives of the study (Graph 3).

Furthermore, polyps were also evaluated for inflammation and inflammation absence. The classification of inflammatory polyps according to the degree of dysplasia is as follows. 18 out of 20 inflammatory polyps did not have dysplasia and only two patients (10%) had dysplasia. A statistically significant difference was found between the pathohistological type and size of the removed polyps (p_P <0.001; p_H <0.001), between the histopathological type and dysplasia, and the fact that they belonged to the high-risk group (p_P <0.001; p_H

<0.001). However, no statistical difference was found between the pathohistological type of polyps and their complications (p_P = 0.117, p_H = 0.122) and the number of polyps (p_P = 0.327).



Graph 3. Classification of colon polyps by morphological type.

The relationship of dysplasia of colorectal polyps with their localization in the same and different segments was also studied. In this regard, in 18 out of 118 patients (15.3%) colorectal polyps were localized in different segments. Polyps with signs of dysplasia are more common in the rectosigmoidal part with 9 (18.8%), in the rectum constituting 7 (14.6%), in the transverse colon is 7 (14.6%), and in the S-shaped intestine makes up for 5 (10.4%).

Statistically, the percentage of dysplasia was higher in polyps localized in different segments. However, no statistically significant difference was found between localization and dysplasia in colorectal polyps (p_P = 0.396). As the size of the colon polyps increased, the number of oncological risks due to their morphological structure prevailed.

Research has shown that the number of polyps with dysplasia increases with age. So that the age factor is directly correlated with

dysplasia. As a result, we can say that there is a significant and accurate difference between the pathohistological type of polyps and dysplasia (p_P <0.001), polyp size (p_P <0.001), patient complaints (pP <0.001), and risk (p_p <0.001), the significant variation between complications and risk (p_p <0.001), between the size of the removed polyp and their removal technique (p_p <0.001), the corresponding complications, and colonoscopy for the detection of colorectal polyps

KI-67 EXPRESSION IN COLORECTAL POLYPS

Significance of Ki-67 marker in colorectal polyps. The proliferative activity of tumor cells in tissues is crucial in the growth of colorectal polyps. Ki-67 is an antibody that shows the proliferative activity of cells in the derivatives. Those with a high Ki-67 fraction have a more aggressive course and a faster proliferative course. With Ki-67 dyeing, it is possible to think about how aggressive the derivative is.

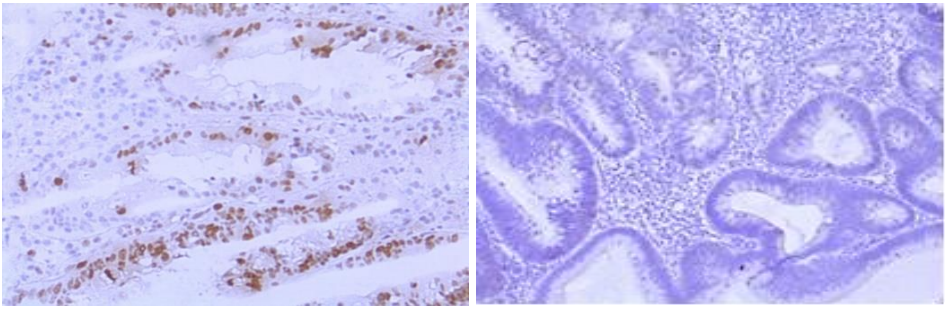
In general, the assessment of Ki-67 is as follows: 0 to 2% is called I degree or lower. If it is between 2-20%, it is called the second or intermediate degree. If it is higher than ≥20%, it is called III degree or higher degree. The Ki-67 marker is severely associated with cell proliferation. Immune histochemical expression of Ki-67 and proliferative activity of polyps were studied in 9 patients included in the study group.

Expression of KI-67 in colorectal polyps. KI-67 expression was performed on polyps obtained from 9 (7.6%) patients included in the study group. The aim was to study the proliferative activity of cells in the polyp tissue of the large intestine, mainly depending on its histological degree, the size of the polyp, with the marker Ki-67. Of the patients included in the examination group, 4 were women (44.5%), and 5 (55.5%) were men. The pathohistological description of the polyps removed from these patients was as follows: tubular adenoma was detected in 5 out of 9 patients (55.5%), tubulovillous adenoma in 3 (33.3%), and inflammatory polyp in 1 (11.1%).

Dysplasia was observed in 2 of the polyps included in the examination group (22.2%) and not found in 7 polyps (77.7 %). In 8

of these patients (88.8%) whose Ki-67 expression was studied, the presence of stem cells with CD 133 sensitivity was also studied. In patients with dysplasia and whose Ki-67 proliferative index was investigated, CD 133 was above the cut-off point (COP = 10). However, Ki-67 showed susceptibility to proliferation, but CD133 <10 was present in polyps without dysplasia.

The increase in the Ki-67 proliferation index was also directly proportional to the increase in the degree of dysplasia. In tubule villous polyps accompanied by dysplasia, the Ki-67 proliferation index was 15-20%. This result showed a significant association between the expression of the Ki-67 marker and the expression of the histologic type of colorectal polyps with high dysplasia (Picture 1a). In 5 tubular adenomas not accompanied by dysplasia in colorectal polyps, the Ki-67 proliferation index was 15-20%. This means high proliferative activity, and the cell intensity was 2 + / 3 + (Picture 1b).



a) tubulovillous polyps b) tubular adenoma

Picture 1. Ki-67 sensitivity in colorectal polyps.

The proliferative activity with the expression of Ki-67 was also studied in inflammatory polyps, being considered non-adenomatous polyps. As a result, the Ki-67 proliferation index of the inflammatory polyp and its sensitivity to cancer stem cells below the cut-off value indicates that it does not carry any oncological risk.

As a result, there is a direct correlation between the Ki-67 proliferation index and dysplasia of colorectal polyps. As the degree of dysplasia increases, the Ki-67 proliferation index also increases.

The colorectal polyp size and Ki-67 expression. Expression of the Ki-67 proliferation index in colorectal polyps was also studied according to the size of the removed polyps. In 3 (33.3%) of the patients in the study group, the size of the polyps was between 1-3 cm, and in the other 6 patients (66.6%) the size of the polyps constitutes up to 1 cm.

We found that the expression of the Ki-67 marker did not have a significant relationship with the size of the removed polyps. Thus, immune histochemical expression of Ki-67 can be considered a part of routine pathological assessments with other conventional prognostic factors in patients with dysplastic colorectal polyps.

CD 133 AND CLINICAL EVALUATION

The determination and consequences of cancer stem cells in polyps. There are studies in the literature on the sensitivity of stem cells to the development of cancer and the pivotal role of cancer stem cells in the transformation of colorectal polyps into cancer. Stem cells, which are small in number in the tissues, divide by a certain number and maintain their numbers as they divide. They are immensely sensitive to growth factors and molecular signals and respond quickly. Stem cells are classified into three main groups: embryonic, fetal, and adult. Stem cell self-renewal occurs due to apoptosis. Research on stem cells, the study of their metabolomics, the presence of new surface markers in their identification raise hopes for a new path in the detection and treatment of diseases in medicine.

In recent years there have been various scientific studies and articles on the role of cancer stem cells in the digestive system. To accurately target the presence of cancer stem cells, a method is needed to find a marker that is sensitive to it. CD133 or prominin -1 is a sensitive marker for colorectal adenomas and cancer. The main objective of the research is to examine the presence of stem cells in colorectal polyps and their expression with CD133, as well as the correlation between the number of cancer stem cells found in each polyp and their risk of dysplasia. To assess the sensitivity of cancer stem cells to CD 133 in colorectal polyps in the histological type, size,

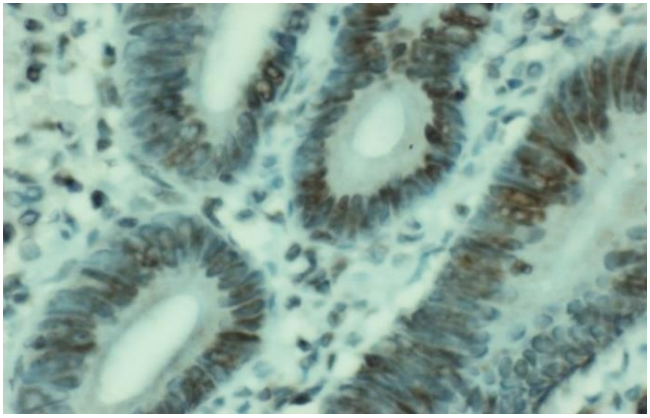
dysplasia, and risk groups of the polyp. Based on the above mentioned, it seems necessary to study the correlation between CD 133 expression, dysplasia, and malignancy in colorectal polyps. Accordingly, it is possible to obtain prognostic information by the amount of CD 133 expression in CD 133 in colorectal polyps.

The relationship between the number and localization of cancer stem cells in colorectal polyps. We first studied the presence of malignant stem cells in the removed polyps and the relationship between the existing cancer stem cell involving the localization, size, and the number of polyps, the sex of the patients, and the technique of removing the polyps. During the clinical study, CD 133 was used to identify cancer stem cells in removed polyps. For this purpose, in the Pathomorfology Department of the Central Customs Hospital, research was continued on colorectal polyps removed from 100 patients who were HE stained and histopathologically assessed.

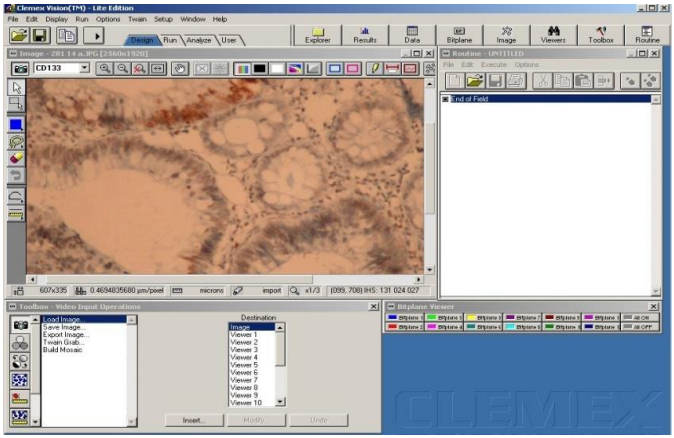
The drugs were evaluated as immune histochemical at the Meram Medical Faculty of Erbakan University in Turkey to investigate the sensitivity of cancer stem cells in removed polyps by staining them with CD 133. According to the study results, two groups were formed with dysplasia and without dysplasia. The CD 133 immune histochemical staining of drugs belonging to both groups was carried out in particular phases based on the staining technique. After dryeing, these preparations were lamellae bonded. At the next stage, CD-133 stained preparations were evaluated under a Nicon Eclipse E400 light microscope (Picture 2).

Once the drugs were properly prepared, the same field of view was selected for each drug, and images of the drugs were taken with a Nikon Coolpix 5000 camera attached to a light microscope. The Nikon micrometer microscope lamp (Scene Micrometer Type A, MBM11100) was also imaged at almost the same microscopic magnification. In the next stage, all pictures taken by the camera were transferred to the PC. 319066.2 μm2 of very similar images were selected using Clemex Vision Lite 3.5 Image Analysis (Longueuil, Canada) in all subsequent images. At the next stage, in each of the 319066.2 μm2 areas selected by the imaging program, cancer stem

cells positively stained with CD 133 were marked with the same imaging program and automatically counted without human factor (Picture 3).



Picture 2. Cells showing positive expression with CD 133 are stained darker.



Picture 3. Positively stained cells were marked on the "Image" analysis system.

The assessments were conducted in the light of several parameters (Table 1).

Table 1
Number of CD-133 according to the studied factors

Factors		Numbers	M	±m	Me	Q1	Q3	p_F	p_H
Gender	Male	60	16,5	2,2	8,5	2,0	31,0	0,816	0,818
	Female	40	15,6	3,1	5,5	2,0	25,5		
Age group	19-40 age	17	8,2	2,1	5,0	3,0	9,0	0,078	0,140
	41-60 age	55	16,2	2,6	5,0	2,0	31,0		
	> 60 age	28	20,8	3,6	16,0	3,5	32,5		
Complain	Check-up	41	10,2	2,0	5,0	1,0	18,0	0,006	0,017
	With complain	59	20,2	2,6	14,0	3,0	33,0		
Size	< 1 cm	80	12,4	1,7	5,0	2,0	19,5	<0,001	0,003
	1-3 cm	17	28,4	5,3	31,0	5,0	41,0		
	> 3 cm	3	45,7	8,0	51,0	30,0	56,0		
Localization	Rectum	20	15,6	5,2	3,5	0,0	30,0	0,681	0,578
	Rectosigmoid	18	14,7	3,7	9,5	3,0	25,0		
	Sigmoid colon	14	12,6	4,5	5,0	0,0	31,0		
	Descending colon	4	19,5	8,8	16,0	5,0	34,0		
	Transverse colon	8	14,1	4,0	15,0	3,5	19,5		
	Hepatic flexure	9	10,6	4,3	5,0	1,0	18,0		
	Ascending colon	8	16,6	5,4	13,5	3,0	31,0		
	Cecum	2	10,0	5,0	10,0	5,0	15,0		
	Combined	17	24,7	5,2	25,0	3,0	38,0		
Combined localization	1 segment	83	14,4	1,9	5,0	2,0	27,0	0,031	0,058
	> 1 segment	17	24,7	5,2	25,0	3,0	38,0		
Number of Polyps	1 polyp	68	13,7	1,9	5,5	1,5	25,0	0,041	0,150
	2 polyps	13	15,5	4,1	9,0	2,0	31,0		
	3 polyps	11	20,1	8,2	5,0	2,0	38,0		
	> 3 polyps	8	32,3	8,0	31,0	15,0	48,5		
Material	Forceps biopsy	55	11,0	1,7	5,0	2,0	18,0	0,002	0,038
	Polypectomy	45	22,3	3,2	15,0	2,0	35,0		
Pathohistology	Hyperplastic	13	2,8	0,8	3,0	0,0	5,0	<0,001	<0,001
	Inflammatory	16	4,7	2,1	2,5	0,0	6,0		
	Serrated adenoma	2	17,5	14,5	17,5	3,0	32,0		
	Tubular	45	15,8	2,5	12,0	4,0	25,0		
	Tubullovillous	23	30,3	4,0	31,0	15,0	48,0		
	Villous adenoma	1	56,0		56,0	56,0	56,0		
Dysplasia	Not available	58	3,5	0,5	3,0	0,0	5,0	<0,001	<0,001
	Available	42	33,6	2,3	31,5	25,0	39,0		
Risk	Not available	74	9,1	1,4	5,0	1,0	9,0	<0,001	<0,001
	Available	26	36,1	3,5	31,0	25,0	49,0		
Complications	Not available	92	13,8	1,6	5,5	2,0	25,0	<0,001	0,003
	Available	8	42,4	8,5	45,0	31,0	51,5		

In the initial stage, dark-stained areas in each field of vision were considered as cancer stem cell units sensitive to the CD 133 marker. With the help of an automatic evaluation of the image analysis system in each polyp, it was found that the number of dark-stained cells in the field of vision is different this difference gives the number of cancer stem cells and varies depending on the nature of the polyp. The number of cancer stem cells present in the polyps was first studied to determine the relationship between the number of cancer stem cells in colorectal polyps and their localization, their relationship between polyp localization, size, dysplasia, and complications.

The relationship between their localization and cancer stem cells in polyps removed from patients was scrutinized. It was found that in 20 patients with polyps removed from the rectum, the average number of cancer stem cells was 15.6±5.2, dysplasia was observed in 6 of these polyps, and the average number of cancer stem cells was 46.3±8.6.

The number of polyps localized in the rectosigmoidal region was 18, the average score of cancer stem cells was 14.7±3.7, dysplasia was found 8 of 18 polyps, the average number of cancer stem cells was 27.8±5.3. 14 polyps were removed from the S-shaped intestine, where the average cancer cell count was 12.6±4.5, and 4 patients with S-shaped intestinal polyp had dysplasia, in which the average number of cancer stem cells detected constitutes 36.8±5.1. In 4 patients, polyps were found in the descending small intestine, so the average number of cancer stem cells in these polyps was 19.50±8.8, 2 dysplastic polyps in the descending colon were observed, the average number of cancer stem cells was 34.0±7.0. In 8 patients, the polyps were localized in the transverse colon, and the average number of cancer stem cells in this segment was 14.1±4.0. There were 5 polyps with dysplasia in the transverse ileum, with an average cancer cell count of 20.8±3.8. In 9 patients, the polyps were localized in the hepatic flexure

The mean number of cancer stem cells found in these polyps was found to be 10.6±4.3. There are 2 polyps with dysplasia, the average number of cancer stem cells makes up for 31.0±4.0, the average number of cancer stem cells in 8 patients who have had polyps removed from the ascending colon is 16.6±5.4, the average number of cancer cells constitutes 4 dysplasia of the ascending colon cancer stem

cell number 30.3±3.5. In only two patients were the polyps localized in the cecum. The mean cancer stem cell count in these polyps was 10.0±5.0. There was one dysplastic polyp in the second, in which the number of cancer stem cells was determined to be 15. In 17 patients, the polyps were localized in different segments, and the average number of cancer stem cells found in them was 24.7±5.2 dysplasia was observed in 10 of the polyps of different localizations, the average number of cancer stem cells was 39.4±4.7. As can be seen from the study the cancer stem cells found in polyps can be present in any segment, regardless of the localization of the polyps. The results were assessed by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis). The localization of polyps does not affect the number of cancer stem cells ($p_F = 0.682$; $p_H = 0.578$).

According to Spearman, a non-parametric correlation analysis, there is no statistically significant correlation between the localization of polyps and CD 133 ($\rho = 0.102$; $p = 0.312$). The study examined whether the change in stem cells in polyps, depending on their localization in one segment of the intestine or different sections was statistically significant. In 83 patients, the polyps were localized in one segment, here the average number of cancer stem cells was found to be 14.4±1.9, whereas dysplasia was observed in 32 polyps, the average number of cancer stem cells in these polyps was 31.8±2.7. In 17 patients, the polyps were localized in different segments. In these polyps, the average number of cancer stem cells constituted 24.7±5.2. Dysplasia was observed in 10 polyps of different localizations. So the average number of cancer stem cells was 39.4±4.7. In this regard, the localization of polyps in a segment increases the visibility of stem cells. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal -Wallis). Statistically significant differences were observed for both criteria. ($p_F < 0.001$; $p_H < 0.001$).

The next evaluation was performed to see whether the polyps were correlated with the removal technique. Here polyps were divided into two groups according to the removal technique. Thus, in 55 (55%) out of the 100 patients, the polyps were removed with a biopsy clamp and 45 out of it (45%) with a snare polypectomy. No complications were observed in any polyps removed with a compression biopsy, and 8

(17.8%) of the complications were detected during snare polypectomy. Then we counted the cancer stem cells in the polyps removed by both techniques. The average number of stem cells in polyps removed with the help of a biopsy clamp was 11.0±1.7, and the maximum number of views was 56. The average number of cancer stem cells in polyps removed by snare polypectomy was 22.3±3.2. We compared both results and made a statistical assessment. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) ($p_F = 0.002$; $p_H = 0.038$).

The results were considered statistically accurate for both criteria. The incidence of stem cells found in patients who complained or went to the clinic for the check-up was studied. Of the 100 (100%) patients included in this study group, 59 (59.0%) were patients with relevant complaints, and 41 (41.0%) were patients who applied to the clinic for check-up. It was found that the average number of cancer stem cells in polyps removed from patients with complaints was 20.2±2.6, and the maximum number of cancer stem cells was 84. The average number of cancer stem cells present in the polyps removed from patients undergoing colonoscopy and polypectomy was 10.2±2.0. In conclusion, we would like to note that the number of cancer stem cells in polyps removed from patients with complaints is almost twice the number of cancer stem cells found in patients who go to the clinic for search. Therefore, colonoscopy is recommended for patients with intestinal complaints. The variance statistical evaluation of the results was performed ($p_F = 0.006$; $p_H = 0.017$), a statistically significant difference was observed for both criteria.

Complications were observed in 8 patients during polypectomy, and 7 out of 8 patients were at risk group. The mean number of cancer stem cells found in polyps removed by without complication polypectomies was 13.8±1.6. The average number of cancer stem cells in polyps removed from 8 patients with complication was 42.4±8.5. The results were assessed by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) and the statistically significant difference was determined for both criteria. ($p_F < 0.001$; $p_H = 0.003$). The study also studied the mean number, maximum viscosity, and statistical correlation of cancer stem cells in polyps

removed from patients with and without complications. The average number of cancer stem cells in a polyp removed from a patient with perforation was 51.0. The average number of cancer stem cells in polyps removed from two patients with delayed bleeding was found to be 57.5±26.5.

The average number of cancer stem cells in polyps removed from 3 patients with early bleeding was 47.3±3.3. The mean number of cancer stem cells in the polyp removed from two patients with a post-polypectomy condition was 15.5±15.5. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis), and statistically, necessary variations were determined for both criteria (P_F <0.001; P_H = 0.003). We also measured the sensitivity of CD 133 in the removed polyps according to the number of polyps. The polyps removed from 68 patients were single (mono) polyps. The average number of cancer stem cells in the polyps removed from these patients was 13.7±1.9, and the number of polyps was two in 13 patients, the average number of cancer stem cells in these polyps was 15.5±4.1, and the number of polyps in 3 patients was 3. The mean number of cancer stem cells was found to be 20.1±8.2. The number of polyps was more than 3 in 8 patients.

The average number of cancer stem cells in polyps removed from these patients was found to be 32.3±8.0. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) (P_F = 0.041; P_H = 0.150). Although a statistically significant difference was obtained according to Fischer, the difference according to the Kruskal-Wallis criterion was not confirmed.

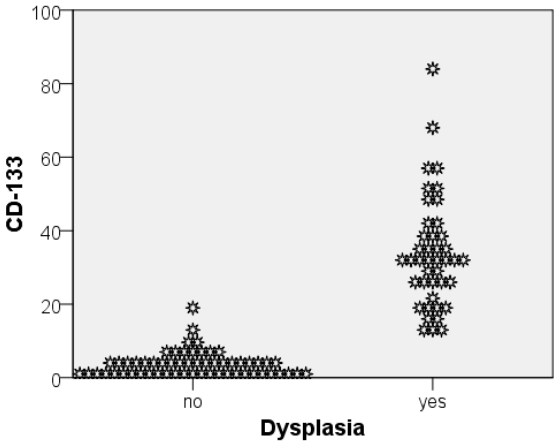
The relationship between sex and age of cancer stem cell numbers in colorectal polyps. The gender differentiation of cancer stem cells found in polyps from male and female patients was also studied, and statistical evaluation was determined by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis). The average number of cancer stem cells seen in polyps from 60 (60.0%) male patients was 16.5±2.2, the maximum number of seen cases was 68, the average number of cancer stem cells from polyps

from 40 female (40.0%) patients was 15,6±3.1. The maximum number of views was 84. The results were based on the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) so that no statistically significant difference (P_F = 0.816; P_H = 0.818) was determined for both criteria.

The incidence of stem cells present in colorectal polyps was assessed according to the age group of the patients. During the study, patients were classified into three age groups. Cancer stem cells found in polyps extracted from patients of all ages were considered. The average number of cancer stem cells found in polyps removed from 17 patients aged 19-40 years constituted 8.2±2.1. The average number of cancer stem cells found in 55 patients aged 41-60 years was 16.2±2.6, 60. The average number of cancer stem cells detected in polyps removed from 28 patients over 20 years of age was found to be 20.8±3.6. The results were based on the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) and were not considered statistically accurate (P_F = 0.078; P_H = 0.140). The number of cancer stem cells detected in colorectal polyps is not directly proportional to the age group of patients and is not statistically accurate. As a result, it should be noted that in large intestinal polyps, cancer stem cells are sensitive to the CD 133 marker, and sensitive stem cells in the visual field are differed by dark staining.

The density of appearance of cancer stem cells in polyps with and without dysplasia. In the next stage, the sensitivity and number of cases of cancer stem cells found in colorectal polyps to the CD 133 marker were examined for polyps that dysplasia and non-dysplasia. This phase of the study included dysplasia in 42 out (42.0%) of 100 (100.0%) patients and polyps without dysplasia in 58 (58.0%). The correlation of the number of cancer stem cells found in polyps with and without dysplasia with their dysplasia and the incidence rate was investigated. It was found that the average number of cancer stem cells in polyps removed from 58 patients without dysplasia was 3.5±0.5, and the average number of cancer stem cells in polyps removed from 42 patients with dysplasia was 33.6±2.3. In the group of polyps with dysplasia, the average number of cancer stem cells stained with CD 133 in the visual field was 33.60±2.3, and in those without dysplasia,

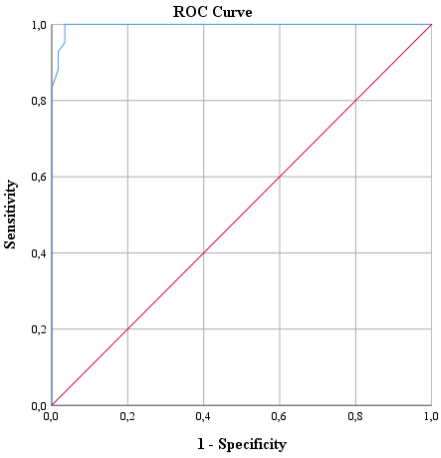
3.5±0.5. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) and the statistically significant difference was determined for both criteria (p_F <0.001; p_H <0.001). Therefore, a statistically significant difference was found between CD 133 and positively stained cancer stem cells in polyps with and without dysplasia. According to Spearman, nonparametric correlation analysis those with and without dysplasia have a high correlation in CD 133 staining and are statistically accurate ($\rho = 0.852$; p <0.001) (Graph 4).



Graph 4. The number of cancer stem cells showing positive expression with CD 133 in those with and without dysplasia.

The informativeness of the CD 133 marker of cancer stem cells was calculated according to the ROC curve, which is an integral indicator of specificity and sensitivity. The area of the ROC curve was determined to be 0.997±0.003 (95% CI: 0.990-1,000; p <0.001) (Graph 5). The point farthest from the reference line of the CD133's ROC curve - the cut-off value point - is set to 10. Sensitivity to CD 133 in dysplastic polyps is ≥10 - high, as they have a higher density of cancer stem cells than non-dysplasia. In the absence of dysplasia, CD 133 sensitivity constitutes <10 - lower. If the number of cancer stem cells is higher than ≥10 according to the coordinates of the ROC curve,

these polyps will belong to the group of polyps with dysplasia. Sensitivity is 100% and specificity is 96.6±2.4% (GDV = 98.0±1.4%). Initially, dark-stained areas in each field of vision were considered a cancer stem cell unit sensitive to the CD 133 marker. With the help of an automatic evaluation of the image analysis system in each polyp, it was detected that the number of dark-stained cells in the field of vision is different because this difference gives the number of cancer stem cells and varies depending on the nature of the polyp.



Diagonal segments are produced by ties.

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Lower Bound
0,997	0,003	< 0,001	0,990	1,000

Graph 5. ROC analysis on CD 133 marker in patients with and without dysplasia.

To determine the relationship between the number of cancer stem cells in colorectal polyps and their localization, the number of cancer stem cells present in the polyps, and whether they are related to the localization, size, dysplasia, and complication of the polyps were first studied.

Dysplasia was observed in 42 polyps, their classification was as

follows. Dysplasia was observed in 27 polyps smaller than 1 cm in size, the number of cancer stem cells constituted 29.6±2.8, dysplasia was observed in 12 polyps between 1 and 3 cm in size, the average number of cancer stem cells was 39.7±4,3. Dysplasia was observed in all polyps of 3, > 3 cm, the average number of cancer stem cells was 45.7±8.0.

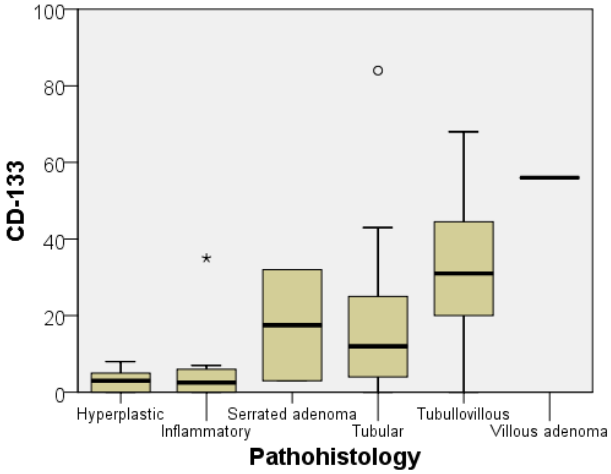
There is a strong correlation between polyp size and dysplasia. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) and a statistically significant difference was determined for both criteria (pF <0.001; pH <0.001). We also studied whether dysplasia varies depending on polyps localized in a single localization or several segments, and CD 133 sensitivity. Dysplasia was detected in 32 polyps localized in a single component. The average number of cancer stem cells seen in these polyps was 31.8±2.7.

During the study, it was revealed that 10 polyps localized in different segments have dysplasia. The average number of cancer stem cells in these polyps was 39.4±4.7. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis), a statistically significant difference (p_F <0.001; p_H <0.001) was determined for both criteria. This was the distribution of dysplastic polyps by pathohistological type. Dysplasia was observed in 21 tubular polyps. The average number of cancer stem cells here is 28.9±3.5. Eighteen of tubulovillous polyps have dysplasia. The average number of cancer stem cells constituted 37.9±3.2, and the villous adenoma was detected to be 1, the number of cancer stem cells was 56. Dysplasia was observed in 1 of the serrated adenomas, then the number of cancer stem cells was 32, and the number of cancer stem cells seen as a result of monitoring dysplasia in an inflammatory polyp was 35. The results were evaluated by analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) here, a statistically significant difference (p_F <0.001; p_H <0.001) was determined for both criteria.

Correlation between histological type of colorectal polyps and CD 133 expression. The evaluation of susceptibility to CD 133

markers depending on the histological type of colon polyps was studied. During the study, the average number of cancer stem cells in 45 (45.0%) tubular polyps was 15.8±2.5, the average number of cancer stem cells in 23 (23.0%) tubulovillous polyps was 30.3±4.0, and in villous adenoma, the number of stem cells was determined to be 56.

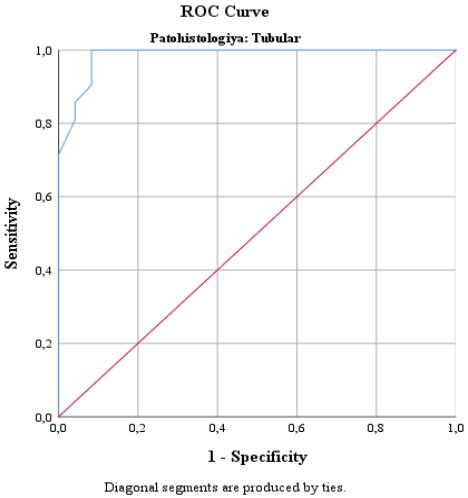
The average number of cancer stem cells in 16 (16.0%) inflammatory polyps belonging to the group of non-adenomatous polyps was 4.7±2.1, the average number of cancer stem cells in 13 (13.0%) hyperplastic polyps was 2.8±0.8, In 8, 2 (2.0%) serrated adenomas, the mean number of cancer stem cells was found to be 17.5±14.5. According to the number of cancer stem cells, 9 (34.6%) tubular polyps, 16 (61.5%) tubulovillous polyps, 1 93.8%) villous polyps were included in the high-risk group. Of these, 25 (96.2%) had CD 133 expression ≥ 14. In 59 (79.7%) of the 74 patients not included in the risk group, the expression of CD 133 was below the cut-off point (COP = 14) (Graph 6).



Graph 6. Expression of CD 133 by histological type of polyps.

ROC analysis was performed on CD-133 indicators, dividing patients with tubular polyps (n = 45) into groups with dysplasia (n = 21) and non-dysplasia (n = 24). As a result of the analysis, the point

farthest from the reference line of the coordinates of the ROC curve was considered the point of intersection value: COP = 10.5. CD-133 expression was above the cut-off value in all 21 patients with dysplasia (100%) and low in 22 (91.7%) of the 24 patients without dysplasia. Sensitivity - 100%, specificity - 91.7±5.6%. Integrated index of specificity and sensitivity GDV (General Diagnostic Value) - 95.6±3.1% (Graph 7). No cancer stem cells were found in 5 of the tubular polyps below the cut-off value (COP = 10.5). In one tubular polyp, 43 cancer stem cells with CD 133 sensitivity were found.



Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Lower Bound
0,985	0,013	<0,001	0,959	1,000

Graph 7. Results of ROC analysis in tubular polyps.

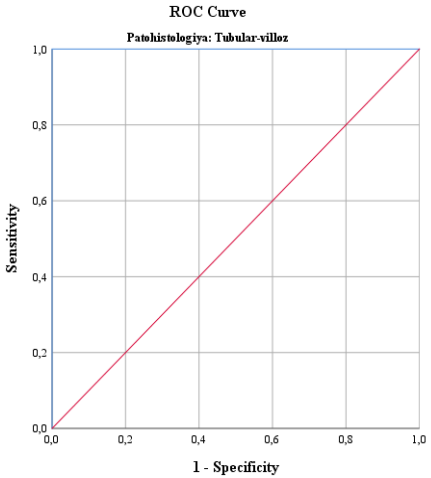
In two tubular polyps, there were 35 cancer stem cells with CD 133 susceptibility, 38 cancer stem cells in two, 39 cancer stem cells in one, 32 cancer cells in one, and 31 cancer stem cells in the other. These polyps are included in the group with dysplasia. Tubular polyps with 35.38 cancer stem cells were polyps smaller than 1 cm. In the polyp localized in the recto-sigmoid junction, 39 cancer stem cells were

observed. There were polyps with a size of 1-3 cm. The tubular polyp containing 32 cancer stem cells is 1.2 cm in size. The size of polyps with cancer stem cell numbers 28, 27, and 25 is 4-5 mm. The cancer was included in the group with dysplasia because the number of stem cells was 28. which was higher than the cut-off value point (COP = 10.5). The number of cancer stem cells was 21, 20, 19, and 17 in 4 tubular polyps. There were 18 cancer stem cells in 3 tubular polyps with CD133 susceptibility, 14 cancer stem cells in 2 tubular polyps, and 12 cancer stem cells in 2. In the field of vision, two tubular polyps, 18 and 14 cancer stem cells, were below the cut-off value.

The cancer was included in the group with dysplasia because the number of stem cells was higher than the cut-off value in tubular polyps with 21, 20, 19. However, in 17 tubular polyps, these polyps did not pose any risk of malignancy because they were below the cut-off value. As a result, signs of dysplasia are observed in tubular polyps and are considered statistically significant (Pp <0.001; pH <0.001). Tubulovillous polyps were more common in patients aged 41-60 years and older. Tubulovillous polyps were observed in 12 patients aged 41-60 years and in 13 patients over 60 years. Although these polyps are often observed as single polyps, the pathohistological result of those with two, three, or more polyps were tubulovillous polyps. Tubule villous polyps were found in 16 patients with single polyps (20.0%), 5 patients with double polyps (33.3%), 2 patients with 3 polyps (14.3%), and 4 patients with more than 3 polyps (44.4%). Tubulovillous polyps were found in all sizes. Tubulovillous polyps occur in 13 (48.1%) of polyps up to 1 cm, in 12 polyps 1 to 3 cm, (44.4%), and 2 (7.4%) polyps with more than 3 cm.

The majority of tubulovillous polyps, 41.8%, were removed with a snare polypectomy. Dysplasia was observed in 77.8% of tubule villous polyps. In the next stage, the CD 133 sensitivity was studied, and the sensitivity of which ranged from 0 to 68. CD 133 expression was not observed in tubulovillous polyps removed from two patients, which means that no cancer stem cells were detected in these polyps. In three patients with a tubule villous polyp, the number of cancer stem cells with CD 133 susceptibility was less than the cut-off value, ie 10. In 18 patients with tubulovillous polyps, the number of CD 133

susceptible cancer stem cells was above the cut-off value (COP = 11.5) (Graph 8).



Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Lower Bound
1,000	0,000	0,001	1,000	1,000

Graph 8. Results of ROC analysis in tubulovillous polyps.

The cut-off point was low in 5 polyps with no dysplasia and tubule villous histological structure. Among tubulovillous polyps with dysplasia, the highest number of cancer stem cells was 68. The number of polyps detected in this patient was more than 3. This patient was included in the high-risk group because the cut-off point was high. Another hypersensitivity, tubulovillous polyp with 58 cancerous stem cells in the visual field was also higher than the cut-off value. Although the number of cancer stem cells seen in tubulovillous polyps in the visual areas varies, most of them are below the cut-off value.

In three polyps, the cut was below the value point and these polyps are not at risk. Tubulovillous polyps contain CD-133 sensitive cancer stem cells and are directly proportional to the symptoms of dysplasia and are above the cut-off value. The results are statistically accurate

for both criteria (p_P <0.001; p_H <0.001). ROC analysis on CD-133 was performed by dividing patients with tubulovillous polyps into groups (n = 23) with dysplasia (n = 18) and non-dysplasia (n = 5).

As a result of the analysis, the point farthest from the reference line of the coordinates of the ROC curve - the point of intersection value was calculated: COP = 11.5. CD-133 expression was above the cut-off value in all 18 patients with dysplasia (100%) and below the cut-off value in all 5 patients without dysplasia (100%).

Thus, the cut-off point for the sensitivity of tubulovillous polyps to the CD 133 marker constituted 11.5 based on the coordinates of the ROC curve. Sensitivity - 100%, specificity - 100%. Integral indicator of specificity and sensitivity GDV - 100%. In a patient with villous polyp (2.9%), the sensitivity of the removed polyp to CD 133 was studied. This polyp was found in a patient over 60 years of age with intestinal complaints, belonging to the group of polyps with dysplasia. The expression of this polyp with CD133 was studied and the number of cancer stem cells in this polyp accounts for 56. Dysplasia was found in the polyp and was higher than the cut-off value (COP = 14). Hence, one of the villous polyps included in the study also has a cancer stem cell, and its cut-off point (COP = 14) is high and belongs to the high-risk group. The number of hyperplastic polyps was 13, the size is small, 16% of polyps up to 1 cm are hyperplastic polyps. No signs of dysplasia were observed in 93.8% of hyperplastic polyps. In the next step, CD 133 sensitivity was studied in 13 hyperplastic polyps. The CD 133 sensitivity of cancer stem cells in polyps ranged from 0 to 8. In all of these polyps, the cut-off was below the value point. CD 133 expression was almost not observed in 5 polyps , ie no stem cells were found in these polyps. Hyperplastic polyps are both histologically and have a small number of cancer stem cells, are below the cut-off value, and therefore do not carry any oncological risk.

The number of inflammatory polyps is 16 and one of them has signs of dysplasia. Most of the inflammatory polyps were polyps up to 1 cm. The sensitivity to CD 133 was studied in 16 polyps belonging to this group of polyps. Sensitivity to CD 133 ranged from 0-35 and merely one of these polyps had a cut-off point above it. Although dysplasia was observed in this polyp, it was not included in the high-

risk group. All 15 other polyps had low cut-off points. Dysplasia was not observed in any of these polyps and was below the cut-off value. Patients in this group do not carry oncological risk, both histologically and in terms of the number of cancer stem cells found in them.

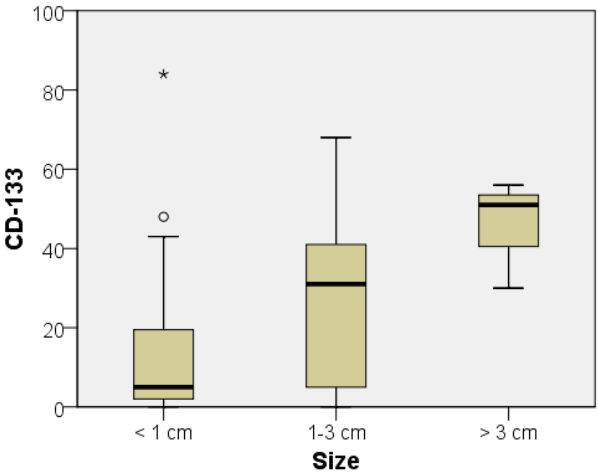
Two polyps were pathohistologically included in the group of serrated adenomas. One of these polyps was in the age group of 19-40 years, and the other was in the age group of 41-60 years and both were considered 1 cm smaller. In one of these polyps (50%) dysplasia was observed, and in the other (50%) it was not observed. Below the polyp cutting value, ie not included in the risk group, the number of cancer stem cells is 3. In other polyps, the number of cancer stem cells is 32. The polyp was included in the group of dysplasia. The number of cancer stem cells found in this polyp was above the cut-off value point (COP = 10), but not above the cut-off value point (COP = 14). Therefore, this polyp was not included in the high-risk group. Serrated polyps are histologically a separate group and it is highly recommended to follow up these polyps.

The CD-133 susceptibility of colorectal polyps was correlated with its pathohistological type. The results were calculated from the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis), and statistically significant differences were determined for both the Fisher ($p<0.001$) and Kruskal-Wallis ($p<0.001$) criteria. According to the non-parametric Spearman value, there is a strong correlation between the pathohistological type of polyps and CD133 ($\rho = 0.543$; $p <0.001$). Consequently, the number of cancer stem cells in adenomatous polyps was higher than non-adenomatous polyps in the visual field. The adenomatous polyps with pathophysiological dysplasia, if the number of cancer stem cells found in them is higher than the cut-off point (COP = 14), these polyps are considered high-risk polyps with a high risk of malignancy.

Correlation between size and number of colorectal polyps and CD 133 expression: colorectal polyps were also classified according to their size. Polyps are divided into 3 groups according to size:

1. Small polyps ≤1 cm in size
2. Polyps 1 to 3 cm in size
3. Polyps larger than 3 cm.

80 out of 100 polyps examined for CD 133 expression were included in group I. The average number of cancer stem cells in this group was 12.4±1.7, and 17 polyps were included in group II as polyps between 1-3 cm. In this group, the average number of cancer stem cells was calculated as 28.4±5.3, 3 polyps 3 cm higher were included in group III, and the average number of cancer stem cells observed in these polyps was calculated as 45.7±8.0. At the same time, the relationship between the size of polyps and their histopathological structure was researched. As the size of the polyp increased, the histopathological changes worsened. Large polyps are associated with dysplasia (Graph 9).



Graph 9. Large polyps are associated with dysplasia.

Dysplasia was observed in 27 out of the 80 polyps included in group I, and no dysplasia was detected in 53 polyps. The average number of cancer stem cells in 1 cm small polyps with 27 dysplasia was 29.6±2.8. The histopathological description of polyps with dysplasia is as follows: 18 polyps are tubular, 7 polyps are tubulovillous, 1 polyp is serrated, and 1 polyp is inflammatory. Of the 53 small polyps without dysplasia, 22 were tubular polyps, 13 were hyperplastic polyps, 14 were inflammatory polyps, 3 were tubule

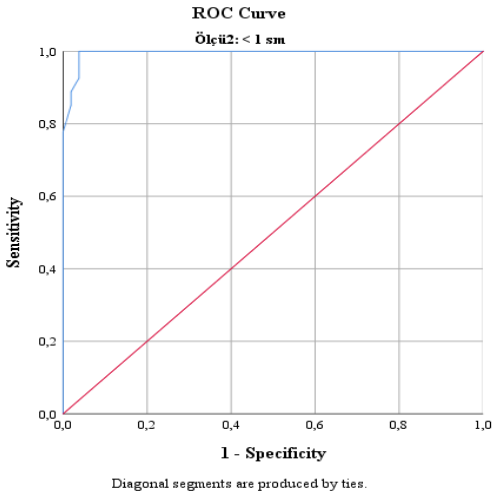
villous polyps, and 1 were serrated polyps. The average number of cancer stem cells in this polyp is 3.7±0.5. The maximum number of cancer stem cells in these polyps was 18. The results were calculated from the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal Wallis), and the results were statistically accurate (P_F <0.001; P_H <0.001).

In group, I tubular polyps, 84 cancer stem cells with CD 133 sensitivity were found. The polyp is localized in the rectum and is about 1 cm in size, which was removed by snare polypectomy. CD 133 was followed up because the number of stained cancer stem cells was high, and the cut-off value (COP = 14) was higher in this polyp. Another group I polyp with a high susceptibility to CD133 was a polyp with a tubule villous structure. CD 133 expression was higher than the cut-off value in 13 polyps in group I. In 12 of the 27 polyps observed for dysplasia, the cut-off value (COP = 14) was higher. These polyps are in the high-risk group, and histologically, 7 are tubular and 5 are tubule villous polyps. ROC analysis on CD-133 indicators was performed by dividing 1 cm small polyps (n = 80) into group I with dysplasia (n = 27) and non-dysplasia (n = 53).

As a result of the analysis, the point farthest from the reference line of the coordinates of the ROC curve - the point of intersection value was calculated: COP = 10.5. At the time of informatization, CD-133 expression was above the COP in all 27 patients with dysplasia (100%) and low in 51 (96.2%) of the 53 patients without dysplasia. Sensitivity is 100% and specificity is 96.2±2.6% (GDV = 97.5±1.7%). Group II included polyps with 1 to 3 cm in size. The number of polyps here is 17.

The average number of cancer stem cells in these polyps was estimated to be 28.4±5.3. According to the pathohistological structure, 5 polyps are tubular, one is inflammatory, and 11 are tubulovillous polyps. Dysplasia was not observed in 5 of 17 polyps, and dysplasia was observed in the other 12. The mean number of cancer stem cells was 1.4±1.0 in 5 polyps without dysplasia. In 12 polyps with dysplasia, the average number of cancer stem cells was 39.7±4.3. The cut-off value (COP = 14) was higher in the CD 133 sensitivity of cancer stem cells in these polyps. In the other five polyps without

dysplasia, the cut-off value was low. The results were calculated from the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis), here the results were statistically accurate (P_F <0.001; P_H <0.002).



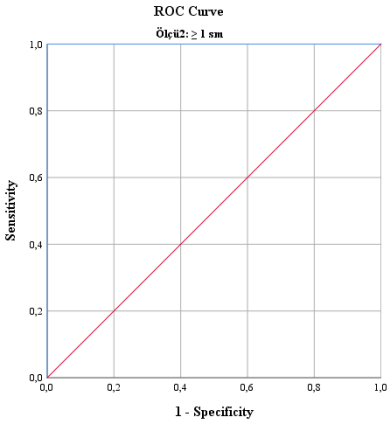
Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Lower Bound
0,995	0,005	0,000	0,985	1,000

Graph 10. Results of ROC analysis for polyps with <1 cm in size.

Group III included 3 large polyps. Dysplasia was observed in all three and the cut-off value point (COP = 14) was calculated above. The average number of cancer stem cells seen in these polyps is 45.7±8.6. The correlation of CD 133 sensitivity with the size of the polyps was also evaluated

The calculation was performed according to Spearman and a strong positive correlation was detected to be ρ = 0.331; p <0.001. ROC analysis was performed on CD-133 indicators by dividing 1 cm large (n = 20) dysplasia into groups (n = 15) and non-dysplasia (n = 5). As a result of the analysis, the farthest point of the coordinates of

the ROC-curve from the reference line - the cut-off point was calculated: COP = 10.0 In all 15 patients with dysplasia (100%) CD-133 expression above the cut-off point, in all five (5) patients without dysplasia (100%) was low. Sensitivity 100%, specificity 100% (GDV= 100%) (Graph 11).



Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Lower Bound
1,000	0,000	0,001	1,000	1,000

Graph 11. Results of ROC analysis for polyps with ≥ 1 cm size.

A polyp size of 1 cm increases the risk of dysplasia and sensitivity to the CD 133 marker by 100%. Here, the obtained results are statistically accurate. The sensitivity of CD 133 to polyp count and its effect on the number of cancer stem cells were also studied. It was found that the number of cancer stem cells increases with the number of polyps. So that the average number of cancer stem cells counted in polyps removed from 68 patients with 1 polyp in the intestine was 13.7±1.9. Dysplasia was not detected in 42 of these, and the average number of cancer stem cells in these polyps was estimated to be 3.0. Dysplasia was found in 26 polyps, in which the average number of

cancer stem cells was 30.2±2.5. The results were calculated from the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) and the results were statistically accurate (P_F <0.001; P_H <0.001).

The number of patients with two polyps is 13. The average number of cancer stem cells seen in them is 15.5±4.1. Dysplasia was not observed in 8 patients in this group, the average number of cancer stem cells was 4.6±1.2. 5 patients were accompanied by dysplasia. The average number of cancer stem cells seen in these polyps is 33.0±0.9. The results were calculated from the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis) and the results were statistically accurate (P_F <0.001; P_H = 0.003).

The number of patients with three polyps is 11. The mean cancer stem cell count in this group was 20.1±8.2. Dysplasia was not observed in 6 out of 11 patients, the average cancer stem cell count was 2.2±0.8, and the cancer stem cell count constituted 41.6±12.4 in 5 patients with dysplasia. The results were calculated from the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis), and the results were statistically accurate (P_F = 0.007; P_H = 0.006).

The number of patients with more than three polyps constituted 8. The average cancer stem cell count here is 32.3±8.0. Dysplasia was observed in polyps of 6 patients in this group. The average number of cancer stem cells was 42.0±6.6, and no dysplasia was observed in the two polyps. The average number of cancer stem cells counted here is 3.0±2.0. The results were calculated from the analysis of variance (F-Fisher) and non-parametric variation (H-Kruskal-Wallis), and the results were statistically accurate (P_F = 0.046; P_H = 0.018).

Number and correlation of cancer stem cells in high-risk patients group: Twenty-six (61.9%) dysplastic polyps were included in the high-risk group, with the higher cut-off point (COP = 14). This group included patients with colorectal polyps who were inflamed, showed high proliferative activity, were at high risk, had a large number of polyps, and had a very high number of cancer stem cells in the visual field. Of the 100 patients in the study group, 26 (26.0%)

were at high risk. The average number of cancer stem cells in this group was 36.1±3.5. All of these polyps have dysplasia. In high-risk polyps, the number of CD133-stained cancer stem cells in a single region was estimated to be 36.1±3.5, while in the other group, CD133-stained cancer stem cells were estimated to be 9.1±1.4 (P_F <0.001; P_H <0.001).

Of these, 10 (38.5%) were female and 16 (61.5%) were male. The distribution of patients by age was as follows: only 1 (5.9%) patients between the ages of 19-40, 11 (20.0%) patients between the ages of 41-60, and 14 (50.0%) patients over the age of 60. Patients are more likely to be included in the risk group with age, and a statistically significant difference between the patient's age and risk was determined (P_P = 0.002; P_H = 0.002). The more the patient complains, the more likely it is to have a painful polyp, ie. polyps with high proliferative activity, large in size, with signs of dysplasia. Statistically, a difference in accuracy was established between the patient's complaints and his risk, ie 22 of the patients in the risk group were patients with relevant intestinal complaints (Pp = 0.002; P_H = 0.002). Polyps in the high-risk group were divided into several groups according to their size, 12 (46.2) polyps up to 1 cm, 11 (42.3%) polyps between 1-3 cm, 3 (11.5%) Concentrated in a group of polyps up to 3 cm.

The large size of the removed polyps indicates an increase in the dysplasia symptoms, high proliferative activity. Statistically, there was a strong correlation between polyp size and risk (pp≤0.001; pH≤0.001).

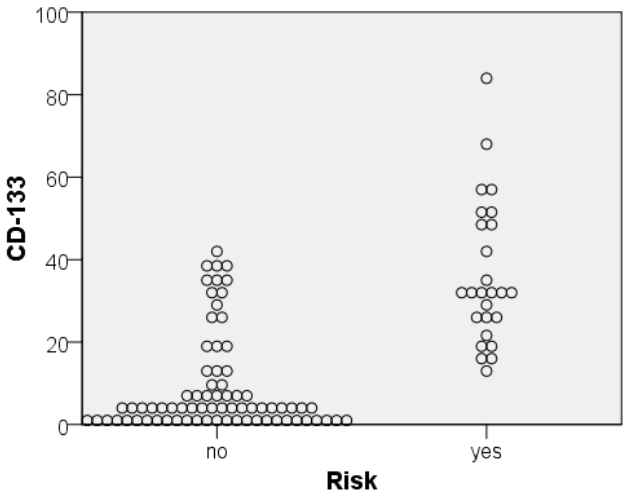
The number of polyps in this group also varied from patient to patient. Thus, 13 (50.0%) patients had single polyps, 3 (11.5%) had double polyps, 4 (15.4%) had three polyps, and 6 (23.1%) had more than three polyps.

The presence of multiple polyps statistically confirmed an increase in risk symptoms in the patient (P_P = 0.006; P_H = 0.007). The histological distribution in high-risk patients was as follows: 9 (34.6%) tubular polyps, 1 (3.8%) villous, and 16 (61.5%) tubulovillous polyps were observed. This group mainly included adenomatous polyps. Statistical accuracy was determined between the

pathohistological type and the risk (p_p <0.001; $_{pH}$ <0.001). Dysplasia was observed in all patients in this group and accounted for 61.9% of patients with dysplasia. The symptoms of dysplasia were determined to be statistically significant with their riches. ($_{Pp}$ <0.001; $_{pH}$ <0.001).

ROC analysis was performed on CD-133 parameters of high-risk (n = 26) and non-high-risk (n = 74) patients. As a result of the analysis, the point farthest from the reference line of the coordinates of the ROC-curve - the point of intersection value was calculated: COP = 14. During the informatization assessment, 25 (96.2%) of 26 patients with dysplasia had CD-133 expression above the cut-off point, and 59 (79.7%) of 74 patients not at risk were below: sensitivity 96.2±3.8% and specificity 79.7±4.7%. GDV = 84.0±3.7%.

According to Spearman, a non-parametric correlation method, there is a strong positive correlation (Pho = 0.613; p <0.001) between polyps in the risk group and CD 133 (Graph 12).



Graph 12. Correlation between risk group and CD 133.

In 18 out (69.2%) of the 26 patients at risk, the polyps were localized in one segment, and in 8 (30.8%) they were localized in different localizations, suggesting that the high sensitivity of the CD

133 marker in high-risk polyps and the high number of cancer stem cells are statistically significant. The study found that if the number of polyps detected by colonoscopy in patients was more than 2-3, and these polyps had high proliferative activity, the number of cancer stem cells in the visual field was higher than the cut-off value (COP = 14). Dysplasia was observed in all high-risk polyps. As a result, CD 133 is highly sensitive in polyps with dysplasia and has a high cut-off point (COP = 10). At the same time, the number of cancer stem cells exceeds the cut-off value (COP = 14) in polyps with some polyps greater than 1 and polyps larger than 1 cm, with high proliferative activity and pathohistologically high inflammatory elements. This increases the risk of malignancy in polyps. That is, as the risk of polyp complications increases, so does the number of cancer stem cells found in it.

Investigation of the clinical significance of stem cells in colorectal polyps: There is evidence that stem cells play a crucial role in the development of colorectal cancer. This is because stem cells can cause the formation and development of derivatives. CD133 has been shown to play a crucial role in stem cells determination. Thus, CD 133 was selected as a stem cell marker in our study for these characteristics.

The main purpose of the study was to assess the risk of dysplasia of colorectal polyps examining the staining properties of CD133 and marking stained stem cells. The statistical correlation of changes in the number of cancer stem cells depending on the location of the polyps was studied analyzing the relationship between the number and location of cancer stem cells in colorectal polyps.

The size of colorectal polyps, histological type, and the number of cancer stem cells in dysplastic and non-dysplastic species were calculated. Based on the results of the comparison, with the help of the Image Analysis program and non-parametric criteria, the cut-off point was evaluated with the specificity and sensitivity of the number of cancer stem cells detected in polyps. In the 319066.2-μm2 selected areas, CD133 sensitivity 36.1±3.5 was significantly higher in patients without dysplasia than in 9.1±1.4. This value was higher than the value

of non-malignancy cases ($p < 0.001$).

At the same time, the sensitivity of CD 133 changed according to the size of the polyps. The sensitivity of CD 133 was calculated as 12.4±1.7 in polyps up to 1 cm, 28.4±5.3 in CD 133 in polyps between 1 to 3 cm, and 45.7±8.0 in polyps larger than 3 cm. Hence, the size of the polyp increases so does its sensitivity to CD 133.

As the size of the polyps increased, their histopathological changes worsened. In addition, we found that as the size of the tumor increased, so did the number of cells stained positively with CD 133 in the single field of vision. If CD 133 values are associated with the development of dysplasia and deterioration, then the prognosis will worsen as the measurement increases.

Considering the urgency of the relationship between dysplasia and exacerbation and the fact that the positive staining of cells in the field of vision with CD 133 in patients with dysplasia is statistically higher than in those without dysplasia, then the sensitivity and specificity of cancer stem cells in polyp is calculated can be recommended. Uniform vision for dysplasia according to the coordinates of the ROC curve can be proposed as the cut-off value point (COP = 10) of cells stained with CD133. In adenomatous polyps in the risk group, a cut-off point (COP = 14) may be suggested according to the coordinates of the ROC curve of sensitivity to the CD 133 marker.

The cut-off value point is used to calculate the prognostic criterion for cancer stem cells found in large intestinal polyps. Because of the low number of cancer stem cells in polyps with a COP of 10, they are not at risk of developing cancer. Polyps with a COP greater than 10 are at risk of dysplasia but not cancer. However, polyps from the adenomatous polyps group with a high COP> 14 have a high risk of oncology in the risk group. Dysplasia was not found in hyperplastic or inflammatory polyps. CD 133 sensitivity was also low in this group of polyps. Cancer stem cells were found to be highly sensitive to CD 133 in polyps with dysplasia, large polyp size, and high-risk polyps in our study. Several studies have found a statistically significant link between CD 133 expression and the development of dysplasia and cancer.

CONCLUSIONS

1. Failure to detect colorectal polyps in time, not only increase the size of polyps, dysplasia, aggravate them, but also lead to the risk of colorectal cancer [2, 5, 17, 19, 26, 30].

2. Cancer stem cells are detected in all polyps of the large intestine, regardless of the number, size and localization of colorectal polyps. Finding the cut-off point of cancer stem cells in colorectal polyps has a significant impact upon improving outcomes by predicting their risk of developing colorectal cancer [1, 4, 5, 7, 9, 10, 20, 25, 29].

3. Although the number of cancer stem cells in colorectal polyps is directly correlated with the histological type, size, and severity of the polyps, there was no significant difference in their number or incidence depending on the patient's sex, age, and localization of the polyps [11, 12, 24, 22, 25].

4. The direct correlation of cancer stem cells with polyp dysplasia was found in colorectal polyps. The number of cancer stem cells in polyps with dysplasia constituted 33.6±2.3, and in those without dysplasia was estimated 3.5±0.5 ($p < 0.001$) [1, 21, 22, 29].

5. In colorectal polyps with and without dysplasia, the cut-off point of cancer stem cells is calculated from the ROC curve =10 (cut of point): ROC curve – is an integral indicator of specificity and sensitivity (ROCs = 0.997±0.003.95% CI: 0.990-1.000) [22, 29].

6. The incidence density of cancer stem cells is directly correlated with the size of colorectal polyps. The incidence of cancer stem cells in polyps smaller than 1 cm constitutes 12.4±1.7, in polyps between 1-3 cm 28.4±5.3, and in polyps larger than 3 cm 45.7±8.0 ($p < 0.001$) [11, 12, 22, 24].

7. The incidence density of cancer stem cells in colorectal polyps varies depending on its pathohistological type. The number of cancer stem cells in tubular polyps was 15.8±2.5, in tubulovillous polyps constituted 30.3±4.0, in villous polyp (n = 1) was 56,0, in hyperplastic polyps with estimated 2.8±0.8, in inflammatory polyps was 4.7±2.1, and in serrated adenomas was 17.5±14.5 ($p < 0.001$) [7, 4, 11, 21, 22].

8. The incidence density of cancer stem cells in colorectal polyps in the high-risk group was 36.1±3.5. The cut-off value of cancer stem cells in these polyps was calculated as COP=14 according to the ROC curve. Sensitivity 96.2±3.8%, specificity 79.7±4.7% (GDV = 84.0±3.7%) [22, 29].

9. The cut of value of cancer stem cells in colorectal polyps is prognostically the most useful for sensitivity and specificity. The cut of point indicates COP > 10 dysplasia and COP > 14 malignancy [22, 29].

PRACTICAL RECOMMENDATIONS

1. Cancer stem cell detection in colorectal polyps provides information on dysplasia, risk of complications, and malignancy.
2. The expression of cancer stem cells in colorectal polyps can be used in routine clinical practice to predict dysplasia, risk of complications, and malignancy.
3. To determine the number of cancer stem cells, the immune histochemical examination of the CD 133 marker and counting with the Clemex Vision Lite 3.5 Image Analysis program may be recommended.
4. In patients with cancer stem cell expression >10, a follow-up examination can be recommended as early as 3 months after polypectomy.
5. In patients with > 14 expression in cancer stem cells, the approach is recommended under the principle of treatment of malignant tumors.

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List of abbreviations

CD-133 – prominin 1
COP – cut of point
CVL – Clemex Vision Light 3.5 (Image Analysis Program)
CI – confidence interval
EIF – efficiency influence of factor
HE – hematoxylin-eosin
CSC – cancer stem cells
IHC – immunohistochemistry
KI-67 – proliferation index
CRC – colorectal cancer
CRP – colorectal polyp
OR – Odds ratio
CT – computed tomography
ROC – receiver operating characteristic (integrated value of sensitivity and specificity)
GDV – general diagnostic value
TV – tubulovillous

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