

# Kudo's pit pattern classification for *in vivo* optical diagnosis and discrimination of advanced colorectal polyps

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**Abstract. – OBJECTIVE:** Colonoscopy is currently the basic diagnostic tool for the large intestine. The size of lesions assessed during the investigation is one criterion for assessing the risk of polyps transforming into colorectal cancer. The technological development of endoscopes and the possibility of direct assessment of lesion's surface during the endoscopic examination and to use appropriate treatment. The aim of this study is to analyze the consistency between the histopathological assessment of high-risk lesions in colonoscopy and the determination according to Kudo's pit pattern classification.

**PATIENTS AND METHODS:** The analysis included the results of colonoscopies performed over a 2-year period, in which polyps were diagnosed endoscopically and either polypectomies were performed, or sections were taken from these polyps and a pit pattern analysis was done according to Kudo's classification.

**RESULTS:** A total of 1038 patients (age, 67.2 ± 12.7 years) were enrolled in the study. Of the 1981 samples taken in total, polyps larger than 1 cm were found in 96 cases, laterally spreading tumors (LSTs) were found in 48 cases, and macroscopic infiltration or tumors were found in 110 cases. The results of the histopathological examination were obtained in 248 cases. A value of 4 or higher in the Kudo classification turned out to be the best parameter to differentiate malignant lesions from benign ones for lesions larger than 1 cm and laterally spreading tumors, with a sensitivity of 91.2% and a specificity of 70.4%.

**CONCLUSIONS:** The assessment of polyps according to Kudo's classification is a useful tool for assessing the malignancy of lesions as part of a routine colonoscopy.

*Key Words:*

Colon polyps, Pit pattern, Advanced colon adenomas.

## Introduction

Colorectal cancer (CRC) occupies a leading position among malignant neoplasms. Epidemiological data indicate that its frequency is on the rise<sup>1,2</sup>. Data from Polish registers show that annually there are about 18,000 new cases and about 12,000 deaths in Poland. Over the last decade or so, a 3- or 4-fold increase in the incidence rate of CRC and a 2- or 3-fold increase in the mortality rate have been observed. Screening tests represent an attempt to reduce the incidence of CRC; they are intended for healthy people, not for those who already have CRC symptoms. The simplest screening test is a per rectum examination of patients, regardless of the reason for visiting a doctor. The studies whose effectiveness in the prevention of CRC have been studied most are stool examination for occult blood, endoscopic examination limited to the rectum and sigmoid colon (sigmoidoscopy), and full colonoscopy<sup>3-5</sup>. Other tests include rectoscopy, a whole group of radiological tests, and various types of genetic tests to detect the genetic material of a tumor in the stool.

The role of all screening tests is to detect precursor lesions. Colonoscopic examination offers both the detection and removal of precursor lesions in the entire colon. In many cases, such colonoscopy smoothly passes from the diagnostic to the therapeutic stage and at the same time encompasses the entire diagnostic and therapeutic process<sup>6</sup>. A high-quality colonoscopy and the removal of all lesions reduces the risk of CRC development by 75% to 90%. It seems that for most patients it may be sufficient to perform only 1 colonoscopy in their lifetime<sup>7,8</sup>. Database analysis

shows that the presence of early precursor lesions in the intestine is common, affecting as many as 30% to 40% of patients in the population over 50 years of age. Among the precursor lesions, the most important are high-risk lesions, defined as polyps with any of the following characteristics: a size of more than 1 cm, villous elements, high-grade dysplasia, or already transformed into CRC. In recent years, right-sided colorectal lesions – previously considered to be completely harmless hyperplastic polyps – have been found to be the result of an alternative path of carcinogenesis and are now classified as serrated adenomas<sup>9-11</sup>.

The initial element that impacts the entire process of endoscopic colon diagnostics is the proper preparation of the intestine for examination. Poor preparation means that even large, advanced adenomas are likely to be overlooked, which is reflected in the deterioration of other indicators of examination quality<sup>12</sup>. This parameter largely depends on the patient's attitude toward the required dietary restrictions and discipline in taking the laxative for bowel preparation before colonoscopy<sup>13</sup>. The number of examinations in which at least 1 polyp with adenoma structure was found is the basis for determining the adenoma detection rate (ADR). This parameter is the basis for comparing both new endoscopic techniques and endoscopists. It has been proven that patients examined by doctors with higher ADRs have a lower risk of developing interval cancer, that is, cancer that occurs between the scheduled dates of follow-up examinations<sup>14,15</sup>.

The Kudo classification used in the analysis is based on the evaluation of the pit pattern. The baseline is the pit pattern in a normal mucosa. The pits are round and regular (type 1). In type 2, the pits are star-shaped a slightly larger than in type 1. The assessment is made by comparison with the normal mucosa surrounding the lesion. Within the second type, the 2-O subtype (open shape) can be distinguished, which differs in that the pits are larger than the adjacent ones due to the distension of the glandular tubes by a large amount of mucus. Type 3 also has two subtypes: 3L and 3S. In type 3L, the pits are elongated and in type 3S, they are round and smaller than in type 1. In type 4, the pits are elongated and dendritic and the appearance of the lesion itself can be compared to the brain. In type 5, two subtypes can be also distinguished: 5I (irregular), characterized by the presence of various pit patterns within the lesion irregularly distributed. Type 5N

(nonstructural) denotes a complete disappearance of pits and an amorphous appearance of the lesion surface<sup>16</sup>.

The Kudo classification is based on the observation that the pit pattern is related to the histopathological structure of the polyp. Type 1 is intended to correspond with normal mucosa, submucosal lesions, and hyperplastic polyps. Type 2 is characteristic of hyperplastic polyps, while subtype 2-O is associated with serrated adenomas. Type 3L is characteristic of adenomas; subtype 3S corresponds to the foci of severe dysplasia. Type 4 is associated with the development of the villous element within the polyp. Type 5I shows the presence of high-grade dysplasia, while type 5N corresponds to cancer foci<sup>16</sup>.

The aim of this study is to analyze the consistency between the histopathological assessment of high-risk lesions in colonoscopy and the determination according to Kudo's pit pattern classification.

## Patients and Methods

All colonoscopic examinations performed at the Endoscopic Unit of the City Hospital between January 2014 and December 2017 were analyzed retrospectively. Examinations in which no specimens were taken, examinations in patients with bowel inflammation of any etiology, and those in which specimens were taken from the normal mucosa were excluded. The indications for the examination, its scope, the degree of preparation of each segment of the bowel, the laxative used for the bowel preparation, and the manner of its admission were recorded. The size and removal technique of polypoid lesions were recorded. After the Kudo classification was introduced into routine clinical practice, polyps were additionally classified according to the pit pattern. In order to improve the tolerance of the examination, patients reporting pain received analgosedation: fentanyl and/or midazolam. Small polypoid lesions up to 2 or 3 mm in size were removed with biopsy forceps. Endoscopic loops were used to remove lesions larger than 3 mm and lesions up to 10 mm in size were removed using the technique without the use of electricity. Lesions that spread laterally – carpet polyps – were removed piece by piece with an endoscopic loop. This method of removing large lesions is called piecemeal resection. The morphology of the polyps was assessed based

on the Paris classification, as well as the pit pattern according to Kudo classification. The Paris classification of polyps assigns lesions to 1 of 3 groups: polypoid (protruding) lesions (sessile or pedunculated), non-polypoid lesions (flat-elevated, flat, or slightly depressed), and excavated (ulcerated) lesions.

The Kudo classification was introduced into routine clinical practice in October 2016. Lesions considered by the endoscopist to be candidates for endoscopic treatment, in the absence of contraindications – e.g. antiplatelet and anticoagulant treatment or insufficient bowel preparation – were removed during the same examination and the material was subjected to histopathological evaluation.

The collected material was placed in containers with formalin; 1 container could contain several polyps of different sizes and morphologies, removed with both forceps and a loop (if they came from the same anatomical location).

The study was conducted with the consent of the Bioethics Committee at the Military Institute of Medicine, issued on April 18, 2018 (resolution No. 94/WIM/2018).

### Statistical Analysis

Qualitative variables are presented as counts in multi-way contingency tables or as a percentage share. Quantitative variables are presented as means with standard deviations. The chi-square test was used to test the differences between the qualitative data. In order to determine the best cut-off point for the Kudo classification in the identification of histopathologically malignant lesions, ROC analysis was used. A significance level of  $p < 0.05$  was considered statistically significant. Statistica v. 12.0 software (Statsoft, Poland) was used to perform the statistical analysis.

## Results

A total of 1038 patients (age  $67.2 \pm 12.7$  years) were enrolled in the study. Slightly more than half (55%) were men. Of the 1981 samples taken in total, polyps larger than 1 cm were found in 96 cases, laterally spreading tumors (LSTs) were found in 48 cases, and macroscopic infiltration or tumors were found in 110 cases. In total, 254 samples were considered high-risk lesions in the initial evaluation, which represented almost 13% of all samples. The remaining material was polyps smaller than 1 cm.

The results of the histopathological examination were obtained in 248 cases. The pit pattern was determined in 25 of the polyps larger than 1 cm, in 22 of the LSTs, and in 14 of the macroscopic infiltration/tumors. In total, the pit pattern was determined in 61 cases of lesions that were endoscopically considered advanced (Table I).

In the group of polyps larger than 1 cm, there was no lesion with the type 1 pit pattern. Four lesions were classified as having a type 2 pit pattern and all of them were classified as benign in histopathology. A type 3 pit pattern was found in 9 cases. Six of them turned out to be histopathologically benign, and 3 were malignant. A type 4 pit pattern was assigned to 11 lesions, 4 of which were benign and 7 of which were malignant. A type 5 pit pattern was assigned to 1 lesion, and it was found to be histopathologically malignant (Table II).

For the LSTs, a type 1 pit pattern was recognized in 1 case, a type 2 pit pattern was found in 1 case, and a type 3 pit pattern was found in 7 cases; all of them turned out to be histopathologically benign. A type 4 pit pattern was found in 9 lesions, 3 of which were benign and 6 of which were malignant. Four lesions had a type 5 pit pattern, and all were histopathologically malignant. Among these lesions, statistical significance was

**Table I.** Histopathological diagnoses depending on the size class of polyps.

Size of the polyps	Normal mucosa/lymphoid nodules	Polyp/inflammatory infiltrate	Hyperplastic polyp	Tubular/serrated adenoma	Tubular adenoma with high-grade dysplasia	Tubulovillous adenoma	Cancer	Number of samples
Greater than 10 mm	0	1	4	52	9	20	9	95
LST	0	1	8	21	5	5	7	47
Tumor /infiltration	0	17	1	0	9	0	79	106
Total	0	19	13	73	23	25	95	248

Abbreviation: LST - laterally spreading tumors.

**Table II.** Comparison of the nature of the lesions assessed by Kudo's classification and of the histopathological assessment in individual polyp size classes.

Polyp size	Expected type of lesion according to the Kudo classification	The nature of lesions in the histo-pathological examination: benign lesion	The nature of lesions in the histo-pathological examination: malignant lesion	Total
Greater than 10 mm	Benign lesion	9	3	12
Greater than 10 mm	Malignant lesion	5	8	13
Total		14	11	25
LST	Benign lesion	9	0	9
LST	Malignant lesion	3	10	13
Total		12	10	22
Tumor/infiltrate	Benign lesion	0	0	0
Tumor/infiltrate	Malignant lesion	1	13	14
Total		1	13	14

Abbreviation: LST - laterally spreading tumors.

obtained in terms of the structure of the distribution of the pit pattern ( $p < 0.01$ ).

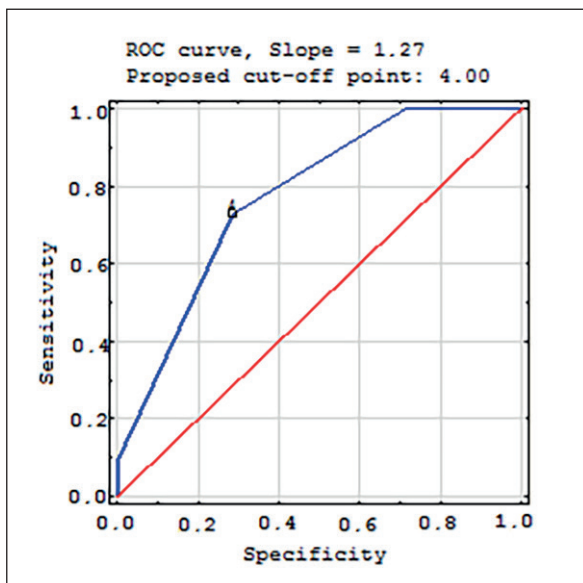
In all 14 of the lesions with an infiltration/tumor morphology, only the type 5 pit pattern was found. One lesion was histopathologically benign, while the other 13 were malignant.

In order to determine the Kudo classification cut-off point that best identifies malignant lesions, ROC analysis was performed. For the lesions larger than 1 cm, a value of 4 in the Kudo classification turned out to be the best parameter

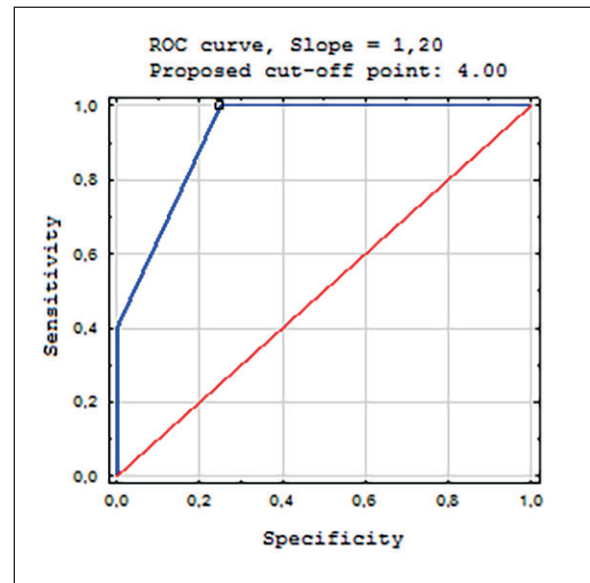
to differentiate malignant lesions from benign ones in histopathological examination (sensitivity, 72.7%; specificity, 71.4%; accuracy, 0.720; AUC, 0.773;  $p = 0.004$ ) (Figure 1).

For the laterally spreading tumors, the best distractor for histopathologically confirmed malignancy was a type 4 pit pattern (sensitivity, 100.0%; specificity, 75.0%) (Figure 2).

It was not possible to determine the ROC curve for lesions of the macroscopic infiltration/tumor type, since all the lesions were



**Figure 1.** ROC diagram for Kudo classification in the differentiation between malignant and benign intestinal lesions larger than 10 mm in diameter.



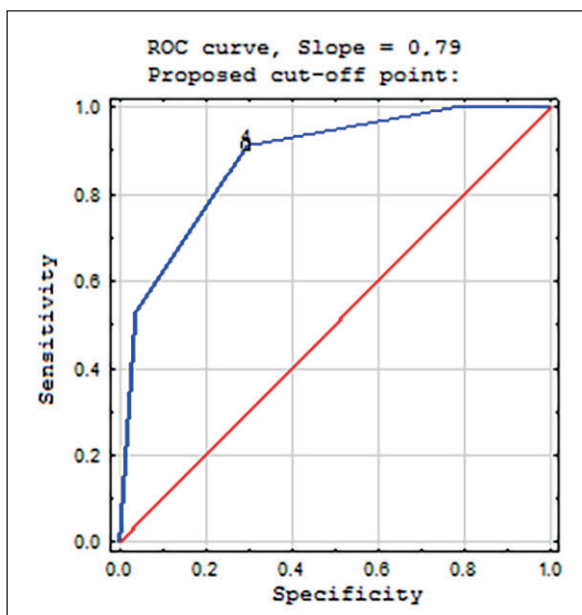
**Figure 2.** ROC diagram for Kudo classification in the differentiation between malignant and benign laterally spreading tumors.

classified as type 5 pit pattern, and in 13 out of the 14 cases, the lesion was confirmed to be malignant.

Considering all the lesions suspected of being malignant in the colonoscopy, the diagnosis of at least type 4 in the Kudo classification allowed the histopathologically malignant lesions to be identified with a sensitivity of 91.2% and a specificity of 70.4% (AUC, 0.879;  $p < 0.001$ ) (Figure 3).

## Discussion

The basis of therapeutic success is to perform a high-quality examination and to describe any detected lesions in a way that is understandable to other physicians. Validated scales and classifications should be used. The morphology of polyps in the large intestine is described using the Paris classification. It was introduced almost 20 years ago, but nevertheless shows high concordance between endoscopists and, additionally, it facilitates therapeutic decision-making<sup>17,18</sup>. The Paris classification does not include LSTs. These are flat lesions larger than 10 mm that show a tendency toward peripheral growth. In the described study, the lesions were classified based on this classification, in accordance with the quality requirements for the description of endoscopic examinations.



**Figure 3.** ROC diagram for Kudo classification in the differentiation between malignant and benign high-risk intestinal lesions.

One of the most important parameters determining the quality of colonoscopy is the ADR<sup>19</sup>. If the doctor performing the examination has a sufficiently high ADR, the risk of interval cancer in their patients is much lower. Such doctors find more polyps, which results in a more effective removal of polyps from the bowel and a shorter time to follow-up examination<sup>20</sup>. It is estimated that a 1% improvement in ADR reduces the risk of CRC by 3%. Additionally, it reduces CRC mortality by about 5%. The study population was older than those subjected to CRC screening in the Polish screening program. This explains the proportion of advanced lesions being greater than that calculated for screening tests. Additionally, the methodology adopted for the study, whereby all polyps from a given anatomical location were placed in a single container, meant that it was the largest of the polyps, or the lesion suspected to have the furthest histological advancement, that determined the group to which all other lesions in the same container were assigned.

During the endoscopic examination, all lesions that can be safely and radically removed should be removed. One important parameter is the risk of severe dysplasia and cancer in the removed lesions. For polyps larger than 10 mm, the risk of high-grade dysplasia and cancer is estimated at approximately 73%<sup>21</sup>. In the study group, among lesions greater than 1 cm, advanced lesions were found in 38 out of 95 (40%) cases. However, using the Kudo classification, 12 samples were considered histopathologically benign, 9 of which were benign (75%); 13 samples were considered malignant, 8 of which were malignant (61%). As can be seen, the Kudo classification provides a good prediction for benign lesions larger than 1 cm. For histopathological diagnosis of a malignant lesion, the Kudo classification only offers a high probability in cases of lesions of at least category 4.

For LSTs, malignant lesions were found in 17 out of 47 cases (36%). Lesions considered benign based on the Kudo scores turned out to be benign in each of the 9 cases; lesions determined to be malignant were so according to the histopathological assessment in 10 out of 13 cases (76%). Therefore, in this sample, the Kudo classification made it possible to exclude malignancy in 100% of lesions and to confirm malignancy in 76%.

In the infiltration/tumor group, advanced lesions accounted for 88 cases out of 106 (83%). Among the histopathologically advanced lesions, 89% of them turned out to be a cancer. In the

group of lesions for which the Kudo classification was determined, only 1 turned out to be histopathologically benign, while in 13 out of 14 cases, cancer was histopathologically confirmed; this represents 92% of the lesions. As can be seen, the Kudo classification allows for the diagnosis of advanced lesions with a very high probability, although the morphology of the lesion itself speaks for its malignant nature.

For endoscopic treatment, only lesions affecting the mucosa or infiltrating the submucosa to a depth of 1000  $\mu\text{m}$  are qualified. There are no good endoscopic parameters to assess the risk of deep infiltration. Indirect features suggesting the presence of deep infiltration are a stiffening of the intestinal wall and the presence of ulceration within the flat lesion<sup>16,22</sup>. Therefore, additional tools have been introduced into clinical practice to assess the risk of high-grade dysplasia and cancer based on an assessment of the microstructure of the lesion surface, including Kudo classification, Sano classification, and NBI international colorectal endoscopic classification<sup>16,22-29</sup>. Training a physician to use these classifications is neither costly nor time-consuming. Usually, several hours of training and the evaluation of a few dozen endoscopic images under the supervision of an expert are sufficient. The presented study used the Kudo classification, which assesses the pit pattern. This classification does not require the purchase of dedicated endoscopes, as the resolution and magnification of standard endoscopes is already sufficient<sup>30-34</sup>.

Despite the large number of patients enrolled, our study also had a few limitations. Firstly, the evaluation of the results is retrospective, and the studies were performed by several specialists under normal time constraints, which resulted in limited reliability and complementarity of the data, including a reduced number of Kudo assessments. Secondly, it was not possible to assess the impact of variability within and between researchers on the results. In view of the above, it seems justified to verify the results obtained in this study with a prospective study.

## Conclusions

The introduction of the Kudo classification into common clinical practice is easy and does not entail additional costs. The use of the Kudo classification allows the histopathological structure of lesions to be predicted during the endoscopic

examination. The Kudo classification classifies lesions with a high risk of malignancy more precisely than an assessment of only the size and morphology of lesions.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

## Funding

This research received no external funding.

## Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Military Institute of Medicine Ethics Committee 18.04.2018 (NR 94/WIM/2018).

## Authors' Contribution

Conceptualization, C.A, M.D, M.F.; methodology, C.A and M.F.; formal analysis, M.F.; investigation, C.A, M.F.; resources, C.A.; data curation, C.A.; writing—original draft preparation, C.A, M.F, K.K.; writing—review and editing, M.F, K.K, W.M, M.D, K.A.; visualization, M.F, K.K.; supervision, W.M, M.D, K.A; All authors have read and agreed to the published version of the manuscript.

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