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COMPARISON OF TUNNEL AND CLASSICAL METHODS OF ENDOSCOPIC SUBMUCOSAL DISSECTION IN EPITHELIAL COLON TUMORS (systematic review and meta-analysis)

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BACKGROUND: endoscopic submucosal dissection (ESD) is a modern effective method for patients with benign epithelial tumors and early colorectal cancer.
The use of such a technique for ESD as a submucosal tunnel ('pocket') – creation under a tumor creates conditions for improving the surgical specimen qualityand reducingfragmentationrate.
AIM: to study the effectiveness and safety of the tunnel method of ESD (TESD) in comparison with classical ESD (CESD) in colorectal adenomas and early colorectal cancer.
MATERIALS AND METHODS: literature search and meta-analysis were performed in accordance with the PRISMA recommendations using the PUBMED search system in the Medline electronic database without limiting publication datesin the English language literature. The systematic review included all the studies on comparison of the tunnel and classical ESD methods.
RESULTS: the analysis included 4 studies (1,422 patients, 458 in the TESD group and 961 in the CESD group). The groups were comparable in the number of adenomas (OR=1.25; 95% CI=0.87-1.79; p=0.22), adenocarcinomas (OR=0.96; 95% CI=0.49-1.87; p=0.90), in the size of neoplasms (95% CI=-6.26-1.22; p=0.19), and in the presence of submucosal fibrosis (p=0.69). There were no significant differences in intraoperative bleeding rate (OR=1.24; 95% CI 0.53-2.88; p=0.61); however, perforations occurred more often when using CESD (OR= 0.35; 95% CI=0.15-0.83; p=0.02). The CESD took significantly longer time than the TESD (OR=-19.1; 95% CI=33.89-4.45; p=0.01). The frequency of en bloc resections (OR= 16.06; 95% CI=4.95-52.11; p<0.0001) and R0-resections (OR=3.28; 95% CI=1.30-8.32; p=0.01) were significantly higher in the TESD.
CONCLUSION: the tunnel method of endoscopic submucosal dissection is an effective and safe alternative to the classical method. However, there is currently a lack of data for the choice of submucosal dissection method for large colorectal adenomas and early colorectal cancer, which requires further comparative studies.

[Key words: endoscopic submucosal dissection; pocket method; tunnel method]

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INTRODUCTION

Currently, a number of endoscopic methods are widely used to safely remove colon tumors.
However, such relatively simple and common methods as endoscopic mucosectomy and electro-excision have a number of negative features such as fragmentation and bad quality of removed specimens, which makes it difficult to perform a complete morphological assessment [1].
To overcome these drawbacks, the method of endoscopic dissection in the submucosal layer (ESD) was developed [1], which allowed to improve the quality of removed specimen in general, increasing the rate of R0-resection up to 90%, and reducing the fragmentation rate to 10% [2,3]. However, with large neoplasms (more than 40 mm), the R0-resection rate can be reduced to 70%. Most likely, this is due to technical difficulties in visualizing the submucosal layer in large tumors, which in most cases inevitably leads to removal of a tumor by its fragmentation [4,5,6].
The classical method of ESD (CESD) involves the injection of a solution into the submucous layer under a tumor ('lifting') and circular dissection of the mucosa

around the tumor at a distance of at least 1 mm. At the next stage, the submucosal layer is separated from the muscle layer. In this case, the previously introduced solution for lifting begins to flow along the entire length of the surgical wound, which significantly complicates the differentiation of the layers. This requires frequent additional injections of the solution, often accompanied by formation of hematomas and other adverse effects that impair visualization.

As an improvement of the ESD technique, the method of tunnel («pocket») creation in the submucosal layer under the tumor by dissecting the mucosa from only one of the edges of the tumor was proposed, which allows maintaining adequate lifting throughout the entire surgery, creating better conditions for a high-quality specimen removal without resorting to its fragmentation [7-9]. The method is called tunnel endoscopic submucosal dissection (TESD).

AIM

The aim of this meta-analysis was to compare effectiveness and safety of the classical ESD (CESD) and tunnel ESD (TESD).

MATERIALS AND METHODS

The systematic review and meta-analysis were performed in accordance with the PRISMA recommendations using the PUBMED search system in the Medline electronic database without limiting dates of publications in the English language literature [10]. The search was conducted using the keywords: «endoscopic submucosal dissection», «pocket-creation», «endoscopic tunnel». The systematic review included all the studies on comparison of the CESD and TESD. The study included full-text English language articles.

Two-hundred eighty-four studies containing the keywords were found. When screening those works, 87 studies were selected from them. Then, the analysis excluded 78 studies on the use of this technique for diseases of other localities: esophagus, stomach, duodenum, one animal study and 6 descriptions of clinical cases.

Also, 1 observational study was excluded as it described preliminary results of treatment of patients with rectal tumors by using TESD.

It should be noted that in the available scientific literature there are no direct comparisons of the tunnel and classical ESD methods for only large (more than 30 mm) epithelial colorectal tumors.

Eventually, 4 studies were included in the meta-analysis: 1 prospective and 3 retrospective studies.

Thus, the meta-analysis included 1,422 patients; 458 of them were in the TESD group and 964 – in the CESD group.

The comparative analysis of the TESD and CESD methods was carried out with the study of such criteria as the size of the removed tumors, their histological structure (adenoma/adenocarcinoma), the presence of fibrosis in the submucosal layer, the frequency and nature of complications (bleeding and perforation),

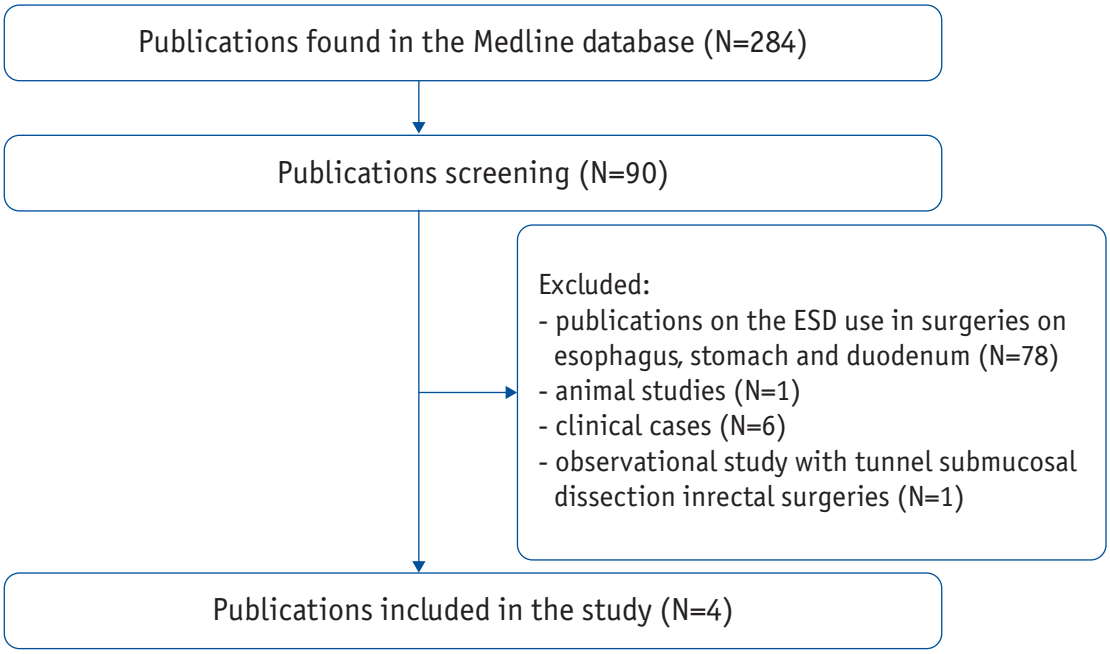

Figure 1. *Publications screening*

the duration of each procedure (minutes), the *en bloc* resections rate and the R0-resections rate.

STATISTICAL ANALYSIS

The statistical analysis for direct comparison of the methods was performed using the Review Manager 5.3 program. The total value of the dichotomous data is represented as an odds ratio (OR) with a 95% coincidence interval (CI). The statistical heterogeneity of the studies was evaluated using the χ^2 test. I^2>50% and p<0.1 were considered statistically significant heterogeneities.

RESULTS

Data on the size of the removed tumors with standard deviation values were found in 2 studies (Fig. 2).
In the statistical analysis of the lesion size based on the results of morphological examination of surgical specimens, in the TESD group the size was on average 2.5 mm larger than in the CESD group, but the differences were not statistically significant (95% CI=6.26-1.22; p=0.19).
Data on the histological structure of the removed tumors (adenoma/adenocarcinoma) were available in all 4 publications. The ratio of adenomas and adenocarcinomas was 3:1. There were no significant differences between the TESD and the CESD groups for this indicator (OR=1.25; 95% CI=0.87-1.79; p=0.22).
According to many authors, the submucosal fibrosisat the removed tumor base is a significant risk factor for intra- and postoperative complications, as well as an increase in the probability of ESD conversion to transabdominal surgery [6] (Fig. 4).
It was found that the study groups were comparable in the rate of submucosal fibrosis (OR=1.12; 95% CI=0.64-1.97; p=0.69).
The incidence of intraoperative bleeding was also comparable in both groups (OR=1.24; 95% CI=0.53-2.88; p=0.61) (Fig. 5).
When analyzing the intraoperative bowel perforation rate, it was found that this complication developed significantly less frequently in TESD (OR=0.35; 95%

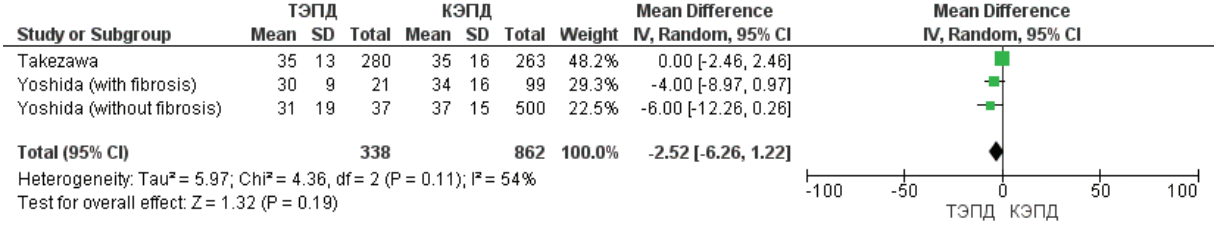

Figure 2. *Tumor sizes in the TESD and the CESD groups*

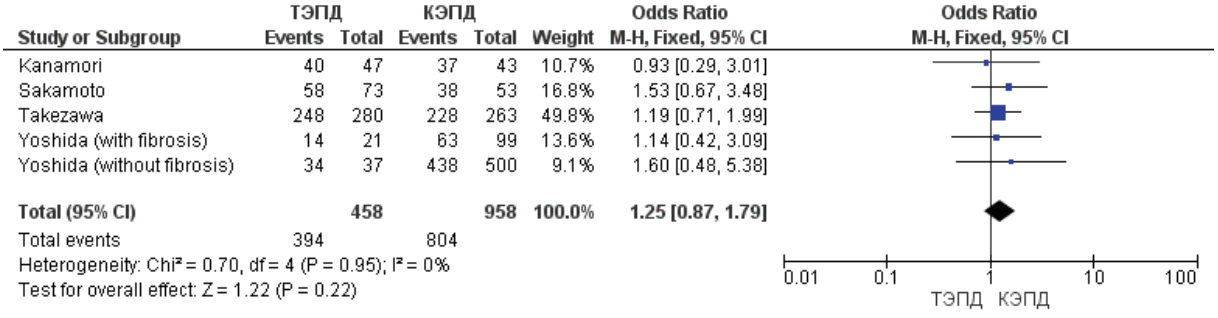

Figure 3. *The number of adenomas in the TESD and CESD groups*

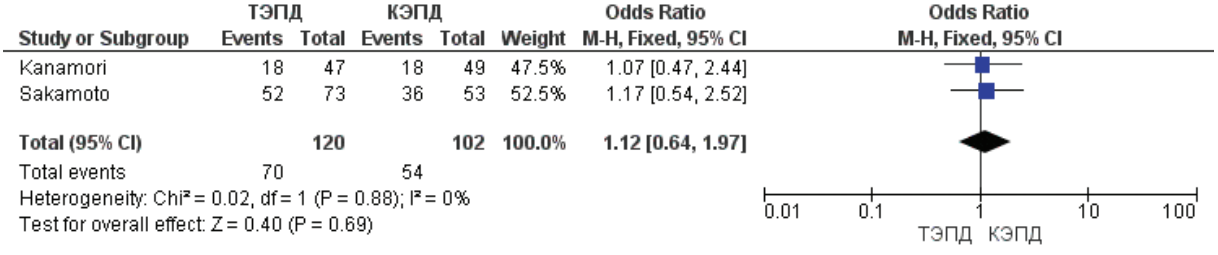

Figure 4. *Submucosal fibrosisincidence in the TESD and CESD groups*

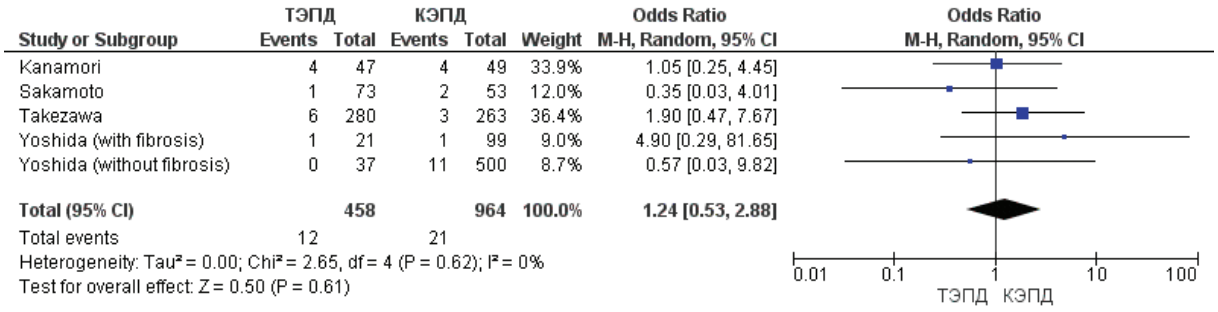

Figure 5. *The bleeding incidence in the TESD and CESD groups*

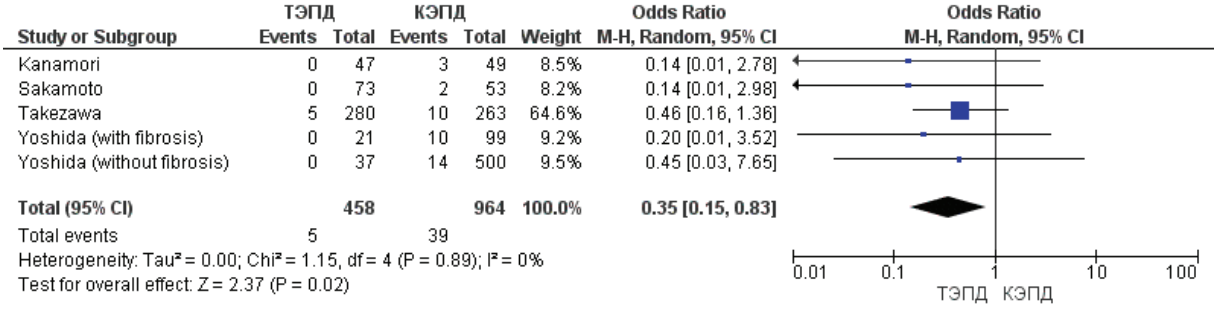

Figure 6. *Perforations in the TESD and CESD groups*

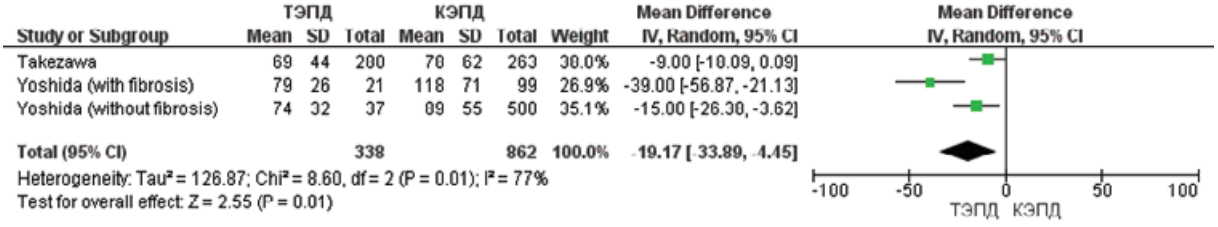

Figure 7. *Procedure time*

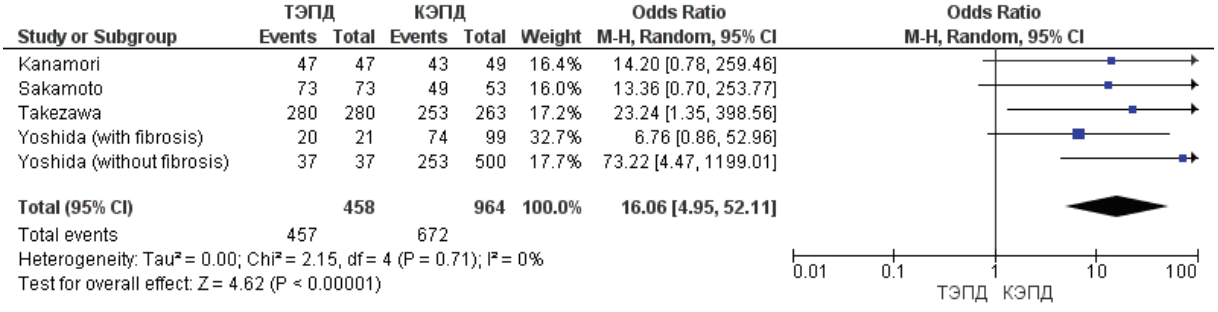

Figure 8. *En bloc resections in the TESD and CESD groups*

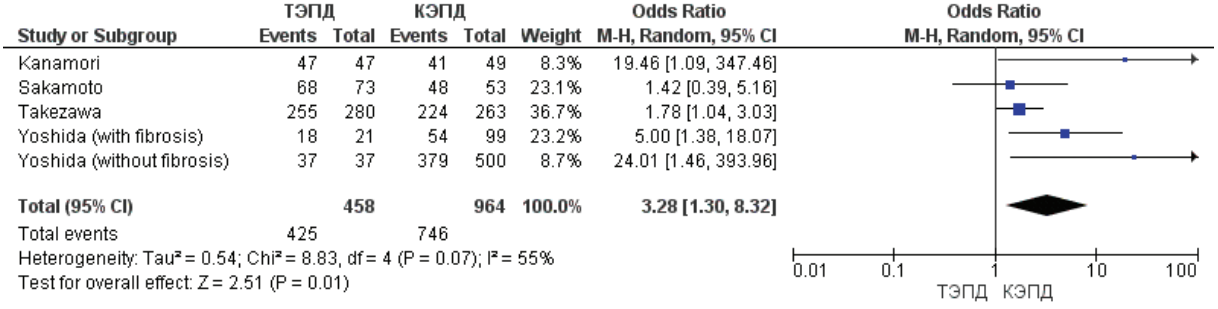

Figure 9. *R0 resection rate in TESD and CESD groups*

CI=0.15-0.83; *p*=0.02) (Fig .6).
The TESD time was significantly less than the CESD by an average of 19 minutes (OR=19.1; 95% CI=33.89-4.45; *p*=0.01) (Fig. 7).
The *en bloc* resection rate in the TESD was significantly higher than inthe CESD (OR=16.06; 95% CI=4.95-52.11; *p*<0.0001) (Fig. 8).
The incidence of R0-resections was significantly higher in the TESD group (OR=3.28; 95% CI=1.30-8.32; *p*=0.01) (Fig. 9).

DISCUSSION

Currently, endoscopic submucosal dissection (ESD) is the method of choice for surgical treatment of colorectal adenomas and early colorectal cancer [11].
At the same time, the classical and the tunnel methods are known.
It should be noted that initially the tunnel ESD was used for upper gastrointestinal neoplasms as well as the classical ESD [12].
The pocket-creation method for ESD was developed by Miura Y. et al. (2015). Its effectiveness and safety were first demonstrated in endoscopic removal of duodenal tumors.
The authors concluded that due to the confident stabilization of the endoscope manipulator in the submucosal layer, this method is safer for difficult neoplasms localization [13].
However, Yuyong Tan et al. consider that the proposed by Miura et al., the 'pocket-creation'method of submucosal dissection is a TESD modification, in which the formed tunnel has only one dead end 'pocket' [14].
Gradually, publications began to appear in the literature, indicating an improvement in the removed specimen quality in patients with large colorectal neoplasms when using TESD, since this issue is very important when evaluating the pathomorphological study of removed specimens and analyzing the oncological effectiveness.
So, Kanamori et al. revealed that even with large adenomas, the tunnel submucosal dissection allows to perform R0-resections in 100% of cases, whereas with the classical ESD this indicator is less by 15-20% [15].
The meta-analysis also revealed the advantage of TESD over the classical one in the rate of both *en bloc* resection and in the R0-resection.
It should be noted that the obtained results confirm the data of a few observational studies. So, Jin-Lin Yang et al., when analyzing the initial experience of TESD use in 19 patients with rectal tumor, found that the rate of *en bloc* resections was 98% and the rate of R0-resections with tumors less than 50 mm in size was 83%.
When the tumor size was over 50 mm, these indicators were 99% and 87%, respectively [8]. Aslan F. et al. described a case of successful removal of a rectal 'giant' (18-cm) laterally spreading tumor (LST) in a single *en bloc* resection with the TESD.
According to the authors, this was possible only by using the submucosal tunnel-creation method [16].
It should be noted that ESD is a relatively safe method for surgical treatment of colorectal tumors [12,17]. The risk of bleeding in this case is 3.5%, and perforations– 1.5% [11]. The meta-analysis results confirm these results. We did not obtain statistically significant differences between tunnel and classical submucosal dissection methods in the intraoperative bleeding rate (OR=1.24; 95% CI=0.53-2.88; *p*=0.61).
However, classical ESD significantly more often leads to intraoperative perforations (OR=0.35; 95% CI=0.15-0.83; *p*=0.02).
In addition, as shown by the meta-analysis data, TESD in comparison with CESD significantly reduces the procedure time (OR= 19.1; 95% CI= 33.89-4.45; *p*=0.01) just by a submucosal tunnel-creation.
In this regard, it is interesting to conduct research aimed at comparing different ways of performing submucosal dissection, which will primarily lead to decrease of local recurrence rate, as well as to improvement of the treatment results of patients with colorectal tumors.

CONCLUSION

The use of tunnel endoscopic submucosal dissection for colorectal adenoma removal and early colorectal cancer makes it possible to obtain a higher quality of removed specimen compared to the classical method. In this case, the procedure time is significantly less, as well as the bowel perforation rate. There is a lack of information about effectiveness and safety of the tunnel method for large neoplasms, which indicates the need for further research in this area.

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