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Results of surgical treatment of patients with rectal cancer with submucosal invasion and factors of negative prognosis

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ABSTRACT *Challenges in determining the optimal extent of surgical treatment for patients with rectal cancer with submucosal invasion is still an actual problem in oncoproctology.*

AIM: to evaluate the oncological efficacy of "salvage" secondary total mesorectal excision (sTME) in patients with T1 rectal cancer combined with risk factors for metastasis to regional lymph nodes.

PATIENTS AND METHODS: the study included 126 patients with T1 rectal cancer combined with risk factors for regional metastasis, who were treated at the A.N. Ryzhikh National Medical Research Center of Coloproctology from January 1, 2015, to December 31, 2025. Primary total mesorectal excision (pTME) was performed in 40/126 (31.7%) patients due to suspected involvement of regional lymph nodes or depth of invasion of T2 or greater. Transanal endoscopic microsurgery (TEM) for local tumor excision was performed in 86/126 (68.3%) patients. After identification of risk factors for metastasis upon comprehensive pathological examination, all patients were offered salvage surgery — secondary total mesorectal excision (sTME) — which was performed in 22/86 (25.6%) patients, while 64/86 (74.4%) refused radical surgery.

RESULTS: there were no mortalities in any group. The rate of postoperative complications did not differ significantly between the sTME group 6/22 (27.3%) and the pTME group 10/40 (25%) (p = 1). However, complications after TEM occurred 6 times less frequently 4/86 (4.7%) compared to resections (pTME + sTME) 16/62 (25.8%) (p = 0.0003). Patients in the sTME and pTME groups demonstrated a high rate of locoregional metastasis: 22.7% (5/22) after sTME and 32.5% (13/40) after pTME, respectively. The quality of the surgical specimen after sTME was significantly worse than after pTME: 13/22 (59.1%) vs. 10/40 (25%), p = 0.01. The two-year disease-free survival (DFS) was 86.2% (95% CI: 77.2–100) in the pTME group, 100% (95% CI: 100–100) in the sTME group, and 71.6% (95% CI: 67.7–92.6) in the TEM group. Applying the Bonferroni correction, where differences were considered significant at p < 0.017, a certain trend toward worse outcomes was observed in the TEM group compared to the sTME group (p = 0.03). The probability of recurrence in the TEM group without subsequent resection increased by 4.1 times (HR = 4.1; 95% CI: 1.1–15.2; p = 0.03). A similar trend was found in the rate of locoregional recurrences between the sTME and TEM groups (p = 0.05). The probability of local recurrence was 4.8% (95% CI: 0–13.4) in the pTME group, 0% (95% CI: 0–0) in the sTME group, and 23.9% (95% CI: 4.0–25.0) in the TEM group. Thus, the probability of local recurrence in the TEM group was 4.1 times higher (HR = 4.1; 95% CI: 1.0–17.3; p = 0.05) compared to the sTME group.

CONCLUSION: the treatment strategy for patients with rectal cancer invading the submucosal layer and presenting negative prognostic factors represents a complex challenge. The necessity of sTME is dictated by the lack of difference in postoperative complication rates compared to pTME, as well as the high frequency of metastases to locoregional lymph nodes. Refusal of sTME after identifying high-risk factors for metastatic involvement of regional lymph nodes is associated with a significant decrease in disease-free survival rates.

KEYWORDS: *rectal cancer, early rectal cancer, transanal endomicrosurgery, mesorectumectomy, secondary mesorectumectomy*

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INTRODUCTION

In patients with rectal cancer with invasion of the submucosal layer (T1), local excision looks like an attractive alternative to resection, associated with significantly lowermorbidity and mortality, the need for stoma and adverse functional outcomes. However, this approach is possible in the absence of distant and locoregional metastases, as well as risk factors for metastasis [1–4]. If a high-risk tumor is detected, including after local excision and subsequent total pathomorphological examination of the removed specimen, indications for a salvage surgery, secondary total mesorectomectomy (sTME), may be done.

Difficulties in choosing the volume of surgery in such patients and its impact on long-term treatment outcomes remain an actual problem in oncological proctology. There is a problem of patients refuse to salvage surgery in the volume of sTME, associated with a high risk of postoperative morbidity and temporary, and in some cases permanent intestinal stoma.

AIM

AIM: to estimate the oncological efficacy of sTME in patients with colorectal cancer with invasion of the submucosal layer T1 and factors of negative prognosis of metastasis.

PATIENTS AND METHODS

In the period from 01.01.2015 to 31.12.2025, 312 patients with rectal cancer with invasion of the submucosal layer (T1) were selected. The study included 126/312 (40.4%) patients who had high risk factors for metastatic lesions of regional lymph nodes. Primary total mesorectomectomy (pTME) was performed in 40/126 (31.7%) patients due to suspected lesion to regional lymph nodes or a depth of invasion of T2 or more. Surgery to remove a rectal tumor was performed in 86/126 (68.3%) patients. After the detection of risk factors during a total pathomorphological examination of the surgical specimen, rectal resection in combination with TME was offered to all patients, but was performed only in 22/86 (25.6%). 64/86 (74.4%) patients preferred active surveillance tactics (Fig. 1).

Among the 126 patients included in the study, 73/126 (57.9%) were women, and the median (min–max) age of the patients was 63 (27–88) years.

The primary point of the study was to assess 2-year disease-free survival. The secondary

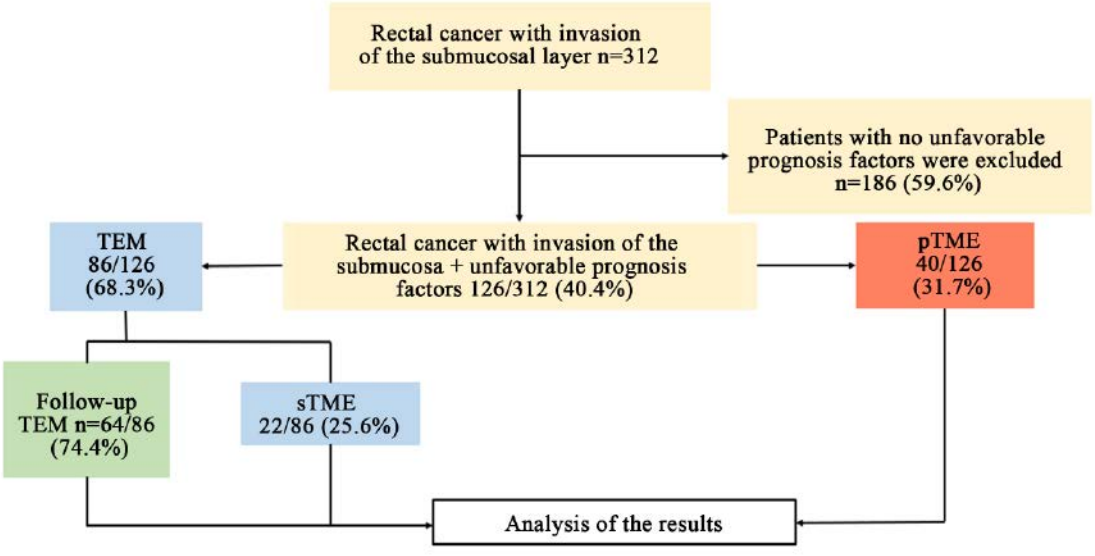

Figure 1. *Research design*

Table 1. *Characteristic of operations of patients, undergoing various surgical procedures*

Indicator	sTME N = 22	pTME N = 40	P
Surgery type			0.06
Intersphincteric resection	8 (36.4%)	6 (15%)	
Low anterior resection	14 (63.6%)	34 (85%)	
Access			0.4
Laparoscopic	18 (81.8%)	27 (67.5%)	
Open	4 (18.2%)	13 (32.5%)	
Stoma kind			When comparing the frequency of preventive stoma removal $p = 1$ When comparing the frequency of terminal stoma removal $p = 0.5$
Ileostoma (preventive)	21 (95.5%)	33 (82.5%)	
Transversostoma (preventive)	1 (4.5%)	3 (7.5%)	
End sigmostoma	–	2 (5%)	
End transversostoma	–	1 (2.5%)	
No stoma	–	1 (2.5%)	

points were: the frequency and severity of postoperative complications, the rate of detection of residual tumors after TEM, the incidence of metastasis to regional lymph nodes in sTME and pTME, the quality of the surgical specimen after sTME and pTME, the incidence of local recurrence and distant metastasis.

Statistical Analysis

The data analyzed in the study was entered into a Microsoft Excel 2021 spreadsheet. All quantitative values are presented as the median, lower and upper quartiles (Me (Q1; Q3)), and the comparison was carried out using Mann-Whitney's U-test. Differences in dichotomous values between the groups were assessed using two-side Fisher's exact test. The survival curves were constructed, using Kaplan-Mayer's method, and the time before the event was analyzed using Nelson-Aalen's curves. The comparison between the groups was carried out using a log-rank criterion, the hazard ratio (HR) was calculated with a 95% coincidence interval (CI). The differences were considered statistically significant at $p < 0.05$. When conducting pairwise comparisons, Bonferroni's correction was applied, and the differences were considered statistically significant at $p < 0.017$. Descriptive statistics and group comparisons were calculated in the Statistica 13.3 program (TIBCO, USA), survival analysis was performed in GraphPadPrism10 (Graph Pad Software, USA).

RESULTS

The early and long-term results of three groups of patients were analyzed: 40/126 (31.7%) patients who underwent primary mesorectomectomy (pTME), 22/126 (17.5%) after salvage surgery (sTME) and 64/126 (50.8%) TEM patients.

Surgery with primary anastomosis and sphincter preservation was performed in all patients from the sTME group and 37/40 (92.5%) in the pTME group. However, in 3/40 (7.5%) patients from the pTME group, surgery was completed with end colostomy, and 1 patient subsequently underwent stoma take down. Laparoscopic access was used in 27/40 (67.5%) patients from the pTME group and in 18/22 (81.8%) patients from the sTME group (Table 1).

There were no mortality in any group (Table 2). When comparing the rate of postoperative morbidity, there were no significant differences ($p = 1$): sTME — 6/22 (27.3%) vs. pTME — 10/40 (25%). However, with TEM, complications developed 6 times less (4/86 (4.7%) than after rectal resections (pTME + sTME) (16/62 (25.8%) ($p = 0.0003$).

When comparing the results of the pathomorphological study of surgical specimens of patients in the sTME and pTME groups, we found almost the same incidence of locoregional metastasis, which was 22.7% (5/22) and 32.5% (13/40) after sTME and pTME, respectively (Table 3).

Unsatisfactory quality of the surgical specimen was significantly more often obtained after sTME

Table 2. *Severity and nature of postoperative complications in patients undergoing various surgical procedures*

The nature of complications	Clavien-Dindo	TEM N = 86	sTME N = 22	pTME N = 40
Wound dehiscence	II	3 (3.5%)	–	–
Bleeding	IIIa	1 (1.2%)	–	–
Prolonged, more than 5 days, gastrointestinal ileus	I	–	2 (9.1%)	3 (7.5%)
Neurogenic bladderdys function	I	–	–	1 (2.5%)
Pneumonia	II	–	1 (4.5%)	–
Infection of a laparotomy wound	II	–	–	1 (2.5%)
Hematoma of the small pelvis	II	–	2 (9.1%)	–
Hematoma of the small pelvis	IIIb	–	–	1 (2.5%)
Anastomosis leakage	IIIb	–	1 (4.5%)	3 (7.5%)*
Small intestinal obstruction	IIIb	–	–	1 (2.5%)
Bleeding in the pelvis	IIIb	–	–	1 (2.5%)*
Total:	**–**	4 (4.7%)	6 (27.3%)	10 (25%)

*Note: * One patient developed 2 complications*

Table 3. *Comparison of the results of the pathomorphological examination of the removed drugs of the pTME and sTME groups*

Indicator	sTME N = 22	pTME N = 40	*p*
Condition of regional lymph nodes N0 N1a-N2b	 17 (77.3%) 5 (22,7%)	 27 (67.5%) 13 (32.5%)	0.56
Number of lymph nodes examined, Me (Q1;Q3)	25.5 (22;34)	23 (18.5;28.5)	0.3
Residual tumor after TEM	4 (18.2%)	–	–
R1 resection (at the lateral margin) and CRM+	1 (4.5%)	1 (2.5%)	1
Distal resection margin mm, Me (Q1;Q3)	15 (8;27)	20 (12;35)	0.3
Quality of mesorectumectomyas per Quirke Grade I–II Grade III	 13 (59.1%) 9 (40.9%)	 10 (25%) 30 (75%)	0.01

than after pTME: 13/22 (59.1%) and 10/40 (25%) ($p = 0.01$).

It is important to note that a residual tumor, after previously undergoing TEM, was detected in 4/22 (18.2%) specimens of patients from the sTME group.

Long-term outcomes were assessed within 1 to 120 months with a median follow-up of 23 months. In the sTME group, the Me (min–max) traceability was 24 (5–62) months, in the TEM group — 18 (3–120), in the pTME group — 23.5 (2–86). In the TEM group, 11/56 (19.6%) patients had a return of the disease (locoregional recurrence in 9/56 (16.1%) and distant metastases in 2/56 (3.6%) patients). No recurrence of the disease was detected in the sTME group during the follow-up. In the pTME group, a disease relapse within 12 to 24 months developed in 3/34 (8.8%) cases: of these, locoregional recurrence in 1/34 (2.9%) patient and distant metastases in 2/34 (5.9%) patients.

Two-year disease-free survival in the pTME group was 86.2% (95% CI: 77.2–100), in the sTME group, 100% (95% CI: 100–100), and in the TEM group, 71.6% (95% CI: 67.7–92.6). When analyzing these indicators, taking into account Bonferroni's correction, in which the differences were recognized as significant at $p < 0.017$, we identified a downward trend in the indicators in the TEM group compared with the sTME group ($p = 0.03$). When analyzing the risk ratio, it was noted that the probability of recurrence in the observation group, without subsequent resection after TEM, increases by 4.1 times (HR = 4.1; 95% CI: 1.1–15.2; $p = 0.03$) (Fig. 2).

A similar trend was found when comparing the rate of locoregional recurrences between the sTME and TEM groups ($p = 0.05$), the probability of local recurrence was 0% (95% CI: 0–0) and 23.9% (95% CI: 4.0–25.0), respectively. The risk ratio (HR) analysis showed a 4.1-fold increase in the

probability of local recurrence in the TEM group (HR = 4.1; 95% CI: 1.0–17.3; p = 0.05) compared with the sTME group (Fig. 3).

DISCUSSION

Early rectal cancer is a heterogeneous group of adenocarcinomas, which, depending on the presence of aggressive factors: lymphovascular invasion, low differentiation, the presence of 'tumor budding' and poorly differentiated clusters, etc.) may be tumors of low or high risk of locoregional metastasis. If a low-risk tumor is detected in a patient, organ-preserving treatment (local excision) with a favorable oncological result may be the method of choice. In situations where a tumor is at high risk of metastatic lesion of the lymph nodes and distant organs, performing organ-preserving treatment is not sufficient for local disease control [14]. In this context, delay or refusal, after previously performed TEM, of surgical treatment in the volume of sTME may cause a deterioration in oncological results. The group of patients represented is a relatively small and rare category. Thus, over a 10-year period, only 126 patients with rectal cancer with invasion of the submucosa and negative prognosis factors were selected. All of these patients had indications for TME. However,

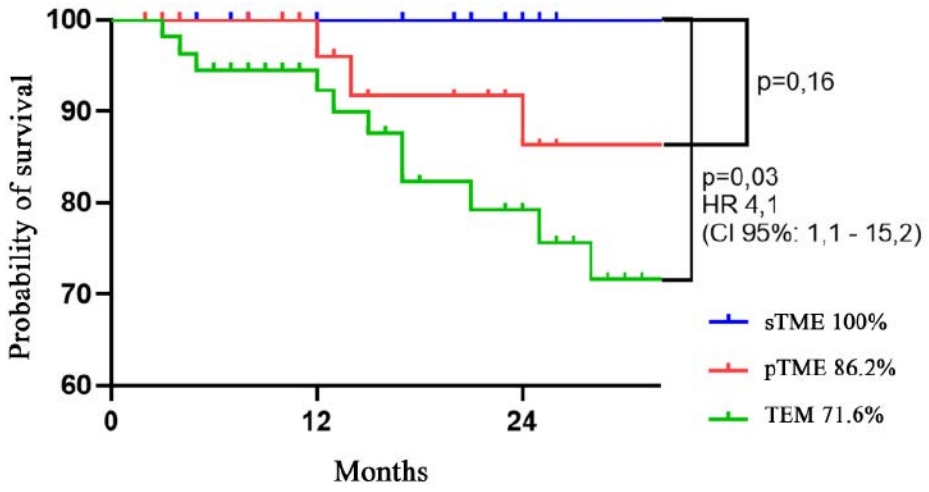

Figure 2. *2-year disease-free survival of patients depending on the method of surgical treatment (TEM, sTME, pTME)*

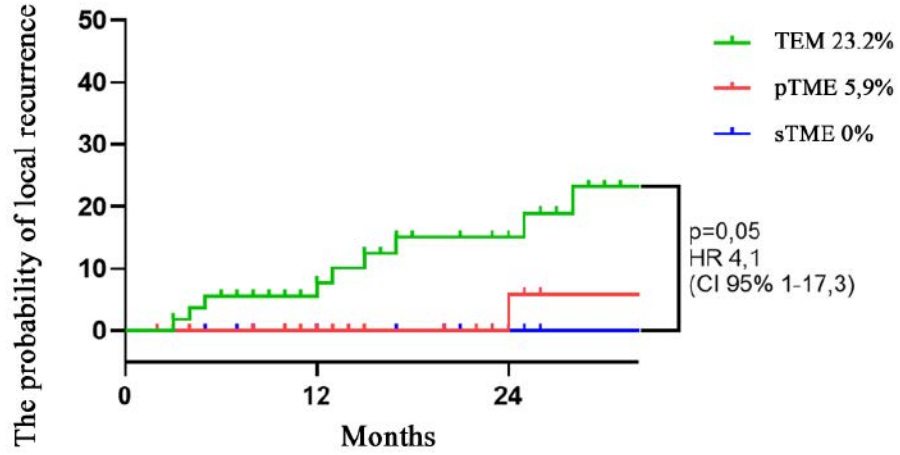

Figure 3. *Probability of local relapses in patients depending on the method of surgical treatment (TEM, sTME, pTME)*

after TEM, only 22/86 (25.6%) patients agreed to continue the treatment. According to the results of a pathomorphological study of surgical specimens after mesorectomectomy, the incidence of locoregional metastasis in our study in the pTME group was 32.5%, and in the sTME group — 22.7%. According to Morino M. [9] and Levic Souzani K. [10] regional metastases after mesorectumectomy for T1 rectal cancer were detected in 30% of cases.

It is also important to emphasize that in the presented study, 18.2% of patients after TEM and subsequent sTME had a residual tumor. The quality of mesorectumectomy in patients who had previously undergone TEM was significantly worse, which is explained by the pronounced fibroinflammatory changes in the pelvic cavity and impaired differentiation of layers, which coincides with literature data [5,13]. At the same time, Morino M. and Roodbeen [12,13] found that the unsatisfactory quality of TME after TEM leads to an increase in the frequency of local recurrences. However, according to our data, there was not a single recurrence in the sTME group with a median follow-up of 24 months.

There is an opinion that the previous TEM is the reason for the increase in the rate of APE [9–11]. However, within the framework of our study, all transabdominal interventions were sphincter-preserving, and the previous TEM did not lead to the abandonment of sphincter-preserving surgery.

An analysis of the early results shows that local excision in the volume of TEM removal of the rectal tumor is a safer method of surgery compared with sTME and pTME in terms of postoperative complications ($p = 0.0003$). However, the disease-free survival in patients from the TEM group who refused to perform sTME decreases to 71.6%, while the risk of disease recurrence increases by 4.1 times (HR = 4.1; 95% CI: 1.1–15.2; $p = 0.03$).

CONCLUSION

The strategy of treating patients with colorectal cancer with invasion of the submucosa and the presence of negative prognosis factors is a difficult task. The need for sTME is dictated by the absence of a difference in the rate of postoperative complications compared with pTME, and the high incidence of metastases to the locoregional lymph nodes. The rejection of sTME after the detection of high-risk factors for metastatic lesions of regional lymph nodes is associated with a significant decrease in disease-free survival.

AUTHORS CONTRIBUTION

Concept and design of the study: *Stanislav V. Chernyshov, Evgeny G. Rybakov, Evgeniy A. Khomyakov, Philipp I. Kirgizov*

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