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Endoscopic injections of autoplasma rich in platelets in the treatment of post-radiation ulcers of the rectum

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ABSTRACT *AIM: to develop a technique and evaluate the effectiveness of endoscopic injections of platelet-rich plasma (PRP) for post-radiation rectal ulcers.*
PATIENTS AND METHODS: the pilot study included 41 patients with post-radiation rectal ulcer which underwent endoscopic injections of PRP to epithelialize the ulcer.
RESULTS: the average number of injections for epithelialization of a post-radiation ulcer is 5. Thirty-one (75.6%) patients during the manipulation developed pain. In 39 (95.1%) patients, complete healing of the post-radiation ulcer of the rectum was verified after endoscopic injections of PRP.
CONCLUSION: PRP endoscopic injections are a technically feasible, safe and effective method in the treatment of patients with post-radiation rectal ulcers.

KEYWORDS: *rectal ulcer, radiation therapy, autoplasma rich in platelets, late radiation complications*

CONFLICTS OF INTEREST: *The authors declare no conflicts of interest*

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INTRODUCTION

Treatment of late complications of radiation therapy remains an urgent and unresolved problem of the 21st century. Due to the absence of pathogenetic methods of treatment, empirical therapy of patients with post-radiation rectal ulcers leads to complications like rectovaginal and rectovesical fistulas, as well as rectal strictures, which, in turn, dramatically reduces the quality of life and invalidates patients [1–3]. Treatment of late radiation rectal lesions requires resections associated with a high incidence of intra- and postoperative complications [4].

The introduction of cellular technologies into clinical practice could solve the problem [5–7]. However, the legislative framework of the Russian Federation does not allow the widespread use of cellular products in the treatment of various diseases, in particular post-radiation ulcers [8]. The use of platelet-rich plasma (PRP) has proven itself as an alternative, safe and with pronounced regenerative potential method, successfully used in traumatology and orthopedics, burn units, gynecology, aesthetic medicine, dentistry and other medical specialties [9,10].

The regenerative effect of PRP is due to the ability of platelets to release platelet growth factors (PDGF, TGF-b1, VEGF, EGF, FGF, IGF), cyto- and chemokines during degranulation which allow damaged cells to activate [11].

Thus, the use of PRP can improve the results of treatment of post-radiation rectal ulcers, avoid severe complications and reduce financial costs.

AIM

To work out a technique and evaluate the effect of endoscopic injections of PRP for post-radiation rectal ulcers.

PATIENTS AND METHODS

Forty-one patients with late complications of radiation therapy like rectal ulcers were treated on an outpatient basis. This study had a pilot nature and was approved by the local Ethics Committee of the State Medical University of Moscow State Medical Center named after A.S. Loginov within the framework of a comprehensive research topic 'Treatment of patients with late radiation lesions of the rectum and anoperianal area'. All the patients were fully informed before starting the treatment that the use of PRP was not included in the national clinical guidelines and was not a generally accepted method of treatment for that category of patients. Before starting the treatment, patients with post-radiation rectal ulcers signed an informed consent to participate in this clinical trial. And also, before each injection of PRP, an informed consent for procedure was signed. Radiotherapy was carried out according to a radical program or as part of a comprehensive treatment for pelvic malignant tumors. Before the beginning of the endoscopic administration of PRP, according to the comprehensive check-up (abdominal and chest CT with contrast, MRI of the pelvis with contrast), no patient had a recurrence and progression of a malignant tumor. In all patients, post-radiation ulcers existed for 6 months or more after the end of treatment and were diagnosed by colonoscopy, with morphological verification of the margins of the lesion. During the endoscopy, the site, the largest diameter and depth of the post-radiation ulcer were evaluated. Before starting the treatment, patients were monitored for a general blood test in order to assess the level of platelets more than 100 thousand/μl and hemoglobin more than 100 g/l. Seven days before the start of endoscopic injections of PRP, disaggregate agents were cancelled. Initially, in the outpatient conditions, venous blood was taken in 4 vacuum tubes with a total volume of 32 ml, with liquid

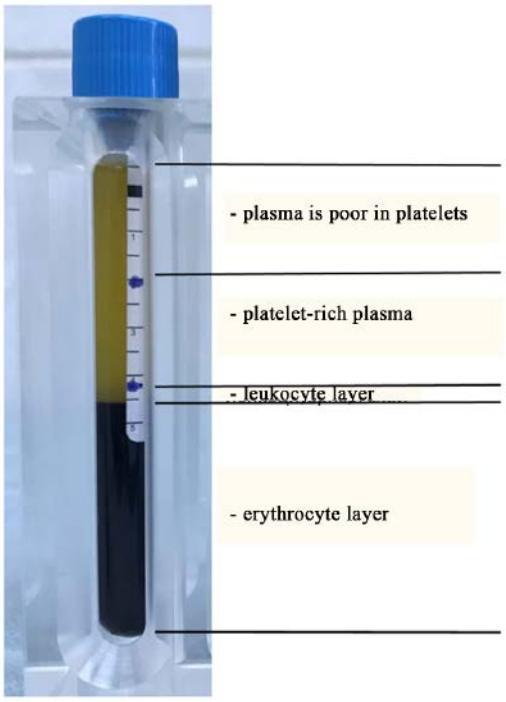

Figure 1. *Test tubes after separation of blood cells*

tri-substituted sodium citrate at a concentration of 32.0 g/l. 2.6 ml of blood was taken separately to determine the number of platelets in the patient on the day of injection. Then 4 tubes with venous blood of 8 ml were subjected to centrifugation in order to separate the shaped elements (Fig. 1). The collection of PRP was carried out in 5 ml syringes. Endoscopic injection of PRP was performed in endoscopic room. The patient was positioned on his/her left side. The first stage was diagnostic rectoscopy for the purpose of targeted assessment of the ulcerative lesion. To perform the manipulation, a gastroscope and an endoscopic injector with a needle diameter of 25 G (0.5 mm) were used (Fig. 2).

The injection of PRP was performed under visual control along the margins of the ulcerative lesion with a total volume of up to 6 ml, depending on the area and depth of the ulcerative lesion. The injection was carried out into the submucosal layer, with lifting. Endoscopic injections were performed once every three weeks till complete epithelialization of the ulcer. To assess the safety and effectiveness of the use of endoscopic injections of PRP, an analysis of the patient's condition

Table 1. *Distribution of patients depending on the location of the tumor process*

Tumor site	Abs.	%
Cervical cancer	19	46.3
Cancer of the uterine body	3	7.3
Prostate cancer	8	19.5
Anal canal cancer	8	19.5
Rectal cancer	3	7.3

during manipulation was carried out, characterized by pain and the occurrence of bleeding during injection, as well as infectious complications and bleeding in the late period after procedure. The end point of the effectiveness evaluation and the end of treatment was the complete epithelialization of the post-radiation ulcer. In the late period, the presence of a recurrence of the ulcerative lesion and the effect of endoscopic injections of PRP on local recurrence and progression of the primary malignant tumor were evaluated. For data processing, statistical analysis was carried out using the StatTechv program 3.0.9 (the developer is Stattech LLC, Russia).

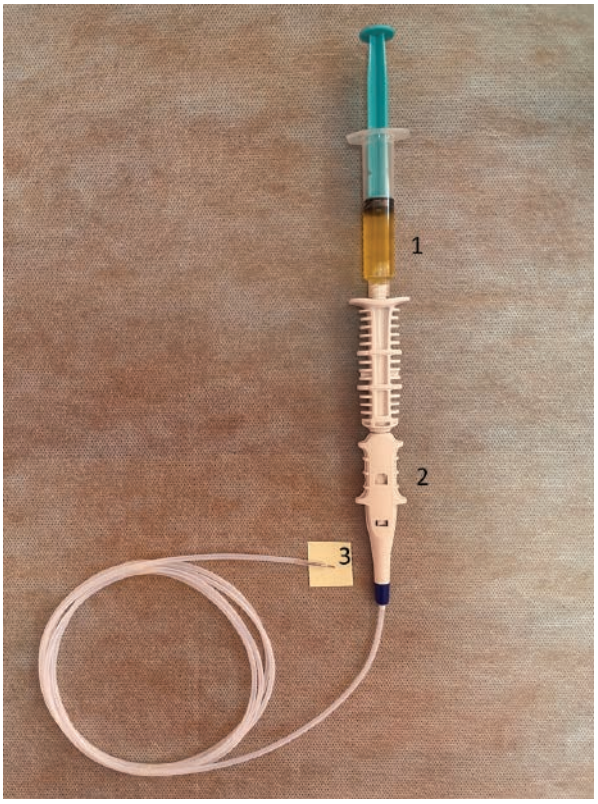

Рисунок 2. *Набор для эндоскопического введения АПБТ: 1 — шприц с АПБТ; 2 — эндоскопический инъектор; 3 — игла 25 G (0.5 мм)*

Figure 2. *Set for endoscopic administration of PRAP: 1 — syringe with PRAP; 2 — endoscopic injector; 3 — needle 25 G (0.5 mm)*

RESULTS

Of 41 patients included in the study, there were 33 (80.5%) females and 8 (19.5%) males. Their average age was 62.5 ± 10.7 years. The youngest female patient was 42 years old, and the elderly male was 80 years old. In females, radiation therapy was mainly performed for cervical cancer (46.3%). All males were previously treated for prostate cancer (Table 1). The study included 3 patients who received radiation therapy for rectal cancer. Against the background of the treatment, those patients had a complete regression of the tumor, in connection with which the oncological MDT chose a strategy of watch-and-wait, and surgery was not carried out. At the time of endoscopic injections of PRP, there was a period of more than 6 months after the end of the treatment. The ulcers were not in the site of the post-radiation cicatrix where the tumor had previously been.

When assessing the general status on the ASA scale, 26 (63.4%) patients had mild comorbidities, 13 (31.7%) patients had severe systemic diseases in the compensation stage. Twenty-one (51.2%) patients had chronic anemia of varying severity, of whom 18 (85.7%) patients with mild anemia and 3 (14.3%) patients with moderate one. In 21 (51.2%) patients, post-radiation ulcer developed after remote radiation therapy. Twenty (48.8%) patients underwent combined radiation treatment with the addition of intracavitary therapy. The total focal dose after which late radiation complications occurred was 65.1 ± 10.4 Gr. The characteristics of TFD received by patients are presented in Table 2.

A correlation analysis of the effect of the total dose of radiation therapy on the size of the ulcerative lesion established a weak direct correlation. With an increase in the total dose of radiation therapy by 1 Gr, an increase in the size of the ulcerative lesion by 0.194 mm should be expected.

Table 2. *Parameters of radiation therapy that led to post-radiation ulcer (n = 41)*

Indicators	M ± SD / Me	95% CI Q_1–Q_2	min	max
Total dose of radiation therapy, M ± SD (Gr)	65.1 ± 10.4	61.8–68.4	40.0	85.0
Dose of remote radiation therapy, Me (Gr)	50.0	47.0–60.0	30.0	75.0
Intra-cavity therapy dose, Me (Gr)	20.0	15.0–25.0	14.0	35.0

Table 3. *Characteristics of post-radiation rectal ulcers*

Indicator	Categories	Abs.	%
Ulcer site (circumference)	Anterior wall	39	95.1
	Left lateral wall	1	2.4
	Right lateral wall	1	2.4
Ulcer site (part of the rectum)	Upper rectum	1	2.4
	Mid rectum	6	14.6
	Low rectum	34	82.9
Ulcer depth	Superficial	20	48.8
	Deep	21	51.2

The resulting model explains 4.9% of the observed variance (Fig. 3).

The period of appearance of rectal ulcers after the end of radiation therapy was 7.85 ± 3.77 months. Post-radiation ulcer, occurred in a given period of time and persisted for more than 6 months. Mainly post-radiation ulcers were located along the anterior semicircle of the low rectum (Table 3).

The size of the ulcerative lesion was different and its median was 15.0 mm (8;25). Twenty-one (51.2%) patients had rectal ulcers up to the muscle layer, 20 (48.8%) patients had superficial ulcers. In 10 (24.4%) patients, an intestinal stoma was previously formed and endoscopic injections were performed on the diverted rectum. Those patients had deep post-radiation ulcers located along the anterior wall of the rectum. Diverting intestinal stoma was formed in various hospitals before applying to the Center. All patients underwent colostomy more than 2 months

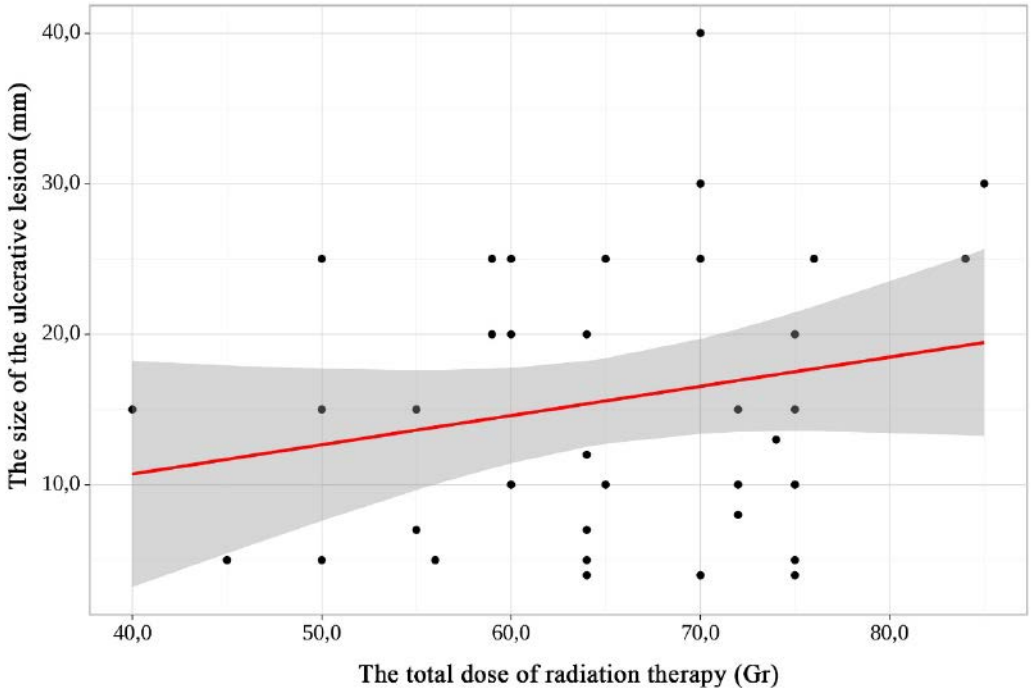

Figure 3. *Influence of the total dose of radiation therapy on the size of the rectal ulcer*

before the start of endoscopic injections of PRP. The purpose of colostomy was to decrease the risk of post-radiation internal fistulas and to reduce pain. Initially, the median blood platelet level in all patients was 234 thousand//μl. After centrifugation, the median platelet concentration in the injected plasma was 2.1 times higher than the baseline level. The median number of injections for complete epithelialization of post-radiation ulcer was 5 (3; 6). In a female patient with a superficial ulcer of 4 mm in size, 1 injection of platelet-rich plasma was enough for complete healing. The maximal number of endoscopic injections reached 8 in a female patient with a deep post-radiation ulcer to the muscular layer of the rectum. A correlation analysis of the relationship between the size of the post-radiation ulcerative lesion of the rectum and the number of endoscopic injections before complete epithelialization of the ulcer revealed a noticeable close direct relationship. With an increase in the size of the ulcerative lesion by 1 mm, an increase in the number of injections by 0.113 should be expected. The resulting model explains 32.2% of the observed variance in the number of injections (Fig. 4).

During endoscopic injections of PRP, 31 (75.6%) patients experienced pain of varying strength on a visual-analog scale. Thirteen (41.9%) patients had mild pain, 14 (45.2%) — had moderate pain, 4 (12.9%) had severe pain syndrome. There were no complications during the endoscopic injections of PRP and the follow-up period. When analyzing the pain during injections depending on the depth of the ulcerative lesion, we revealed significant differences ($p = 0.032$) (Fig. 5).

The chances of pain during injections in the group of patients with deep ulcerative lesion were 6.33 times higher, compared with the group of patients with superficial ulcer, the odds ratio was statistically significant (95% CI: 1.15 — 35.01).

When analyzing the intensity of pain during endoscopic injections of PRP, a dependence on the depth of the ulcerative lesion was revealed (Table 4).

According to the table presented, significant differences ($p = 0.009$) were revealed when analyzing the pain syndrome by severity during injection depending on the depth of the ulcerative lesion (Fig. 6).

Two (4.9%) patients developed recurrence and progression of the underlying cancer during the

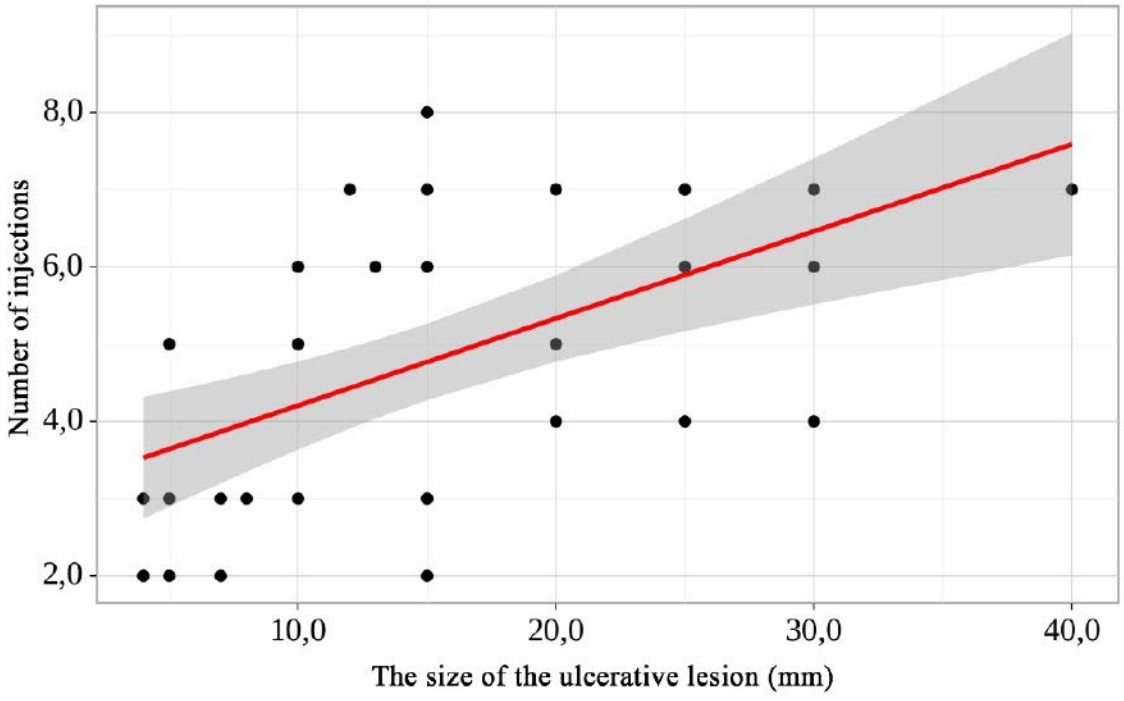

Figure 4. *Dependence of the number of injections on the size of the rectal ulcer*

Table 4. *The nature of the pain during the injection depending on the depth of the rectal ulcer*

Indicator	Categories	Ulcer depth		*p*
		Superficial	Deep	
Pain during injection	Mild	9 (75.0)	4 (21.1)	0.009*
	Moderate	3 (25.0)	11 (57.9)	
	Severe	0 (0.0)	4 (21.1)	

*Note: * — differences in indicators are statistically significant (p < 0.05)*

treatment. After the first injection of PRP, one female patient had a local recurrence of anal cancer. Another female patient was diagnosed with a recurrence of cervical cancer in the pelvis after 4 injections of PRP.

In 39 (95.1%) cases, complete epithelialization of post-radiation ulcerative lesion of the rectal wall was diagnosed (Fig. 7). The median follow-up was 11 months (5; 16). In the late follow-up period 39 (95.1%) patients had no recurrence of post-radiation rectal ulcer, as well as no recurrence and

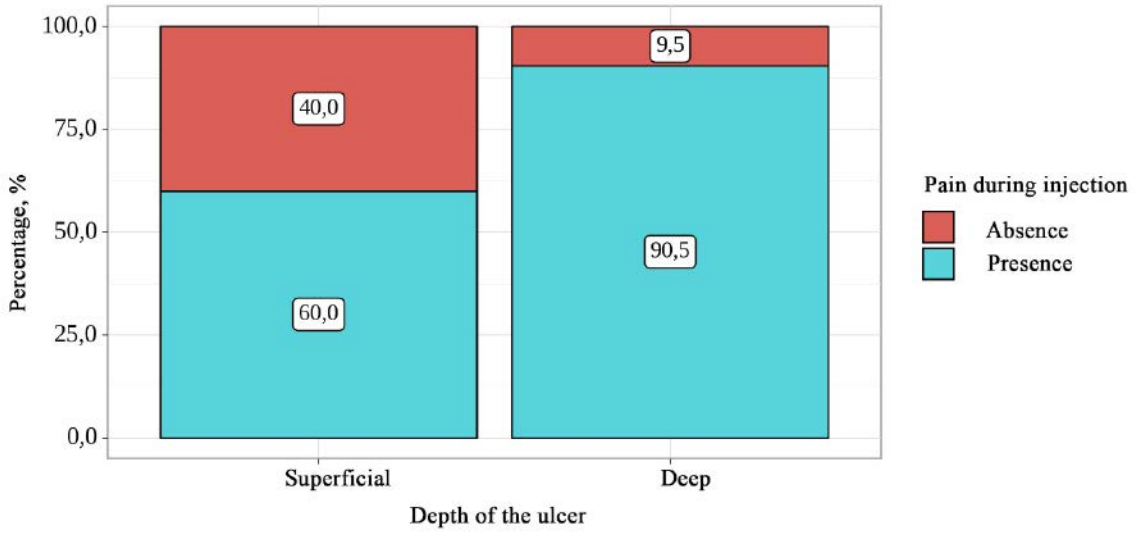

Figure 5. *Pain during injections depending on the depth of the ulcer*

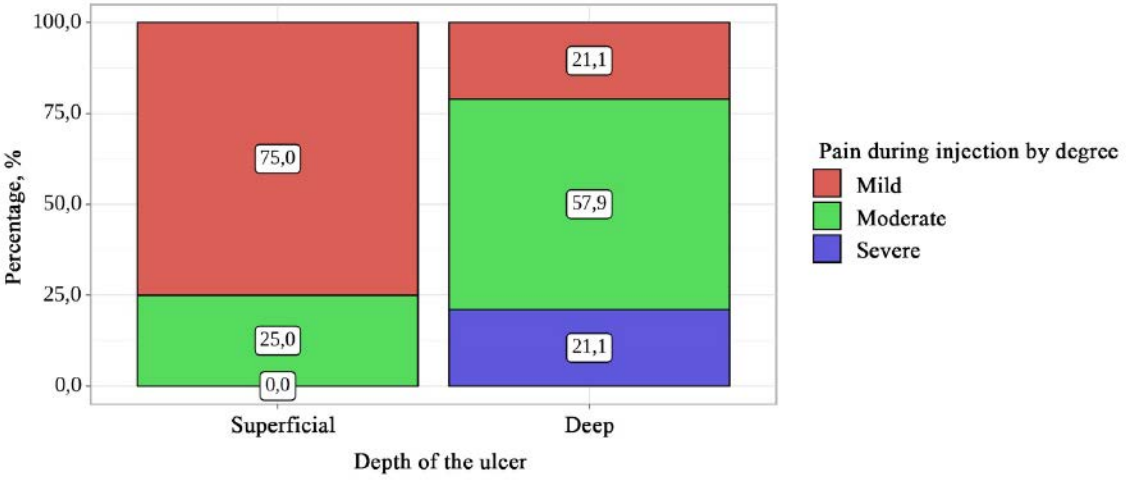

Figure 6. *Severity of pain syndrome during injection depending on the depth of the rectal ulcer*

progression of malignant tumor was diagnosed during follow-up. Ten patients with intestinal stoma underwent stoma takedown 3 months after the healing of a post-radiation ulcerative lesion of the rectum. There were no complications after the stoma closure.

DISCUSSION

Treatment of patients with post-radiation ulcers of the rectum is a serious problem for coloproctologists, due to the lack of pathogenetic methods of treatment.

Drug therapy regimens are often ineffective for superficial ulcerative lesions and practically ineffective for deep ulcers. It should be noted that conservative treatment is long and requires large costs [12]. The technique demonstrated in this article for the use of endoscopic injections of PRP in the treatment of patients with post-radiation rectal ulcers is effective and alternative to other methods of treatment, including the use of stromal vascular fraction of adipose tissue [5–7]. This is evidenced by the effectiveness of this technique in 39 (95.1%) patients included in the study. To obtain PRP, no special and time-consuming preparatory measures are required, unlike obtaining cellular products from adipose tissue. The issue of oncological safety of endoscopic injections of PRP in the treatment of patients with late radiation rectal ulcers requires further study and long follow-up. In our opinion, the reason for the recurrence of pelvic cancer of the uterine body in 1 patient and a local recurrence of anal cancer in another patient, identified during the study, is a preoperative check-up in a non-specialized oncological institution. All the patients before starting the treatment of post-radiation rectal ulcers with the use of endoscopic injections of PRP need

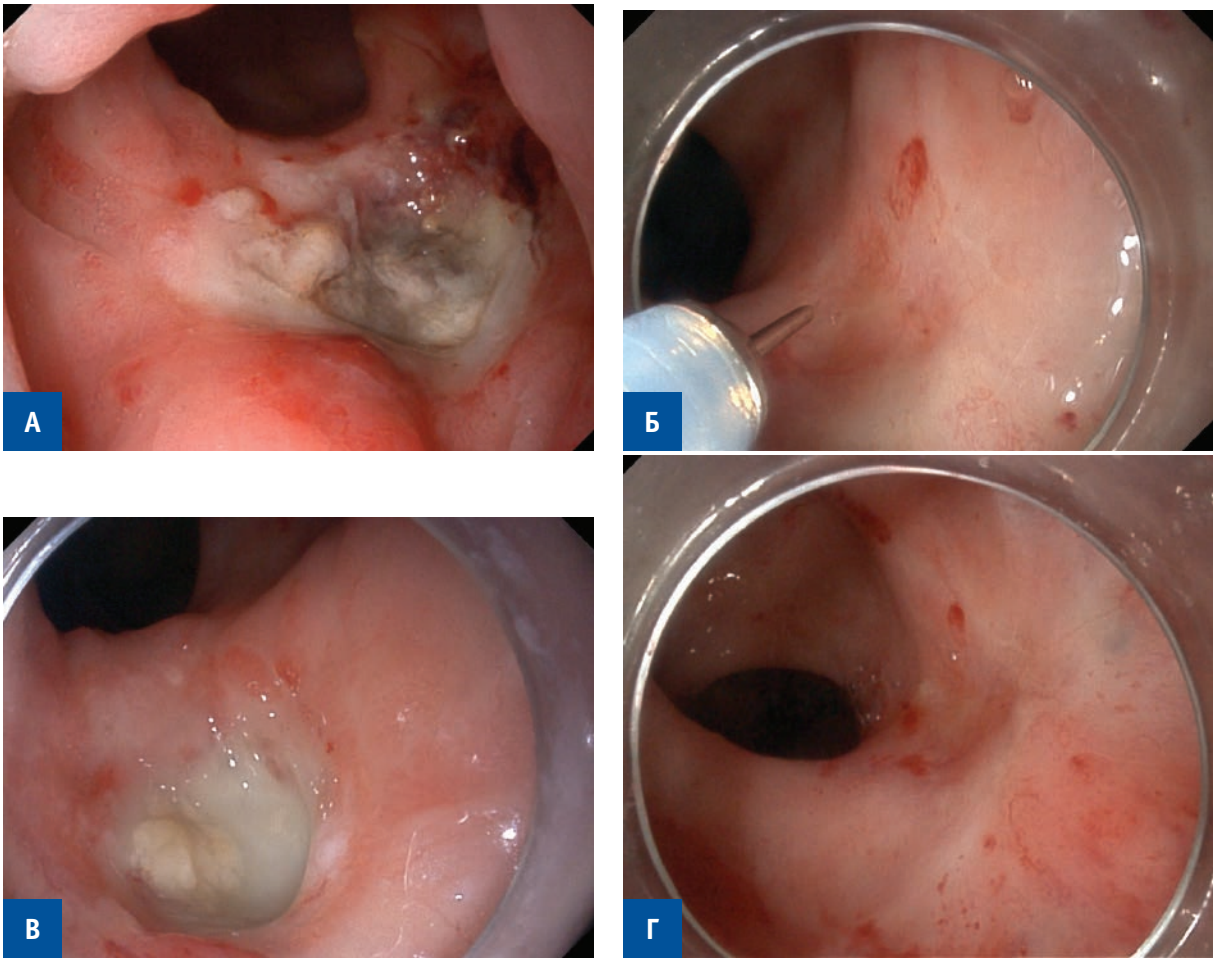

Figure 7. *Stages of healing of a post-radiation ulcer of the rectum*

a comprehensive check-up in order to exclude recurrence and progression of a malignant tumor. Patients are required to undergo computed tomography of the thoracic and abdominal cavities with contrast, MRI of the pelvis with contrast, as well as morphology of the endobioptate from the margins of the ulcerative rectal lesion.

The nature of the pain experienced by patients during endoscopic injections depends on the size and depth of the post-radiation ulcerative lesion of the rectal wall. Its intensity indicators demonstrate that the use of endoscopic injections of PRP does not require the use of general anesthesia and can be performed on an outpatient basis. In patients with deep ulcerative lesions of large size, it is possible to perform endoscopic injections of PRP under sedation.

CONCLUSION

The presented technique of endoscopic injections of PRP is technically feasible, safe and effective in the treatment of patients with post-radiation rectal ulcers. Before starting the treatment, patients with post-radiation rectal ulcers should undergo a comprehensive check-up.

AUTHORS CONTRIBUTION

Concept and design of the study: *Alexander V. Leontev, Elena A. Grishina*

Collection and processing of the material: *Alexander V. Leontev, Elena A. Grishina, Irina V. Nadina*

Statistical processing: *Alexander V. Leontev, Irina V. Nadina*

Writing of the text: *Alexander V. Leontev, Mikhail A. Danilov, Elena A. Grishina*

Editing: *Mikhail A. Danilov, Kirill V. Shishin*

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