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The efficacy of neoadjuvant chemoradiotherapy in signet ring cell carcinoma of the rectum: a retrospective propensity-score matched study

Sergey S. Gordeev[1,2], Yana V. Belenkaya[3], Zara N. Magarramova[1], Igor G. Komarov[1], Arkadiy G. Malikhov[1], Zaman Z. Mamedli[1], Ivan S. Stilidi[1]

[1]N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russia (Kashirskoje Shosse, 23, Moscow, 115478, Russia)
[2]Tyumen State Medical University (Odesskaya st., 54, Tyumen, 625023, Russia)
[3]I.M. Sechenov First Moscow State Medical University (Sechenov University) (Trubetskaya st., 8-2, Moscow, 119992, Russia)

ABSTRACT *AIM: to evaluate the efficacy of preoperative CRT in patients with signet ring cell carcinoma of the rectum (SRCCR).*
PATIENTS AND METHODS: a retrospective analysis of medical records from the archive of Research Institute FSBI "N.N. Blokhin Cancer Research Center" of the Ministry of Health of Russia and multicenter registry of the Russian Society of Specialists in Colorectal Cancer (RSSCC) from 2000 to 2020 was done. Patients with histologically confirmed primary SRCCR who received preoperative CRT were included in the study. A control group with rectal adenocarcinoma was created using propensity-score matching from the institutional database 1:1 taking into account sex, age, tumor size, the cT and cN clinical stage. We estimated the rate of Dworak tumor regression grade 3-4, RECIST, 5-year overall survival (OS) and disease-free survival (DFS).
RESULTS: the main and control group included 22 patients each. The study group included 11 patients (50%) with cT3 and cT4 clinical stage. Ten (45.5%) patients had cT3 clinical stage and 12 (54.5%) patients had cT4 clinical stage in the control group (p = 0.76). The number of patients with cN1-2 clinical stage was 17 (77.3%) and 16 (72.7%) in the study and control group, respectively (p = 0.728). The rate of Dworak tumor regression grade 3–4 was 40.9% in the group of patients with SRCCR and 45.5% in the group of patients with rectal adenocarcinoma (p = 0.761).When assessed by RECIST scale, 9 (40.9%), 12 (54.5%) and 1 (4.5%) patients with SRCCR had partial tumor response, stabilization and progression, respectively. Partial response was observed in 18 (81.8%) patients and stabilization — in 4 (18.2%) patients with rectal adenocarcinoma (p = 0.018). Median followup was 58.8 months. The 5-year OS was 34% in the SRCCR group and 71.3% in the group with rectal adenocarcinoma (p = 0.024), and the 5-year PFS was 30.2% with SRCCR and 52.2% with adenocarcinoma (p = 0.115).
CONCLUSIONS: CRT leads to comparable grade 3–4 tumor regression in SRCCR and rectal adenocarcinoma, but the objective response rate is lower. This histological subtype has significantly lower OS values.

KEYWORDS: *colorectal cancer, signet ring cell carcinoma, chemoradiotherapy, adenocarcinoma, neoadjuvant therapy*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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ADDRESS FOR CORRESPONDENCE: *Belenkaya Y.V., I.M. Sechenov First Moscow State Medical University (Sechenov University) (Trubetskaya st., 8, p.2, Moscow, 119992, Russia; e-mail: yana-belenkaya@bk.ru*

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INTRODUCTION

There are many histological subtypes of colorectal cancer, each of which has its own prognostic features [1]. Signet ring cell carcinoma is a rare histological subtype of a tumor of this localization and occurs in no more than 1% of patients. SRCCR is associated with a young age, a high degree of malignancy, a high rate of lymph node lesions, often has a proximal localization, metastasizes along the peritoneum, is usually diagnosed at late stages and has unfavorable outcomes [2,3].

In accordance with modern clinical recommendations, the use of neoadjuvant RT or CRT is

recommended for the majority of newly diagnosed rectal adenocarcinomas, since it contributes to improving local control [4,5]. Co-administration of RT and chemotherapy significantly increased the survival rate of patients with rectal cancer [6]. However, in a study by Bratland A., et al., it was shown that SRCCR has less sensitivity to non-surgical methods of treatment, compared with rectal adenocarcinoma [7]. There is little data in the scientific literature on the results of the use of preoperative RT in patients with SRCCR, which indicates the need for further study of this topic.
In this study, we assessed the effectiveness of CRT in patients with SRCCR, and also tried to determine whether patients with that histological subtype of tumor received the same benefit from neoadjuvant CRT as patients with rectal adenocarcinoma.

PATIENTS AND METHODS

We used a database of medical records of patients with the code ICD-X C20 and ICD-O8490/3, 8490/3.1, 84903 — from the archives of the N.N. Blokhin National Medical Research Center of Oncology and the multicenter registry of the RSSCC for the period from 2000 to 2020.
A retrospective analysis of medical histories was carried out. The study group included patients with the following characteristics: histologically confirmed SRCCR, absence of primary multiple malignant neoplasms (PMMN), absence of distant metastases (M0), CRT at stage 1, stage II-III. Patients with mucosal adenocarcinomas with a signet ring cell component were excluded from the study, as well as patients from the RSSCC registry whose follow-up period was less than 1 year.
A control group of patients with rectal adenocarcinoma was selected from a prospectively maintained database using propensity-score matching 1:1in order to minimize systematic errors and ensure maximum comparability of patients. Patients from the study and control groups were selected based on multivariate analysis using logistic regression with the inclusion of the following parameters in the model: gender, age, tumor size, cT, cN. An error of 3% in the values of the risk ratio (RR) was allowed for comparison.
Staging was performed using CT of the thoracic and abdominal cavities with intravenous contrast, MRI of the pelvis. All patients underwent 3D conformal RT with a single focal dose (SFD) of 2 Gr to a total focal dose (TFD) of 50–52 Gr against the background of chemotherapy with capecitabine 825 mg/m^2 2 times a day orally on the days of RT. Surgical treatment was performed in accordance with the principles of total mesorectumectomy. The inferior mesenteric artery was ligated at the level of departure from the aorta or directly below the level of departure of the left colon artery.
In both groups, we assessed the rate of achieving therapeutic pathomorphosis of the 3rd-4thgrade on the Dworak scale, RECIST, five-year OS and DFS. Statistical data processing was carried out in the IBM SPSS Statistics 23 program. We calculated the reliability of differences between categorical variables using chi-square-test. The Kaplan-Mayer method was used to evaluate OS and DFS. Differences in survival were assessed by log-rank-test. OS was evaluated from the moment of diagnosis until the onset of death. DFS was defined as the time interval between the date of diagnosis and the date of death or before the disease progressed.

RESULTS

In the archives of the Blokhin NMRC of Oncology and the RSSCC registry, at the created request were identified 214 medical records, 45 of which were excluded because they were records regarding the revision of histological specimens from other institutions, 4 more were excluded because they corresponded to metastases of gastric signet ring cell carcinoma into pararectal tissue, 20 cases corresponded to mucosal adenocarcinoma with a signet ring cell component, 26 patients did not receive inpatient treatment, in 17 cases the medical records were not found in the archive, 7 records were incomplete or less than 6 months old. The analysis included data of 95 patients, but 46 more records were excluded from them due to the localization of the tumor in the colon, in 27 cases no CRT was performed. As a result, 22 patients with SRCCR were included in the study. For the period of 2000–2020, 251 records of patients with rectal

adenocarcinoma treated with CRT were identified in the clinic prospectively maintained patient database, from which 229 patients were screened out after propensity-score matching (Fig. 1).

The study and control groups included 22 patients each. Each group consisted of 5 (22.7%) females and 17 (77.3%) males, with 19 (86.4%) patients under the age of 70 and 3 (13.6%) patients older than 70 years ($p > 0.99$).

The tumor sizes in the study group were 0–5 cm in 3 patients, 5–10 cm in 16 patients and 10–15 cm in 3 patients (13.6%, 72.7% and 13.6%, respectively). In the control group, 5 (22.7%) patients had a tumor size of 0–5 cm, 15 (68.2%) patients — 5–10 cm, and 2 (9.1%) patients — 10–15 cm ($p = 0.693$). In the study group there were 11 (50%) patients with clinical stages of cT3 and cT4. In the control group, 10 (45.5%) patients had the clinical stage of cT3, 12 (54.5%) had cT4 ($p = 0.763$). The number of patients with stage cN0 was 5 (22.7%) and 6 (27.3%) in the study and control groups, respectively. There were 17 (77.3%) and 16 (72.7%) patients with clinical stages of cN1-2 in the study and control groups, respectively ($p = 0.728$). The general characteristics of both groups are presented in Table 1.

It follows from Table 1 that there were no significant differences between the patients from the study and control groups in the main characteristics that could affect the treatment and prognosis of the disease.

The rate of achieving pathomorphosis of the 3rd-4thgrade in the group of patients with SRCCR (Table 2) was 40.9%, in the group of patients with rectal adenocarcinoma — 45.5% ($p = 0.761$). The rate of achieving therapeutic pathomorphosis of the 4th grade was 9.1% in the study group and 13.6% in the control group ($p > 0.99$).

An additional tool for assessing the effect of preoperative treatment was the RECIST scale. It follows from Table 3 that the distribution of the grades of response to neoadjuvant CRT significantly differed in the groups of SRCCR and rectal adenocarcinoma ($p = 0.018$). With SRCCR in 9 (40.9%) patients, 12 (54.5%) and 1 (4.5%) patients had partial tumor regression, stabilization and progression, respectively. In rectal adenocarcinoma, partial regression was observed in 18 (81.8%) patients, and stabilization was observed in 4 (18.2%).

7–12 weeks after the end of CRT, all patients underwent surgery with a resection volume of R0. It is worth noting that in the SRCCR group, 10 (45.5%) patients underwent sphincter–preserving surgeries and 12 (54.5%) underwent abdominal-perineal extirpation (APE). In the group of rectal

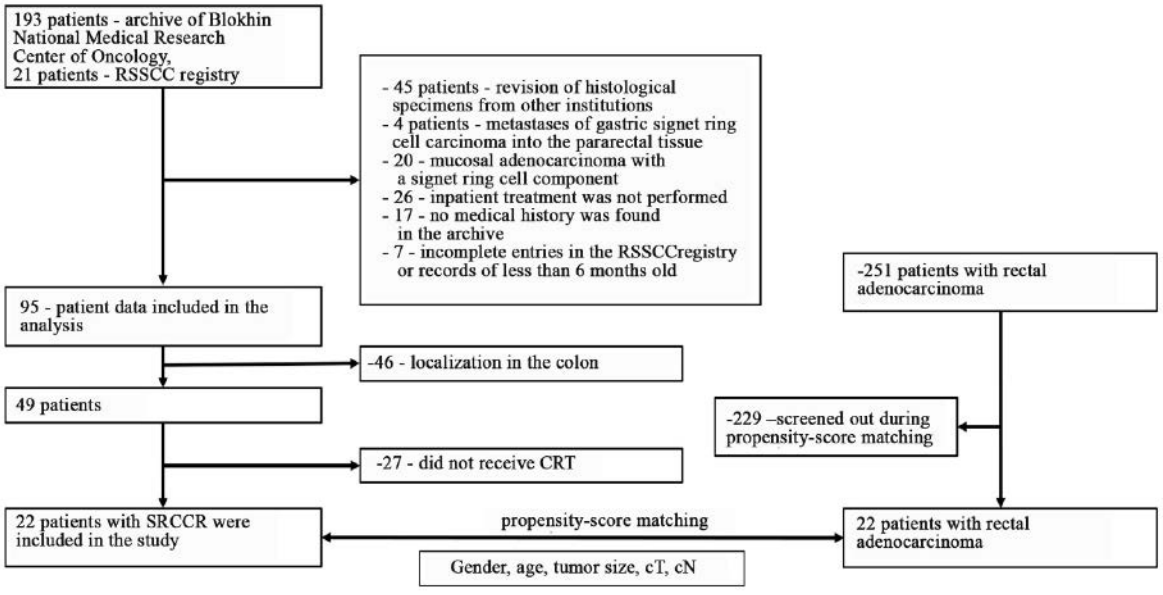

Figure 1. *Block diagram of the selection of medical records of patients for research*

Table 1. *Comparative characteristics of patients*

Category	Study group (SRCCR) N = 22 (100%)		Control group (Rectal adenocarcinoma) N = 22 (100%)		*P*
	N	%	N	%	
Number of patients	**22**	**100**	**22**	**100**	**1.00**
Gender					
Female	5	22.7	5	22.7	1.00
Male	17	77.3	17	77.3	
Age					
< 70 years	19	86.4	19	86.4	1.00
> 70 years	3	13.6	3	13.6	
Tumor size					
0–5 cm	3	13.6	5	22.7	0.693
5–10 cm	16	72.7	15	68.2	
10–15 cm	3	13.6	2	9.1	
Stage T					
cT3	11	50.0	10	45.5	0.763
cT4	11	50.0	12	54.5	
Stage N					
cN0	5	22.7	6	27.3	0.728
cN1, cN2	17	77.3	16	72.7	

Table 2. *Comparative characteristics of Dworak tumor regression grade*

Tumor regression grade (Dworak)	Study group (SRCCR) N = 22 (100%)	Control group (rectal adenocarcinoma) N = 22 (100%)	*P*
0	3 (13.6%)	0 (0%)	0.1
1	6 (27.3%)	2 (9.1%)	
2	4 (18.2%)	10 (45.5%)	
3	7 (31.8%)	7 (31.8%)	
4	2 (9.1%)	3 (13.6%)	

Table 3. *Assessment of the efficacy of neoadjuvant CRT according to the RECIST scale*

Grade	Study group (SRCCR) N = 22 (100%)	Control group (rectal adenocarcinoma) N = 22 (100%)	*P*
Partial regression (> 30%)	9 (40.9%)	18 (81.8%)	0.018
Stabilization	12 (54.5%)	4 (18.2%)	
Progression	1 (4.5%)	0 (0%)	

adenocarcinoma, sphincter-preserving surgeries were performed in 19 (86.4%) patients, and APE — in 3 (13.6%) patients ($p = 0.004$).

The median follow-up was 58.8 months. During this time, recurrences developed in 3 (13.6%) patients in the study group, in 1 (4.5%) patient — in the control group ($p = 0.294$). Metastases during this time appeared in 11 (50.0%) patients in the study group and in 6 (27.3%) patients — in the control group ($p = 0.122$).

Five-year OS was 34% in the SRCCR group and 71.3% in the rectal adenocarcinoma group ($p = 0.024$) (Fig. 2); and five–year DFS was 30.2% in the SRCCR group and 52.2% in the rectal adenocarcinoma group ($p = 0.115$) (Fig. 3).

DISCUSSION

There were no significant differences in the sensitivity of SRCCR and adenocarcinoma to CRT ($p = 0.761$): the rate of therapeutic pathomorphosis of grades 3–4 on the Dworak scale was 40.9% in the group of patients with SRCCR and 45.5% — with adenocarcinoma. The rate of achieving therapeutic pathomorphosis of grade 4 was 9.1% in

the study group and 13.6% in the control group ($p > 0.99$).

At the same time, according to the RECIST criteria a partial response was significantly more often achieved in adenocarcinoma group — in 81.8% of patients compared with 40.9% in SRCCR group. In adenocarcinoma, other authors had similar partial response rates [8,9]. This may be important when making decisions about the tactics of treatment of such patients. We are less likely to expect tumor regression after CRT for SRCCR and, accordingly, the administration of this treatment in order to increase resectability may be less justified. Excellent data were obtained in the study by Attia A.M., et al.: out of 18 patients with SRCCR after neoadjuvant CRT, therapeutic pathomorphosis of grades 3–4 (as per Dworak scale) was achieved in all of them, while out of 177 patients with a tumor without a signet ring cell component — in only 59.9% ($p < 0.0001$) [10]. According to a study by Bratland A. et al., out of 6 analyzed patients with SRCCR, 3 patients had complete disappearance of tumor cells after neoadjuvant CRT, and 3 patients retained residual tumor infiltration into the intestinal wall, mesorectum and adjacent pelvic structures [7]. In a study by Zhou Y., et al., the response to preoperative CRT was studied in 7 patients with SRCCR: 4 of them had TRG1 grade of tumor regression according to Mandard A.M., 2 had TRG2, 1 patient had a partial response, 1 had a poor response [11].

In our study, the five–year OS with SRCCR was 34%, while with rectal adenocarcinoma — 71.3%. Similar data were obtained in a meta-analysis by Fad M.G., et al.: the five-year OS with SRCCR was lower than with rectal adenocarcinoma (HR 2.54; 95% CI 1.98–3.27; $p < 0.001$) [1]. In a study by Nick Hugen et al., five-year OS was 19.5% with SRCCR and 58.5% with rectal adenocarcinoma [12]. San-Gang Wu., et al. in their work revealed that the five-year OS with SRCCR was 39.0% [13], which is comparable with our results. Such an unfavorable prognosis for SRCCR may be associated with a more frequent early development of metastases in patients with this histological subtype in comparison with rectal adenocarcinoma. It has been suggested that the reason for this pattern lies in the fact that with SRCCR there is a reduced expression of E-cadher in and catenin involved in intercellular adhesion and, accordingly, being suppressors

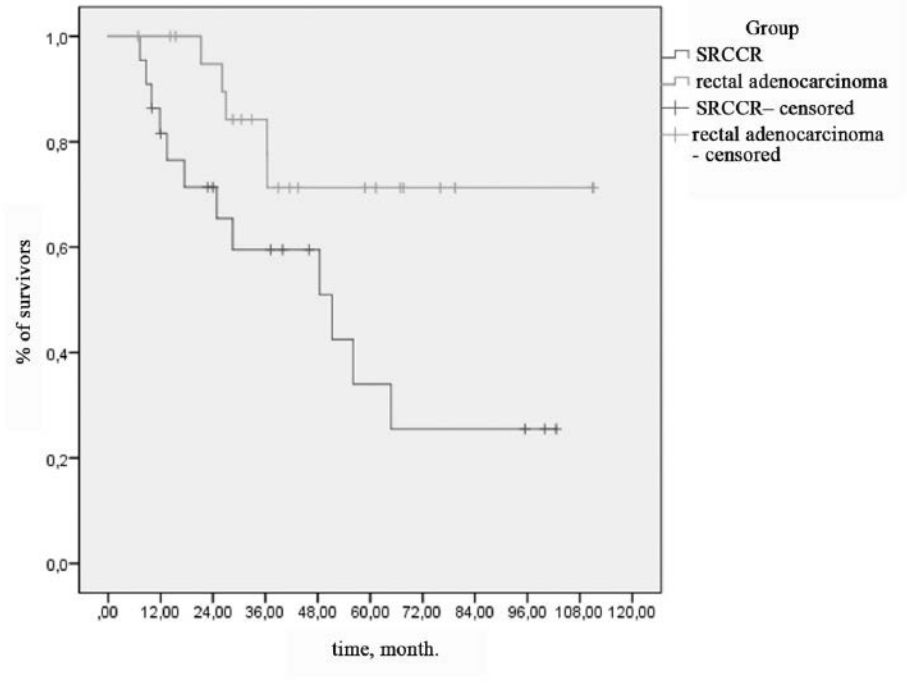

Figure 2. *Kaplan-Meier overall survival (OS) curves. The blue line indicates the study group (SRCCR), the green line indicates the control group (adenocarcinoma).*

of tumor invasion [14–16]. Perhaps, in order to increase OS and DFS with SRCCR, it is worth considering the intensification of neoadjuvant effects on the tumor, since in the study by Mammadli Z.Z., et al., it was shown that when induction and consolidating chemotherapy were added to CRT, a complete morphological response was significantly more often recorded ($p = 0.021$) [17].

The advantage is that our study is one of the few in which a comparative assessment of the long-term results of treatment of patients with SRCCR in comparison with rectal adenocarcinoma was carried out. We were able to select a group of patients with a similar initial clinical picture of diseases that differ only in histological structure.

Our study has some disadvantages. Despite the fact that the incidence of SRCCR is extremely low, there is still insufficient data of 22 patients with SRCCR for an objective assessment. In order to get more information about the correlation between the response to preoperative CRT and the histological subtype of the tumor, it is necessary to analyze the results of a larger number of patients. In addition, it should be taken into account that our study contains information for 20 years of follow-up, and patients who received treatment in later years could have a better prognosis due to the continuous improvement of medical equipment and advances in drug therapy.

CONCLUSION

Based on the results of the study, important data were obtained on the effectiveness of neoadjuvant CRT in patients with SRCCR. Despite the absence of significant differences in the response to preoperative RT, in the SRCCR group, OS and DFS were lower than in the adenocarcinoma group due to early metastasis. The obtained results can be used in the future when planning treatment tactics for patients with this subtype of rectal tumor. However, it is advisable to further accumulate material within a multicenter registry to form a more representative sample.

AUTHORS CONTRIBUTION

Concept and design of the study: *Ivan S. Stilidi, Sergey S. Gordeev, Yana V. Belenkaya, Zaman Z. Mamedli*

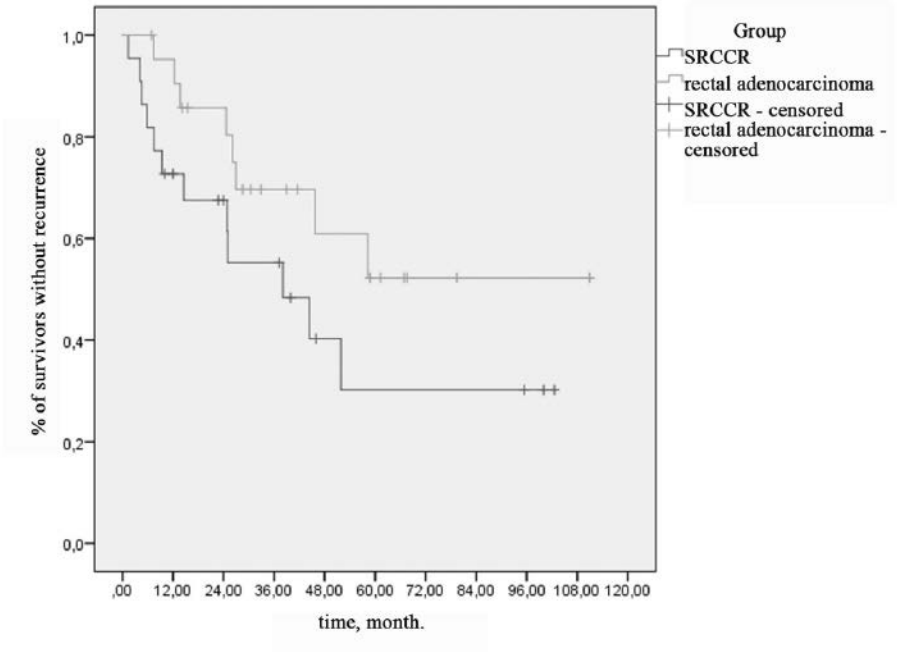

Figure 3. *Kaplan-Meier disease-free survival (DFS) curves. The blue line indicates the study group (SRCCR), the green line indicates the control group (adenocarcinoma of the rectum)*

Collection and processing of the material: *Sergey S. Gordeev, Yana V. Belenkaya, Zaman Z. Mamedli, Igor G. Komarov*
Statistical processing: *Sergey S. Gordeev, Yana V. Belenkaya*
Writing of the text: *Sergey S. Gordeev, Yana V. Belenkaya*
Editing: *Arkadiy G. Malikhov, Zara N. Magarramova*

INFORMATION ABOUT THE AUTHORS (ORCID)

Sergey S. Gordeev — MD, PhD, Leading Researcher, Department of Oncology of Surgical Methods of Treatment № 3 (Coloproctology), N.N. Blokhin National Medical Research Center of Oncology; Docent of Department of Oncology of Tyumen State Medical University; ORCID 0000-0002-9303-8379
Yana V. Belenkaya — a student, Pediatric Faculty, I.M. Sechenov First Moscow State Medical University (Sechenov University)
Zara N. Magarramova — Resident, N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russia
Igor G. Komarov, MD, PhD, DSc, Professor, Leading Researcher, Surgery Department of Tumor Diagnostics № 2, N.N. Trapeznikov Scientific Research Institute of Clinical Oncology, N.N. Blokhin National Medical Research Center of Oncology
Arkadiy G. Malikhov — PhD, DSc, Leading Researcher, Department of Oncology of Surgical Methods of Treatment № 3 (Coloproctology), N.N. Blokhin National Medical Research Center of Oncology
Zaman Z. Mamedli — MD, PhD, DSc, Head of the Oncology Department of Surgical Methods of Treatment № 3 (Coloproctology), N.N. Blokhin National Medical Research Center of Oncology; ORCID 0000-0002-9289-1247
Ivan S. Stilidi — Academician of the Russian Academy of Sciences, Professor, MD, PhD, DSc, Director of N.N. Blokhin National Medical Research Center of Oncology

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