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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

DIAGNOSIS AND TREATMENT OF CHRONIC RADIATION PROCTITIS AFTER CHEMORADIOTHERAPY IN PATIENTS WITH CERVICAL CANCER

Speciality: 3224.01 – "oncology"

Field of science: Medicine

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INTRODUCTION

The topicality of the subject. Chronic radiation proctitis (CRP) is one of the most serious complications of chemoradiotherapy of malignant tumors of the pelvic organs and, in particular, of cervical cancer (CC).[1] In modern oncology, radiotherapy and chemotherapy are among the most important methods of combined treatment for patients with CC.[2] As the scope of the use of radiation therapy in CC treatment expanded, the number of its complications, primarily in the form of CRP, increased.

According to various authors, CRP constitutes the basis of post-radiation pathology and, on average, is detected in 15-30% of patients.[3] Colonoscopy is the most reliable examination method for the confirmation of CRP, especially in the presence of minimal signs of damage.[4]

The general principles for the selection of treatment of CRP depend on the severity of symptoms. Most authors recommend starting treatment of CRP with conservative therapy.[5]

Endoscopic argon plasma coagulation (APC) is the most effective and safe method of hemostasis for patients with CRP with recurrent bleeding. According to the data of numerous clinical studies, the incidence of complications when using APC does not

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[1] Алиев, Д.А. Поражения кишечника после химиорадиотерапии / Д.А.Алиев, Н.Р.Алиева // Azərbaycan onkologiya jurnalı, - Bakı: - 2017. №1, - с. 6-12.

[2] Calo, C. Cervical cancer radiation therapy compliance rates based on location of radiation therapy / C.Calo, J.Elliott, A.Clements [et al.] // Gynecol. Oncol., - 2019. vol.152, № 3, - p. 528-532.

[3] Shadad, A.K. Gastrointestinal radiation injury: symptoms, risk factors and mechanisms / A.K.Shadad, F.J.Sullivan, J.D.Martin [et al.] // World J. Gastroenterol., - 2013. vol. 19, №2, - p. 185-198.

[4] Жариков, А.А. Онкологическая заболеваемость органов малого таза, лучевые повреждения и их диагностика (обзор литературы) / А.А.Жариков, О.В.Терехов // Радиация и риск (Бюллетень национального радиационно-эпидемиологического регистра), - 2013. т. 22, №3, - с. 57-64.

[5] Porouhan, P. Management of radiation-induced proctitis / P.Porouhan, N.Farshchian, M.Dayani // J. Family Med. Prim. Care., - 2019. vol. 8, №7, - p. 2173-2178.

exceed 2-3%.[6] In this regard, the APC method appears to be very promising for widespread use in the treatment of CRP.

Complex conservative treatment can significantly alleviate the condition of patients; in a number of cases it can cure patients suffering from CRP thereby improving their quality of life and increasing social activity.[7] At the same time, it should be noted that the treatment of CRP remains a difficult task, the solution of which requires a differentiated approach. To date, no clinical standards have been developed for the diagnosis, classification and effective treatment of CRP. The results of the existing methods of conservative therapy for CRP remain dissatisfying; they are accompanied by frequent relapses of the pathological process and can please neither patients nor doctors.[8]

Consequently, the improvement of effective methods for CRP treatment and their implementation into everyday practice remains a topical task. Further research is required on the combined treatment of CRP.

The purpose of the study was the improvement of methods for early diagnosis and treatment of chronic radiation proctitis in patients with cervical cancer who received chemoradiotherapy.

Research Objectives

1. To determine the incidence and severity of CRP in patients with CC who received chemoradiotherapy.

2. To investigate the timing of the onset of CRP in patients with CC who received chemoradiotherapy.

3. To investigate the factors influencing the timing of the onset of CRP, its incidence and severity in patients with CC who received chemoradiotherapy.

4. To develop an algorithm of diagnostic examinations (blood tests,

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[6] Peng, Y. Efficacy and Safety of Argon Plasma Coagulation for Hemorrhagic Chronic Radiation Proctopathy: A Systematic Review / Y.Peng, H.Wang, J.Feng [et al.] // Gastroenterol. Res. Pract., - 2018. vol. 18, - p. 308-322.

[7] Grodsky, M.B. Radiation proctopathy / M.B.Grodsky, S.M.Sidani // Clin. Colon Rectal Surg., - 2015. vol. 28, №2, - p. 103-111.

[8] Lenz, L. Chronic radiation proctopathy: A practical review of endoscopic treatment / L.Lenz, R.Rohr, F.Nakao [et al.] // World J. Gastrointest. Surg., - 2016. Feb; vol. 8, № 2, - p. 151-160.

ultrasound, MRI examination, and colonoscopy) for the early diagnosis of CRP in patients with CC who received chemoradiotherapy.

5. To develop standards of effective conservative treatment of CRP in combination with the argon plasma coagulation in patients with CC who received chemoradiotherapy.

Methods of Research

Clinical, endoscopic, instrumental, laboratory and radiological diagnostic methods were used in this study. The statistical data processing method was used to interpret and evaluate the obtained results.

A high degree of reliability is assigned to such issues as the compliance with the criteria for the inclusion and exclusion of patients in the study protocol, the randomization of patients, the timing of assessment of early results, the period of delayed observations, and the protocols of the performed diagnostic examinations.

A sufficient volume of observations (123 patients with CRP being included in the study) and the proportional distribution of patients in the study groups allowed analyzing the factors that influence the incidence and severity of chronic radiation proctitis, as well as determining the effectiveness of the proposed treatment methods for this pathology.

Statistical processing was carried out using the Microsoft Office Excel 2016 software package. The Student's t-test was used to calculate the reliability of the difference between two relative rates. Differences were considered significant with $p < 0.05$.

The Main Provisions for the Defence

1. 7-12 months are the most critical for the development and manifestation of CRP. Colonoscopy is the most reliable and objective examination method for the confirmation of CRP, especially in the presence of minimal signs of damage.

2. In comparison with the LENT-SOMA clinical classification, the VRS endoscopic classification gives a more reliable characterization of pathological changes occurred in the rectal mucosa after chemoradiotherapy.

3. The incidence and severity of CRP depends on many factors, the main of which is the radiation therapy dose and planning (conventional or conformal radiation therapy). Risk factors such as the age of patients, the stage of the disease and the presence of concomitant pathology also significantly impact the incidence and severity of CRP. These factors remarkably increase the risk of the development of CRP.

4. Basic conservative therapy of CRP should include drugs aimed at stimulating the repairment of the rectal epithelium, reducing exposure to intraluminal factor along with eliminating the inflammatory process and correcting the intestinal microflora.

5. The argon plasma coagulation is a highly effective and safe method for endoscopic treatment of CRP complicated by recurrent bleeding.

Scientific Novelty of Research

A comprehensive clinical, radiological and endoscopic examination of the rectal mucosa was carried out in 123 patients with CC, who developed CRP after chemoradiotherapy according to a radical program.

As a result of the study, new updated data were obtained on the incidence, nature and severity of the radiation complications of the rectal mucosa in patients with CC after chemoradiotherapy.

The real terms of occurrence of CRP were identified in patients with CC who received chemoradiotherapy. New information was obtained on the most significant disorders of the rectal mucosa after chemoradiotherapy. For the first time, the dynamics of these disorders was traced throughout various terms after the end of chemoradiotherapy. It was established that clinical and endoscopic manifestations of CRP of Grade 3-4 do not appear immediately after the completion of chemoradiotherapy but develop gradually from minimal signs to a pronounced condition of the disease. This circumstance indicates that the development of CRP is of a staged nature – from minimal clinical and endoscopic manifestations to a pronounced condition of the disease.

As a result of the analysis, it was convincingly proved that the

endoscopic classification of VRS gives a more reliable characterization of pathological changes in the rectal mucosa after chemoradiotherapy in comparison with the clinical classification of LENT-SOMA.

The degree of significance of various factors influencing the incidence, nature and severity of CRP was studied and determined.

The schemes of conservative therapy providing a complex effect on the condition of the rectal epithelium were developed for the CRP treatment. The effectiveness of these conservative therapy schemes that stimulated the repairment of the rectal epithelium, the reduction of exposure to intraluminal factors along with the elimination of the inflammatory process and the correction of the intestinal microflora were investigated.

For the first time, the effectiveness of the argon plasma coagulation in combination with the conservative therapy was investigated in the treatment of CRP.

The Practical Significance of the Study

A comprehensive examination of patients with CC 3 months after the end of chemoradiotherapy and a subsequent follow-up will allow diagnosing CRP in a timely manner and applying an appropriate treatment.

The use of the VRS endoscopic classification will allow objectively assessing the severity of CRP and selecting of the optimal treatment tactics.

The use of the developed schemes of conservative therapy in combination with argon plasma coagulation will increase the efficiency of CRP treatment.

The Implementation of the Obtained Results in Practice

The results of the study were introduced into the practical work of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan. The proposed methods for early diagnosis and combined conservative therapy with endoscopic APC allow for a timely diagnosis and effective treatment of CRP. The provisions set out in the dissertation are also used in the educational process (practical classes and lectures) at the Department of Oncology of the Azerbaijan State Institute for Advanced Training of Doctors named

after A.Aliyev of the Ministry of Health of the Republic of Azerbaijan in the preparation of doctors undergoing advanced training in the "oncology" speciality.

The obtained results of the study were published in the form of methodological recommendations titled "Diagnosis and Treatment of Chronic Radiation Proctitis" and were recommended for use in oncological centers and dispensaries.

The Approbation of Dissertation

The research results were presented in the form of the following scientific reports:

“Uşaqlıq boynu xərçənginə görə radioterapiya almış xəstələrdə radiasion proktosiqmoiditlərin diaqnostkası və müalicəsi”, The II Baku Endoscopic Forum, October 6, 2018;

"Xroniki radiasion proktitin endoskopik müalicəsi üzrə bizim təcrübəmiz", The III Baku Endoscopic Forum, November 9, 2019;

"Эффективность консервативной терапии хронического радиационного проктита после химиорадиотерапии рака шейки матки", The XXIII Russian Oncology Congress, Moscow, November 12-14, 2019.

Two reports based on the results of the dissertation were made at the meeting of the Scientific Medical Society of Oncologists of Azerbaijan in 2018 and 2019.

The main provisions of the dissertation were discussed at the Interdepartmental Conference of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan (Baku, March 12, 2020, protocol No.1) and at the meeting of the Scientific Seminar on the approbation of dissertations for the degree of Doctor of Philosophy in Medicine at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan (Baku, April 30, 2021, protocol No. 4).

The main provisions of the dissertation were reflected in 23 published scientific works (14 articles, 8 theses and 1 methodological recommendation). Twelve scientific works (9 articles and 3 theses) were published in Azerbaijani journals peer-reviewed by the Supreme Attestation Commission of the Republic of Azerbaijan and ten scientific works (5 articles and 5 theses) were published in

foreign journals. The published works fully presented the obtained results, the provisions submitted for defence, and the conclusions of the dissertation.

The name of the institution on the basis of which the dissertation was carried out. The dissertation work was carried out at the Department of Endoscopy of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The volume and structure of the dissertation. The dissertation is presented on 174 pages of computer text, it consists of an introduction, a literature review, four chapters of research, conclusions, results, a list of references, and a list of abbreviations and symbols. The work contains 49 tables and 25 figures. The list of references includes 23 local and 196 foreign sources.

The number of characters in the structural sections of the dissertation: Introduction – 15303 characters; Chapter I – 68995 characters; Chapter II – 25252 characters; Chapter III – 28816 characters; Chapter IV – 23973 characters; Chapter V – 30417 characters; Conclusions – 31701 characters; Results – 2491 characters; Practical recommendations – 1841 characters. In total, the dissertation contains 228789 characters.

THE CLINICAL CHARACTERISTICS OF PATIENTS INCLUDED IN THE STUDY

A clinical and endoscopic examination of 403 patients with a morphologically verified diagnosis of CC of stage II-III was carried out in the present study. The patients received remote radiation therapy in a combination with brachytherapy and chemotherapy for this disease, at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan in 2015-2016. One hundred twenty-three (30.5%) out of 403 patients developed CRP in various terms after the end of chemoradiotherapy [11, 19].

The main number of patients was of the following age intervals:

- 46-55 years – 51 patients (41.5%)
- 56-65 years – 33 patients (26.8%)

There was a significantly a smaller number of patients in the age groups of 35-45 years and over 65 years – 29 patients (23.6%) and 10 patients (8.1%), respectively. The median age of all the analysed patients was 51.7 years (range 35-65 years).

Nineteen patients (15.7%) were of stage IIA, 25 patients (20.3%) were of stage IIB, 37 patients (30.1%) were of stage IIIA, and 42 patients (34.2%) were of IIIB stage.

Depending on the timing of the onset of CRP after the end of chemoradiotherapy, the patients were divided into four groups:

Group I – 3-6 months – 19 patients (15,4%);

Group II – 7-12 months – 36 patients (29,3%);

Group III – 13-18 months – 40 patients (32,5%);

Group IV – 19-24 months – 28 patients (22,8%).

The median timing of the onset of CRP after the end of chemoradiotherapy was 12.9 months (ranging between 3-24 months). Most often, the manifestation of CRP symptoms was observed in 7-12-months and 13-18-months terms. This allows considering these periods as the most critical for the development and manifestation of CRP.

Two classifications were used to assess the severity of the clinical manifestations of CRP: the clinical classification of radiation complications according to the RTOG/EORTC-LENT-SOMA[9] scale and the Vienna Rectoscopy Score (VRS).[10]

The comparative analysis of the results from an objective assessment of the nature and severity of CRP using these classifications revealed the following. The endoscopic classification VRS allows for a more reliable characterization of pathological changes in the rectal mucosa after chemoradiotherapy in comparison with the clinical classification LENT-SOMA. For example, when assessing the severity of CRP by the LENT-SOMA classification, 23 patients (18.7 ± 3.5%) did not show a clinical manifestation of the disease (Grade 0).

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[9] LENT SOMA tables // Radiother. Oncol., - 1995. vol. 35, №1, - p. 17-60.

[10] Wachter, S. Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma / S.Wachter, N.Gerstner, G.Goldner [et al.] // Radiother. Oncol., - 2000. vol. 54, №1, - p. 11-19.

At the same time, in endoscopic examination, 15 of these patients (12.2 ± 2.9%) had CRP of Grade 1 and 8 patients (6.5 ± 2.2%) had CRP of Grade 2 according to the VRS classification [7,11].

The analysis of the informational significance of the two classifications gave grounds to use the endoscopic classification VRS in further work for the analysis of factors affecting the incidence and severity of CRP, and also the results of treatment of this pathology [7, 11].

During an endoscopic examination, all 123 patients who were included in the study showed pathological changes in the rectal mucosa that were characteristic of CRP in accordance with the VRS classification. In 31 patients (25.2%), pathological changes in the rectal mucosa corresponded to Grade 1, in 34 patients (27.6%) – Grade 2, in 45 patients (36.5%) – Grade 3, and in 13 patients (10.7%) – Grade 4 [1].

Remote radiation therapy of CC was carried out on gamma-therapeutic apparatus or Clinac linear accelerators of Varian Company equipped with multi-leaf collimators and with the photon beams energies 6-15 MeV.

The programs with implementation of 3D planning were used when treating with a gamma-therapeutic apparatus (conventional radiation therapy) – 26 patients (21.1%).

The dosimetry programs with implementation of 3D planning were used when irradiating with a linear accelerator (conformal radiation therapy) – 51 (41.5%) patients. 3DCRT, IMRT, VMAT technologies were used.

Forty-six patients (37.4%) with CC received the 3DCRT planning radiation therapy in combination with chemotherapy: Cisplatin 40 mg/m2 – once a week for 5 weeks.

Out of 123 patients included in our study, 35 patients (28.5%) had no concomitant diseases; and diabetes mellitus was revealed in 36 patients (29.2%) before the chemoradiotherapy. Diseases of the digestive system (chronic colitis, cholelithiasis) were diagnosed in 35 patients (28.5%) and 17 patients (13.8%), respectively, before the chemoradiotherapy.

A sufficient amount of observation and a normal distribution of patients in the study groups allowed analysing the factors affecting the incidence and severity of CRP, as well as the determination of the effectiveness of the proposed treatment methods for this pathology, in the following chapters of the dissertation.

CHARACTERISTICS OF EXAMINATION AND TREATMENT METHODS FOR PATIENTS WITH CHRONIC RADIATION PROCTITIS

Colonoscopy was the main instrumental examination method included in the protocol. It was performed in all 123 patients to diagnose CRP. In addition, colonoscopy was performed at different terms of observation to monitor and evaluate the dynamics of the treatment effectiveness.

Conservative therapy, symptomatic therapy, and the argon plasma coagulation (APC) were used in the treatment of patients with CRP.

While developing the concept of conservative treatment of CRP, we considered that the main attention should be paid to the condition of the rectal epithelium, in particular, to the stimulation of repairment, the reduction of exposure to intraluminal factors, the elimination of the inflammatory process, and the correction of microflora [15, 22]. This approach provides for a complex effect, rather than monotherapy, which is often observed in clinical practice.

The conservative treatment included diet, pathogenetic and symptomatic drug therapy.

Two conservative therapy schemes were used when carrying out pathogenetic treatment. The patients included in the study by the method of randomization were divided into two groups depending on the conservative therapy scheme used for CRP: Group I – main (n = 63) and Group II – control (n = 60).

The groups were comparable in terms of the absence of CC recurrence, age, the tolerance levels of the performed chemoradiotherapy, the severity of CRP and concomitant diseases.

In the first (main) group, patients received:

- Sulfasalazine or its analogues 3-4 g/day – 4 weeks;
- Sucralfate in the form of rectal microclysters 2 g per 20 ml of solution 2 times a day – 4 weeks;
- Metronidazole 1.5 g/day – 2 weeks;
- Zakofalk 4g/day – 4 weeks;
- Vitamin E 400 IU/day – 12 weeks.

In the second (control) group, patients received:
- Sulfasalazine or its analogues 3-4 g/day – 4 weeks;
- Hydrocortisone suspension in the form of rectal microclysters 125 mg/day – 4 weeks;
- Metronidazole 1.5 g/day – 2 weeks.

Endoscopic APC was performed in the presence of telangiectasias and pinpoint bleeding, as well as in the cases of conservative therapy ineffectiveness. The ineffectiveness of conservative therapy, as a rule, was due to ongoing bleeding during the treatment or to recurrent bleeding from rectum.

APC was carried out at the Department of Endoscopy of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan. APC was performed through the instrument channel of an EXERA Q160 or Q180 colonoscope (Olympus, Japan) using an ERBE VIO 300S APC-2 high-frequency electrical unit (ERBE Elektromedizin GmbH, Germany), front-firing and side-firing APC probes with a diameter of 2.3 mm, type A/S/C (ERBE, Germany). Two modes were used during APC application: soft coagulation and forced coagulation. The number of sessions performed for one patient varied from one to five depending on the Grade of CRP.

The organization of materials, processing and analysis of medical documentation along with statistical calculations of the obtained data were performed on a personal computer using the Windows 10 operating system and a text editor Microsoft Office 2016 Professional. Statistical processing was carried out using the Microsoft Office Excel 2016 software package.

Taking into account the sufficient volume of observation and normal distribution in two independent groups, the Student's t-test was used to determine the statistical significance of the differences in the obtained results. The median was calculated to determine the following: various characteristics of patients and the indices of examination and treatment.

THE FACTORS INFLUENCING THE INCIDENCE AND SEVERITY OF CHRONIC RADIATION PROCTITIS IN PATIENTS WITH CERVICAL CANCER

The analysis of the incidence and severity of CRP in patients with CC showed that the radiation treatment planning is the most significant risk factor for this complication. The analysis of the impact of chemoradiotherapy on the incidence and severity of CRP shows that chemoradiotherapy is undoubtedly the main cause of this complication. Serious differences are revealed in the incidence and severity of CRP in patients who received conventional irradiation (2DRT) or conformal irradiation (3DCRT or VMAT). Grade 3-4 CRP was observed in 17 patients (65.4 ± 9.3%) when using conventional irradiation. At the same time, conformal radiation therapy allowed reliable reduction of the incidence of CRP of Grade 3-4 – 20 patients (39.2 ± 6.8%) ($p < 0.05$) [8,9,10,14].

The concomitant chemoradiotherapy significantly improves the results of CC treatment, especially of the IIIA and IIIB stages [5,12,16,17]. However, in this case, in comparison with conformal radiation therapy without chemotherapy, the incidence and severity of CRP increases (Fig. 1).

The age of patients with CC is also an important risk factor that significantly affects the incidence and severity of CRP. In younger patients (35-45 years and 46-55 years age groups), CRP was of a lower severity and corresponded to Grade 1-2 – 72.4 ± 8.3% and 58.8 ± 6.8%, respectively. Similar indices in elderly patients (56-65 years and over 65 years age groups) were lower – 36.4 ± 8.4% and 20.0 ± 12.6%, respectively ($p < 0.05$) [14].

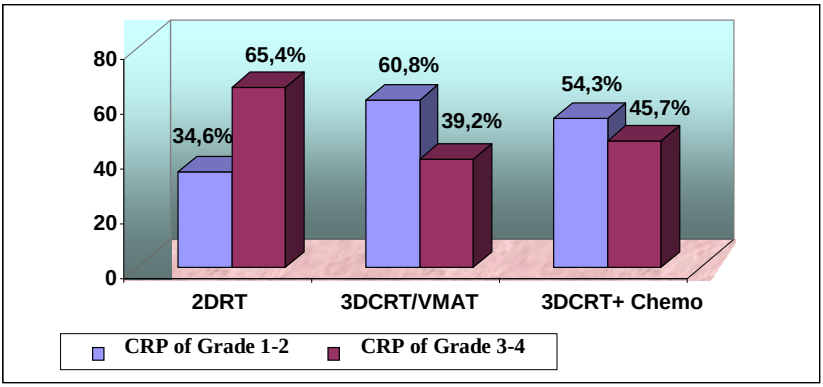

Fig. 1. The incidence and severity of CRP in patients with CC depending on the method of chemoradiotherapy planning

The time of CRP development was no less significant factor than the age of the patients. The incidence and severity of CRP significantly went up with an increase in the length of time after the end of chemoradiotherapy. In the study, the manifestation of CRP was most often observed within 7-12 months – 36 patients (29.3 ± 4.1%) and within 13-18 months – 40 patients (32.5 ± 4.2%). Within 3-6 months and 19-24 months, this index was significantly lower – at 19 patients (15.4 ± 3.2%) and 28 patients (22.8 ± 3.7), respectively [14].

Also noteworthy is the fact that in the early periods, CRP was of lower severity which was associated with minimal trophic disorders of the rectal mucosa. The clinical manifestation and endoscopic picture of CRP significantly worsened at later periods. CRP of Grade 1-2 was most often observed 3-6 months after the end of chemoradiotherapy – at 17 patients (89.5 ± 7.0%). Within 19-24 months, this index significantly decreased – at 5 patients (17.9 ± 7.2%) ($p < 0.05$) [14].

The next important risk factor influencing the incidence and severity of CRP was the initial stage of CC. The incidence of CRP of Grade 1-2 was observed significantly more often in patients with the IIA and IIB stages (73.7 ± 10.1% and 64.0 ± 9.6%, respectively) compared to the patients with the IIIA and IIIB stages (48.6 ± 8.2% and 40.5 ± 7.5%, respectively), $p < 0.05$ [14].

In addition to the above-given factors, the incidence and severity of CRP are also affected by concomitant diseases. A comparative analysis of the incidence and severity of CRP, depending on concomitant diseases, showed that in patients without concomitant pathology, the incidence of CRP of Grade 3-4 accounted for 22.9 ± 7.1% of cases. This index significantly increased in the presence of concomitant diseases (diabetes mellitus, chronic colitis, etc.) [14].

THE RESULTS OF CHRONIC RADIATION PROCTITIS TREATMENT

The analysis of the effectiveness of two investigated conservative therapy schemes for CRP revealed the following. In the patients group I, the incidence of objective remissions – 84.1 ± 4.6% – was statistically significantly higher compared to the same indexes in group II – 68.3 ± 6.0%, $p < 0.05$. At the same time, the lack of effect from the conservative treatment was significantly more often observed in patients of group II compared with patients of group I – 31.7 ± 6.0% and 15.9 ± 4.6%, respectively, $p < 0.05$ (Fig. 2) [15, 20, 22].

The ineffectiveness of conservative therapy was primarily associated with ongoing recurrent rectal bleeding of varying intensity. All of these patients underwent endoscopic APC [21].

Next, the influence of a number of factors (the Grade of CRP, the age of patients, concomitant diseases) on the results of two investigated conservative therapy schemes for CRP was analysed.

The analysis showed that the Grade of CRP has a significant effect on the incidence of the objective remissions after conservative therapy. The incidence of objective remissions decreases and the rate of lack of the effect from treatment increases with an increase in the severity of the reaction. In Group I, the incidence of objective remissions was observed in 31 patients (49.2 ± 6.3%) with CRP of Grade 1-2. In 22 patients (34.9 ± 6.0%) with CRP of Grade 3-4, the same index was significantly lower [15, 20, 22].

In Group II, the incidence of objective remissions was observed in 26 patients (43.3 ± 6.4%) with CRP of Grade 1-2. In 15 patients (25.0 ± 5.6%) with CRP of Grade 3-4, the same index was significantly lower (Fig. 3) [15, 20, 22].

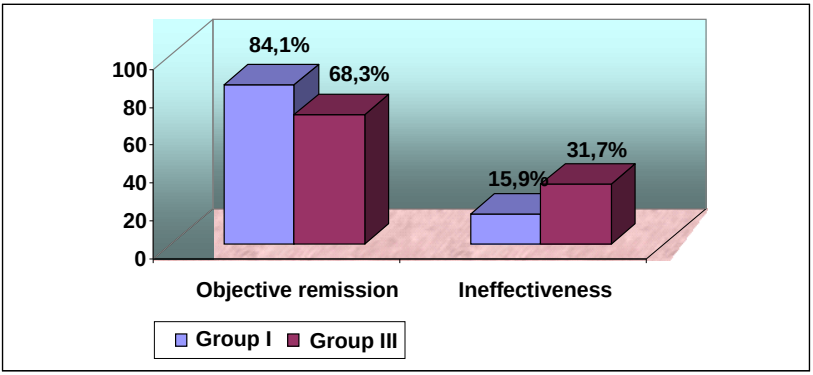

Fig. 2. The comparative assessment of the effectiveness of two conservative therapy schemes for CRP

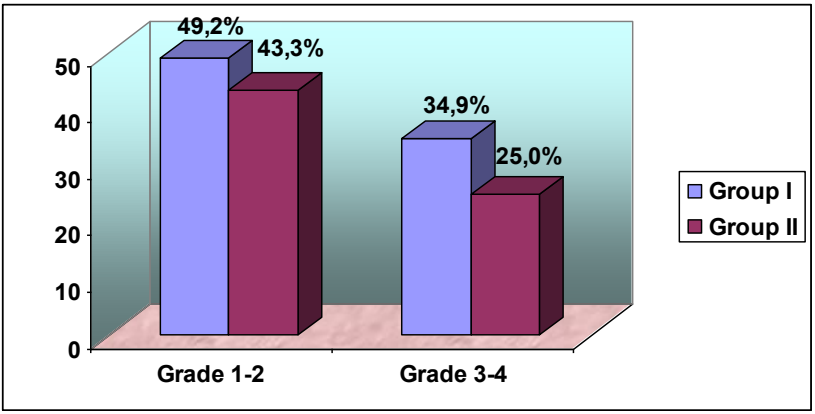

Fig. 3. The incidence of objective remissions, during application of two conservative therapy schemes, depending on the Grade of CRP

In addition to the Grade of CRP, the influence of age on the results of the investigated conservative therapy schemes was also analysed in these patients. The age of patients with CRP has a significant impact on the incidence of objective remissions after conservative therapy. In the Group I with the age intervals of 35-45 and 46-55 years, the incidence of objective remissions was observed in 37 patients (58.7 ± 6.2%). The same index was significantly lower for the

age intervals of 56-65 years and > 65 years – 16 patients (25.3 ± 5.5%).

In the Group II with the age intervals of 35-45 and 46-55 years, the incidence of objective remissions was observed in 33 patients (55.0 ± 6.4%). The same index was significantly lower for the age intervals of 56-65 years and > 65 years – 8 patients (13.3 ± 4.4%) [15, 20, 22].

The next factor significantly influencing the results of CRP treatment was concomitant diseases. The analysis of the impact of concomitant diseases on the effectiveness of CRP treatment revealed a significant decrease in the incidence of objective remissions in the presence of concomitant pathology (Fig. 4).

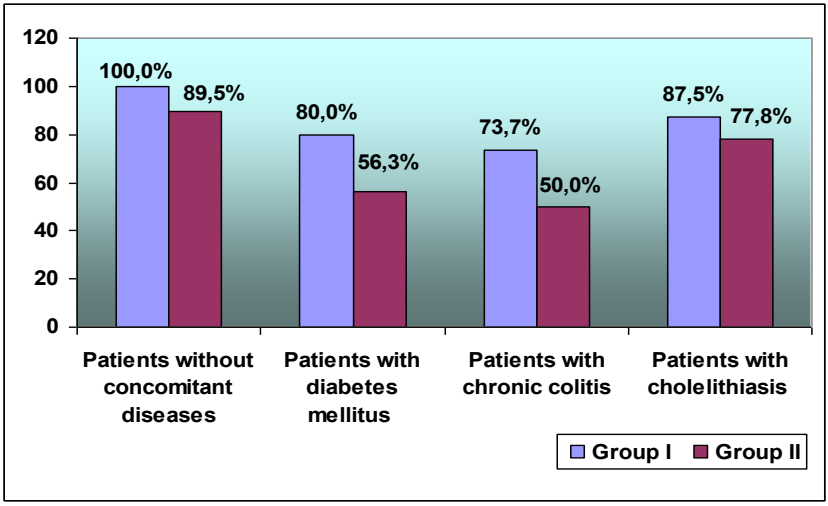

Fig. 4. The incidence of objective remissions, during application of two conservative therapy schemes for CRP, depending on concomitant diseases

In the patients of the Group I without concomitant pathology, objective remissions were observed in 100.0-4.5% of cases after the end of conservative therapy. In the patients with concomitant diabetes mellitus, the incidence of objective remission was 80.0 ± 8.9%. In the group of patients with concomitant chronic colitis, the incidence of objective remissions was observed in 73.7 ± 10.1% of cases; and in the group of patients with concomitant cholelithiasis objective remissions were observed in 87.5 ± 11.6% of cases.

In the patients without concomitant pathology of the Group II, objective remissions were observed in 89.5 ± 7.0% of cases. Among the patients with CRP with concomitant diabetes mellitus, the incidence of objective remissions was 56.3 ± 12.4%. In the group of patients with concomitant chronic colitis, the incidence of objective remissions was observed in 50.0 ± 12.5% of cases; and in the group of patients with concomitant cholelithiasis objective remissions was observed in 77.8 ± 13.8% of cases [15,20,22].

In general, the following conclusion can be drawn from the analysis of the results of two conservative therapy schemes for CRP and of the factors influencing these results. The conservative therapy scheme of the Group I is more effective than that of the Group II. The first scheme allows for a statistically significant increase in the incidence of objective remissions in the treatment of CRP in comparison with the second one.

APC was performed along with basic therapy in 29 patients with CRP, for whom conservative therapy was ineffective, due to ongoing or recurrent rectal bleeding.

A total of 29 patients with CRP underwent 53 APC sessions. Thirteen patients (44.8%) underwent one APC session. Two patients had CRP of Grade 1, 4 patients – Grade 2 and 7 patients – Grade 3.

Two APC sessions were performed for 11 patients (37.9%). Two patients had CRP of Grade 2, eight patients – that of Grade 3 and one patient that of Grade 4.

Three patients (10.3%) underwent 3 APC sessions. All these patients had CRP of Grade 4.

Two patients (6.9%) with CRP of Grade 4 underwent 9 APC sessions (one patient – 4 sessions and another – 5 sessions).

In patients who received two or more APC sessions, the procedure was performed twice a week in the form of sequential sessions. At each session, effect of APC was on an average 50% of lesions.

Colonoscopy was performed on the 2nd and 7th days after APC to control hemostasis. The condition of the scab was investigated and the risk of recurrent bleeding was assessed.

The APC treatment was successful in all cases. No cases of

complications in the form of endoscopically uncontrolled bleeding or perforation of the rectal wall were observed in the application of APC [2,6,13,21].

Rectal bleeding or strictures were not observed in any cases at the follow-up examination, 6-12 months after the completion of APC.

Thus, these data convincingly demonstrate that the high efficiency of the endoscopic treatment of CRP complicated by recurrent bleeding. The endoscopic APC in the combination with conservative therapy is the method of choice for the treatment of CRP in cases of ineffectiveness of the solely applied conservative treatment, especially for CRP accompanied by bleeding.

Results

1. As a result of the study, it was revealed that, 123 (30.5%) out of 403 patients with CC developed CRP at different terms after the end of chemoradiotherapy. In accordance with the VRS endoscopic classification, in 25.2% of cases, pathological changes in the rectal mucosa corresponded to CRP of Grade 1; in 27.6% of those – to CRP of Grade 2; in 36.5% of those – to CRP of Grade 3; and in 10.7% of cases – to CRP of Grade 4 [14,19].
2. Most often, the manifestation of CRP symptoms is on the terms of 7-12 months – in 36 cases (29.3%), and 13-18 months – in 40 cases (32.5%). Somewhat less often, CRP develops within 6 months – in 19 cases (15.4%) and within 19-24 months – in 28 cases (22.8%). The median timing of CRP onset after the end of chemoradiotherapy was 12.9 months [13,14].
3. The main factors influencing the incidence and severity of CRP are the radiotherapy planning and the presence of concomitant diseases. In our study, when using conventional irradiation, CRP of Grade 3-4 was observed in $65.4 \pm 9.3\%$ of the cases. In patients receiving conformal radiation therapy, this index was lower – in $39.2 \pm 6.8\%$ of cases, $p < 0.05$ [8, 10, 14].
4. When assessing the severity of CRP, the endoscopic classification VRS allows a more objective and reliable characterization of pathological changes in the rectal mucosa after chemoradiotherapy in comparison

with the clinical classification RTOG/LENT-SOMA [7].

5. The most informative and objective method for diagnosing CRP is colonoscopy. Taking into account the possibility of CRP development within 6 months after chemoradiotherapy, a mandatory endoscopic examination being performed 6 months after the end of chemoradiotherapy and followed by an endoscopic examinations every 6 months for 3 years is recommended for early diagnosis of this pathology [14, 18].
6. The conservative therapy scheme, including Sulfasalazine, Sucralfate, Zakofalk, Metronidazole and vitamin E, allows obtaining objective remissions in 84.1% of the cases with chronic radiation proctitis.
7. Argon plasma coagulation is a highly effective and safe method of endoscopic treatment of CRP complicated by recurrent bleeding. In cases of ineffectiveness of the solely applied conservative treatment, the endoscopic argon plasma coagulation in combination with conservative therapy is the method of choice for this pathology [19,21].

PRACTICAL RECOMMENDATIONS

1. In clinical practice, CRP should be suspected in any patient with CC who received chemoradiotherapy and who has corresponding symptoms (diarrhea, excess rectal mucus, and intermittent bleeding).
2. Most often, CRP is observed in terms over 12 months (32.5%) after the end of chemoradiotherapy. At the same time, this complication can often occur at earlier terms – 3-12 months (15.4%).
3. The incidence and severity of CRP depends on many factors, the main of which is the radiation dose. The age, the stage of CC, concomitant diseases, and others also have a significant effect on the incidence and severity of CRP.
4. Colonoscopy is the most reliable method to diagnose CRP, especially in the presence of minimal signs of damage. Colonoscopy allows for an objective assessment of the severity and duration of CRP.
5. Endoscopic examination being performed no later than 6 months

after the end of chemoradiotherapy and followed by systematic endoscopic examinations every 6 months for 3 years is necessary for early diagnosis and effective treatment of CRP.

6. The conservative treatment of CRP should include diet, pathogenetic and symptomatic drug therapy. The use of a drug therapy scheme, including Sulfasalazine or its analogues, Sucralfate in the form of rectal microclysters, Metronidazole, and vitamin E is recommended when using pathogenetic treatment. A maintenance therapy for 12 weeks with Sulfasalazine or its analogues is recommended after achieving clinical and endoscopic remission.
7. The endoscopic argon plasma coagulation is recommended in the presence of telangiectasias and pinpoint bleeding.

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THE LIST OF ABBREVIATIONS AND SYMBOLS

APC – Argon plasma coagulation
5-ASA - 5-aminosalicylic acid
ICD-10 – International Classification of Diseases 10th edition
CRP - Chronic radiation proctitis
GC - Glucocorticoids
CC – Cervical cancer
EORTC - European Organization for Research and Treatment of Cancer
ESGE - European Society of Gastrointestinal Endoscopy
LENT-SOMA - LENT = Late Effects Normal Tissues, SOMA = Subjective, Objective, Management and Analytic
RTOG - Radiation Therapy Oncology Group
RTOG/EORTC – Classification of criteria for assessing acute radiation damage
VRS - Vienna Rectoscopy Score – Endoscopic assessment of pathological changes of the rectal mucosa

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