Medical Bulletin of the Main Military Clinical Hospital named after N.N. Burdenko

hospitalburdenko.com

ISSN 2782-1730

2023 №1

2023 №1

ISSN: 2782-1730 (PRINT) / ISSN: 2713-0711 (ONLINE)
DOI: 10.53652/2782-1730-2023-4-1

**PEER-REVIEWED
SCIENTIFIC AND PRACTICAL JOURNAL
MEDICAL BULLETIN
OF THE MAIN MILITARY CLINICAL
HOSPITAL NAMED AFTER N.N. BURDENKO**

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2023 №1

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Evaluation of calculated glomerular filtration rate before and after endovascular correction of renal artery stenosis against the background of resistant vasorenal arterial hypertension

UDK 616.12-008.4
DOI: 10.53652/2782-1730-2023-4-1-7-11

Fursov A.N., Potekhin N.P., Zakharova E.G., Gaydukov A.V., Gorodnichev K.Yu., Makeeva T.G.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. Atherosclerotic stenosis of the renal arteries is the most common cause of renovascular hypertension (RVHT) among middle-aged and elderly people. In this survey a comparative analysis of the calculated glomerular filtration rate (cGFR) in a patient with resistant renovascular hypertension (RVHT) before and after endovascular correction of atherosclerotic renal artery stenosis is given. The medical records (medical history) of 44 patients (34 men, 10 women) with RVHT were analyzed. The criterion for inclusion in the study was renal artery stenosis of more than 75% of the vessel diameter. The mean age of the patients was 50.7±7.2 years. All patients had unilateral lesion of the renal arteries. Patients were divided into three groups according to the initial level of cGFR. The patients were divided into three groups according to initial cGFR value: Group 1 included 12 patients with cGFR over 90 ml/min/1.73 m^2, Group 2 — 19 patients with cGFR from 89 to 60 ml/min/1.73 m^2, Group 3 — 13 patients with cGFR from 59 to 45 ml/min/1.73 m^2. It was revealed that the level of blood pressure after endovascular correction of stenosis decreased significantly among all patients. At the same time, among the patients with initially preserved cGFR (from 90 ml/min/1.73 m^2 and more), there was an improvement in the functional state of the kidneys, a decrease in the number of antihypertensive drugs from 3–5 to a 3-component regimen. Among the patients with initially minimally reduced cGFR (less than 90 ml/min/1.73 m^2), the functional state of the kidneys did not change, and among the patients with cGFR less than 60 ml/min/1.73 m^2, this state continued to worsen progressively; antihypertensive therapy did not change. During the 2-year follow-up period, restenosis of the renal arteries according to duplex scanning was not observed. When deciding whether to perform endovascular interventions for atherosclerotic stenosis of the renal arteries, it is advisable to take into account the calculated GFR data.

Keywords: renovascular hypertension, atherosclerotic renal artery stenosis, estimated glomerular filtration rate, balloon angioplasty with renal artery stenting.

Introduction. Atherosclerotic stenosis of the renal arteries is the most common cause of renovascular hypertension (RVHT) in middle-aged and elderly individuals [1, 12]. Renovascular hypertension accounts for about 1–5% of all cases of arterial hypertension (AH) and is the cause of terminal renal failure in more than 20% of cases [1–3].

Current treatment of RVHT involves drug antihypertensive therapy (AHT) and/or various reconstructive surgical interventions on the renal arteries, in particular using endovascular techniques. Data from a number of randomized trials, including the CORAL and ASTRAL, published in 2013 and 2009, have not shown advantages of endovascular techniques for correction of renal artery stenosis over optimal drug therapy [6, 7, 12, 13]. Therefore, routine revascularization of the renal arteries is currently not recommended [4]. Balloon angioplasty is suggested to be considered only in selected patients, in particular - with unexplained recurrent heart failure or pulmonary edema against the background of AH [4, 6].

The medical community continues to discuss the feasibility of endovascular interventions for atherosclerotic renal artery stenosis [6–10].

In our opinion, when determining the approaches to endovascular treatment of renal artery stenosis, it is necessary to consider different phenotypes of patients with RVHT, especially the clinical variant with resistant AH against the background of multicomponent AHT with stenosis over 75%. At the same time the efficacy of endovascular intervention will be determined not only by the level of arterial pressure (AP) reduction and changes in the nature and volume of AHT, but also by changes in the renal functional indicator — the calculated glomerular filtration rate (cGFR).

Objective. To assess the dynamics of cGFR according to CKD-EPI in patients with RVHT of atherosclerotic genesis before and after endovascular correction of hemodynamically significant renal artery stenosis.

Material and methods. An analysis of medical records of 44 patients (34 men, 10 women) with RVHT of atherosclerotic genesis with renal artery stenosis more than 75% of vessel diameter who were treated in the cardiology center of the hospital from 2016 to 2019 was performed. The mean age of examined patients was 50.7±7.2 years. All patients had unilateral renal artery stenosis (right renal artery in 68% of cases, left renal artery in 32%). 6 (13.6%) patients had type 2 diabetes mellitus, 15 (34.1%) smoked, and 2 (4.5%) abused alcohol.

The patients were divided into three groups according to the initial level of cGFR: Group 1 included 12 patients with cGFR more than 90 ml/min/1.73 m^2, whose mean age was 41.9±7.6 years and duration of AH was 5.1±1.6 years; Group 2 included 19 patients with a cGFR of 89 to 60 ml/min/1.73 m^2, mean age 51.8±6.2 years, duration of AH 6.4±2.5 years; Group 3 included 13 patients with cGFR of 59 to 45 ml/min/1.73 m^2, mean age 58.5±7.3 years, duration of AH 7.4±3.6 years.

All patients, along with general clinical examination, underwent biochemical blood tests, ultrasound duplex scanning of the renal arteries, and blood pressure monitoring. Patients at the time of inclusion in the study received AHT in the form of a combination of ACE inhibitor (iACE) / angiotensin II receptor blocker (ARB) with thiazide diuretics (TD), non-dihydropyridine calcium channel antagonists (CCA), beta-adrenoceptor blockers (BAB) and alpha-adrenoceptor blockers (AAB), mineralocorticoid receptor antagonists (MRA). At the same time, 3-component therapy was used in 56.6% of cases, 4-component therapy in 35%, and 5-component therapy in 8.4%. AHTs were used in doses ranging from medium therapeutic to maximum tolerable.

cGFR was assessed before and 2 years after endovascular intervention. Statistical criteria of significance of differences were used: parametric (χ-criterion for qualitative variables and Scheffe test) and nonparametric Kruskal-Wallis test for quantitative variables, differences were considered significant at $p<0.05$ [5].

Atherosclerotic stenosis of the renal arteries is the most common cause of renovascular hypertension in middle-aged and elderly individuals. Renovascular hypertension accounts for about 1–5% of all cases of arterial hypertension and is the cause of terminal renal failure in more than 20% of cases

The efficacy of endovascular interventions for atherosclerotic renal artery stenosis against the background of resistant vasorenal hypertension is determined not only by the degree of AP level reduction, but also by the initial functional state of the kidneys (the degree of renal dysfunctions and their further dynamics). When deciding on the reasonability of endovascular interventions in patients with resistant vasorenal hypertension against the background of atherosclerotic stenosis of the renal arteries, the initial data of calculated GFR should be considered

Results. In the 1st group patients after endovascular correction of renal artery stenosis, AP significantly decreased: systolic AP (SAP) from 160.2±6.9 to 135.4±4.6 mm Hg, and diastolic AP (DAP) — from 104.5±6.1 to 85.8±7.8 mm Hg ($p<0.05$). cGFR increased from 97.7±10.4 to 118.7±10.2 ml/min/1.73 m^2 ($p<0.05$).

The scheme of AHT has changed. Thus, if initially combined AHT was 3-5-component (mainly by combining iACE/ARB with BAB, CCA, AAB, imidazoline receptor agonists (IRA), MRA or TD), then subsequently 3-component therapy was used as combination of iACE/ARB with CCA and BAB (68% of cases) or in 32% of cases with TD.

Group 2 patients demonstrated a decrease in AP: SAP from 159.4±5.7 to 138.3±3.8 mm Hg, and DAP from 110.4±5.9 to 88.5±6.2 mm Hg ($p<0.05$). cGFR did not change: 69.3±4.2 and 70.4±5.3 ml/min/1.73 m^2, respectively ($p>0.05$). The regimen of AHT did not undergo significant changes and remained a combination of 3 drugs in 36 (82%) patients (iACE/ARB with ACK, TAP or BAB) and 2 drugs in 8 (18%) patients (iAPP/BRA with CCA or TD).

The AP decreased in group 3 patients without reaching the "target" values ($p<0.05$) (SAP from 165.2±5.7 to 144.1±4.7 mm Hg, and DAP from 112.4±7.3 to 91.5±3.9 mm Hg). During the period of observation, there was a tendency for a decrease in cGFR values: 46.3±4.9 and 43.5±3.7 ml/min/1.73 m^2, respectively ($p>0.05$). The regimen of AHT remained unchanged — a combination of 3-4 drugs (iACE/ARB with CCA, AAB or TD). It should be noted that the rate of AAB use increased from 23% to 54%.

No restenosis of the renal arteries according to duplex scanning was observed in all patients during the 2-year follow-up period.

Conclusions. In patients with initially preserved cGFR (from 90 ml/min/1.73 m^2 and more) the improvement of functional state of the kidneys and reduction of the number of antihypertensive drugs from 3–5 to 3-component regimen along with significant decrease of AP levels are registered after endovascular correction of renal artery stenosis.

The functional state of the kidneys did not change in patients with initially minimally decreased cGFR (less than 90 ml/min/1.73 m^2) after surgical intervention, despite the significant decrease of AP levels, and the patients with cGFR less than 60 ml/min/1.73 m^2 continued to worsen progressively, with AP levels not reaching the "target" values, which did not allow significant changes in the scheme of 3–4-component AHT.

The efficacy of endovascular interventions for atherosclerotic renal artery stenosis against the background of resistant vasorenal hypertension is determined not only by the degree of AP level reduction, but also by the initial functional state of the kidneys (the degree of renal dysfunctions and their further dynamics).

When deciding on the reasonability of endovascular interventions in patients with resistant vasorenal hypertension against the background of atherosclerotic stenosis of the renal arteries, the initial data of calculated GFR should be considered.

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Information about the authors:

Andrej N. Fursov — MD, DSc, professor, Head of the Cardiology Department, Cardiology Centre of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Nikolaj P. Potekhin — MD, Honored doctor of the Russian Federation, DSc, professor, Deputy chief of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Elena G. Zakharova — MD, PhD, Department of Hypertension at Cardiology Centre of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts**, **elenazacharova@mail.ru**, ORCID: 0000-0002-3737-778X

Tat'jana G.Makeeva — MD, PhD, Department of Hypertension at Cardiology Centre of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Aleksej V. Gaydukov — MD, Head of the Department of X-ray Surgical Diagnostics and Treatment of vascular diseases, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Konstanin Yu. Gorodnichev — MD, X-ray endovascular surgeon of the Department of X-ray Surgical Diagnostics and Treatment, Center of Cardiovascular Surgery, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 22.02.2023.

Dermatoscopic characterization of various vascular signs in skin tumors

UDK 616.5-006.31
DOI: 10.53652/2782-1730-2023-4-1-12-21

Lamotkin I.A.[1,2], Korabelnikov D.I.[3], Perevalova E.G.[4], Lamotkin A.I.[3]

[1] *Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia*
[2] *Medical Institute of Continuing Education, Russian Biotechnological University, Moscow, Russia*
[3] *Moscow Haass Medical and Social Institute, Moscow, Russia*
[4] *MDElena Dermatology and Cosmetology Clinic, Moscow, Russia*

Abstract. The authors considered the dermatoscopic vascular signs most frequently encountered in the practice of dermatologists, cosmetologists and oncologists in melanocytic and non-melanocytic skin tumors. The paper presents modern views on dermatoscopic diagnosis of skin tumors. Based on clinical experience and data from the literature, dermatoscopic features that occur in various melanocytic and non-melanocytic skin tumors are identified.

Keywords: dermatoscopy, dermatoscopic vascular signs, skin tumors.

Introduction. Dermatoscopy allows to observe the vascularization present in skin lesions of different character as well as to differentiate a wide range of vascular structures. Different variants of vascular pattern along with other accompanying features can help the clinician to correctly distinguish between melanocytic and non-melanocytic skin tumors. Vascular structures are best identified in mildly pigmented or nonpigmented lesions. This is essential in the diagnosis of poorly pigmented melanomas in which classical pigmented structures cannot be identified [1, 2]. When recognizing vascular dermatoscopic structures, it should be taken into account that vessels that run parallel to the skin surface are assessed as lines (Fig. 1). While vessels having perpendicular path to skin surface are usually considered as points (Fig. 2).

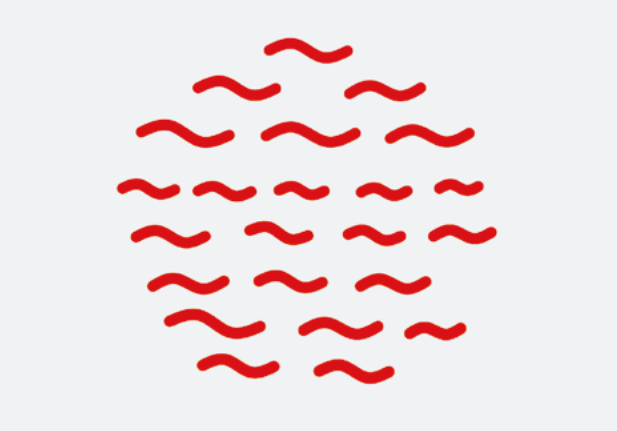


Fig. 1. Vessels parallel to the skin surface

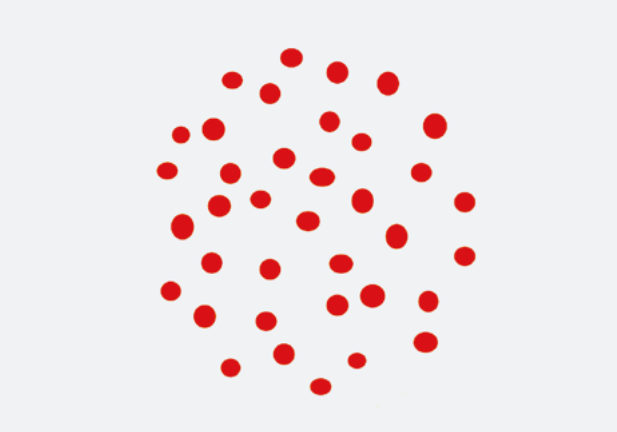


Fig. 2. Vessels perpendicular to the skin surface

In addition, it should be considered that vessels located in the dermis, immediately below the epidermis, appear well-focused and bright red, while those located deeper usually appear pink and unfocused [1, 2]. Different types of dermatoscopic vascular structures can be observed in melanocytic [3–5] and non-melanocytic skin lesions [6–9].

Objective. To compare data from the literature with our own observations of patients with various vascular signs in skin tumors, to investigate features of various vascular dermatoscopic structures for the identification of melanocytic and non-melanocytic skin tumors.

Material and methods. Clinical and dermatoscopic experience in the detection of vascular dermatoscopic signs in skin tumors, as well as data from the literature.

It should be considered that vessels located in the dermis, immediately below the epidermis, appear well-focused and bright red, while those located deeper usually appear pink and unfocused. Different types of dermatoscopic vascular structures can be observed in melanocytic and non-melanocytic skin lesions

Fig. 3. Comma-shaped vessel structures

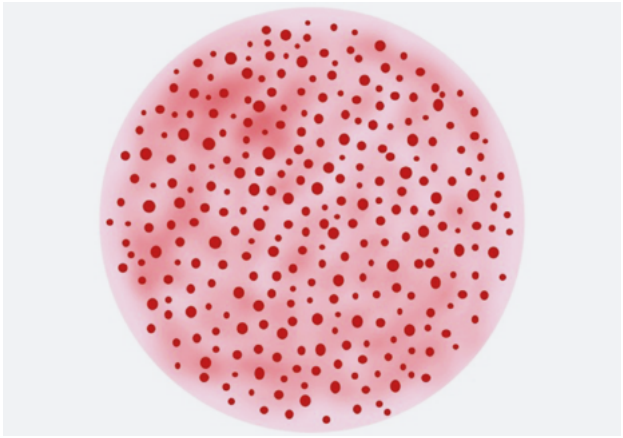


Fig. 5. Dot-shaped vessel structures

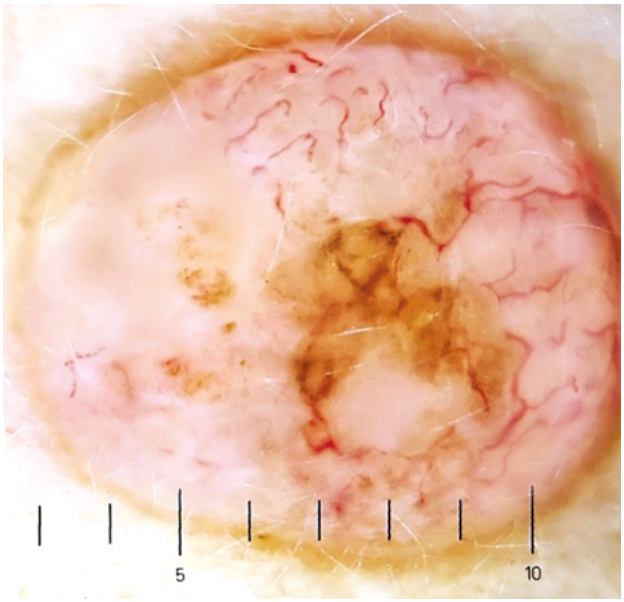


Fig. 4. Comma-shaped vessels in a dermal melanocytic nevus

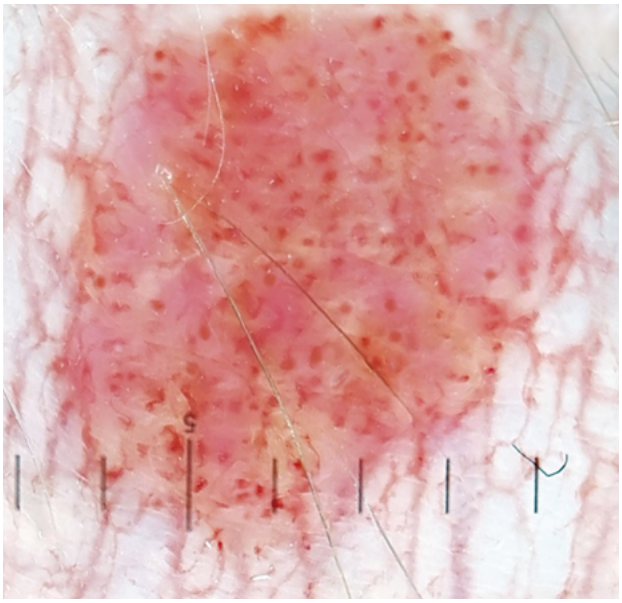


Fig.6. Dot-shaped vessels in the Spitz nevus

Results and discussion. The dermatoscopic vascular signs found in melanocytic and non-melanocytic skin tumors were investigated in this study.

Dermatoscopic vascular signs predominantly found in melanocytic skin tumors:

1. Comma-shaped vessels. A dermatoscopic sign that corresponds to the presence of small vessels resembling a comma or a small hook (Fig. 3). On dermatoscopy, they may appear out of focus due to their deep location in the dermis [6, 7]. In more than 90% of cases, this sign indicates that the tumor is a dermal or mixed melanocytic nevus (Fig. 4) [8]. Comma-shaped vessels may occur in dysplastic nevi. This feature is not typical for melanoma [6, 7, 10].

2. Dot-shaped vessels. Seen as red dots 0.01–0.02 mm in diameter (Fig. 5), they are typical for Spitz nevus (Fig. 6) and melanoma, but can occur in dysplastic and normal nevi, as well as in inflammatory lesions or in traumatized skin. In melanoma, spot vessels are often found in the center of the lesion and in combination with other vessels, as well as in thin melanomas [7, 8, 10, 11].

3. Pink veil (milky red globules). It appears as areas of white-pink (milky-red) coloring (Fig. 7), which is caused by accumulation of a large number of microscopic blood vessels in the tissue. The borders of these areas are most often not clearly expressed, milky-red staining may alternate with brown, gray and black pigmentation,

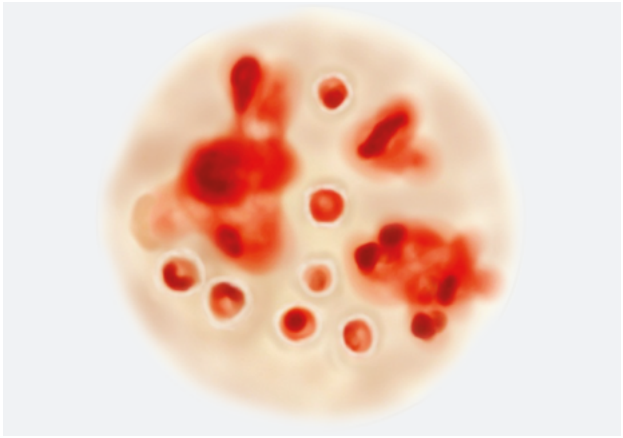


Fig. 7. Milky red globules

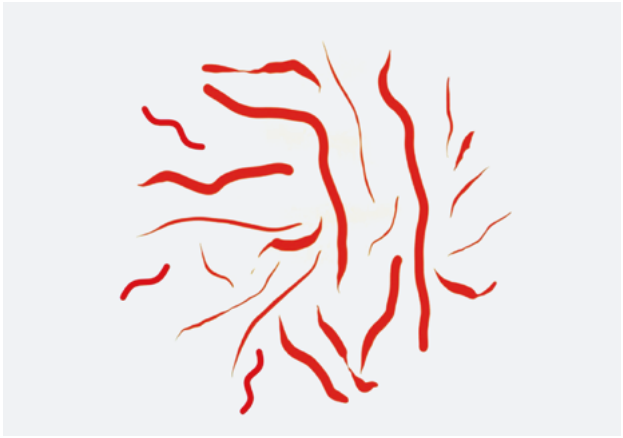


Fig. 9. Linearly twisted vessels

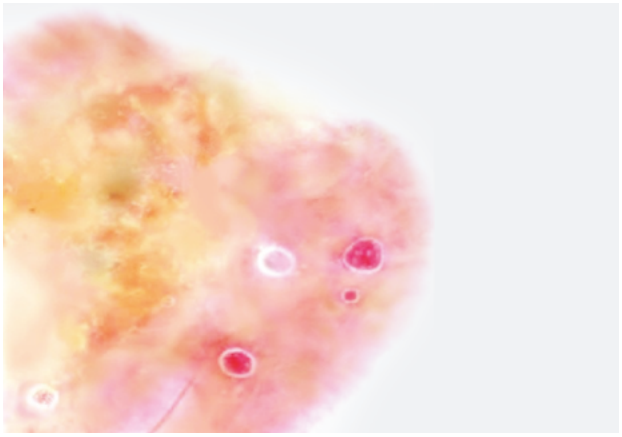


Fig.8. Milky red globules in melanoma

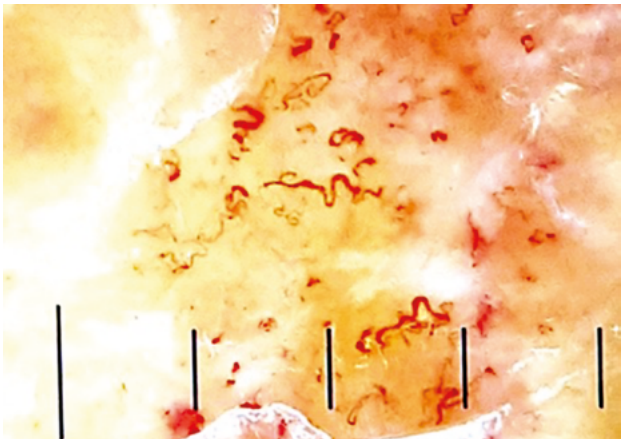


Fig. 10. Linearly twisted and corkscrew-like vessels in melanoma

often combined with vessels in the form of dots and discontinuous lines.

This symptom is typical for hypopigmented melanoma (Fig. 8) [2, 7]. Much less frequently, this sign may occur in benign nevi, dermatofibromas, and vascular tumors such as pyogenic granuloma.

4. Snake-like (linearly twisted) vessels. Irregular linear vessels can have different shapes and sizes (Fig. 9). They are found in melanoma (Fig. 10) [4], basalioma, and dysplastic nevus [2].

5. Corkscrew-like (tortuous) vessels (Fig. 11). Such vessels are observed in nodular and desmoplastic melanoma (Fig. 10) [4], as well as in melanoma metastases [2, 12].

Fig. 11. Corkscrew-like vessels

Fig. 12. Polymorphic vascular structures

Fig. 14. Hairpin-shaped vessels

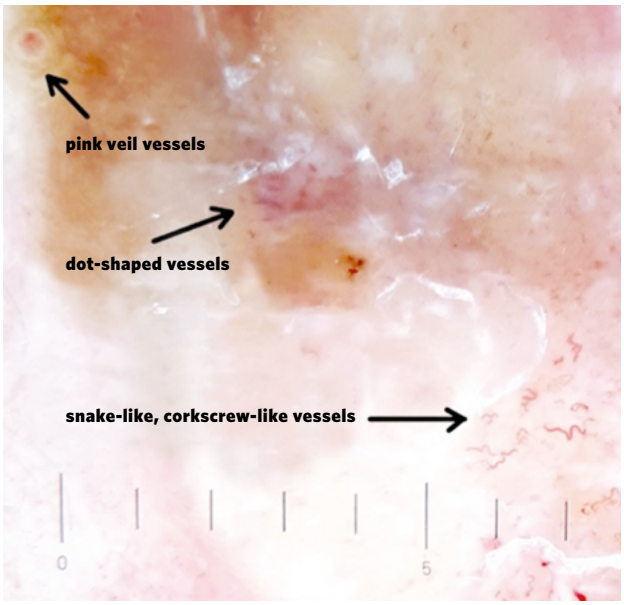


Fig. 13. Combination of snake-like, corkscrew-like, dot-shaped vessels and pink veil in melanoma

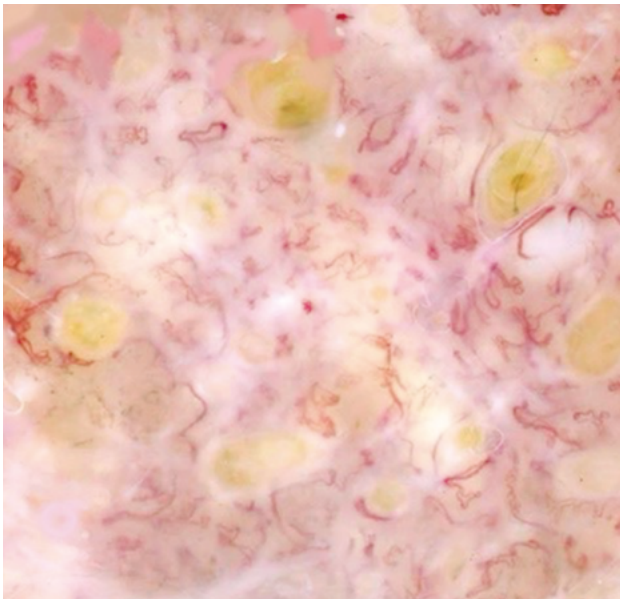


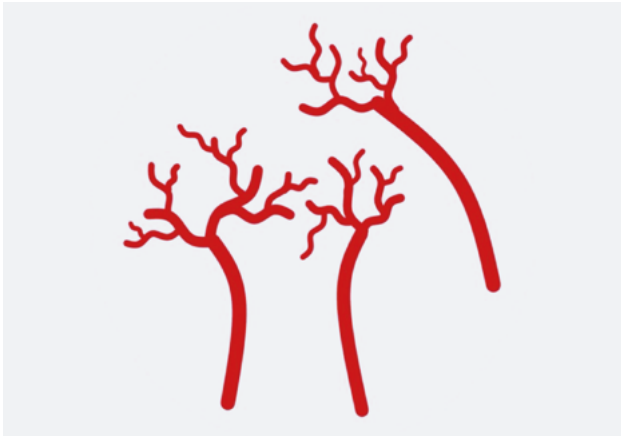
Fig. 15. Hairpin-shaped vessels in seborrheic keratosis

6. Polymorphic vessels. This is a feature in which two or more types of vessels are found (Fig. 12). It is more common in melanomas (Fig. 13) [4] and metastatic melanoma. Extremely rarely this sign is registered in papillomatous melanocytic nevi and eccrine tumors of skin appendages [13].

Dermatoscopic vascular signs predominantly found in non-melanocytic skin tumors:

1. Hairpin-shaped vessels (Fig. 14). They are typical for seborrheic keratosis if they are evenly distributed over the entire surface of the lesion (Fig. 15). In addition, in seborrheic keratoses, there is often a whitish halo around the vessels, a sign of keratinization. However, in the irritated form of seborrheic keratoses, hairpin-shaped vessels may be elongated, unequal in size, irregular in shape, twisted, which leads to the dermatoscopic picture of polymorphic vessels [6–8, 14]. Single hairpin-shaped vessels can be found in melanoma, acquired melanocytic nevi, basaliomas, Spitz nevus, and keratoacanthoma. In keratoacanthoma, hairpin-shaped vessels are located at the tumor periphery; in melanoma, these vessels are often surrounded by a pink halo [2].

2. Tree-like vessels. They are bright red vessels where a vessel of large diameter (from 0.2 mm) branches into smaller and thinner ones (Fig. 16), which is a specific feature of a basalioma (Fig. 17) [2, 6, 7]. Tree-like vessels can be detected in keratoacanthoma and in radiation atrophy of the skin (Fig. 18) [7].



Tree-like vessels can be detected in keratoacanthoma and in radiation atrophy of the skin. They are bright red vessels where a vessel of large diameter branches into smaller and thinner ones

Fig. 16. Tree-shaped vessels

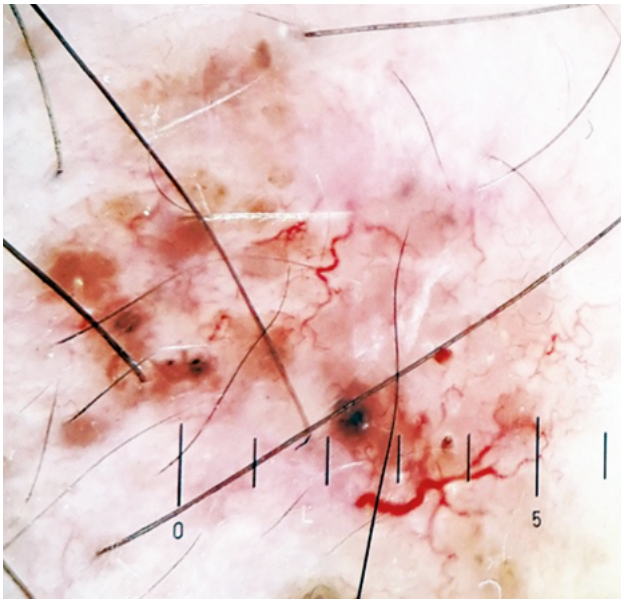


Fig. 17. Tree-like branching of vessels in a basalioma

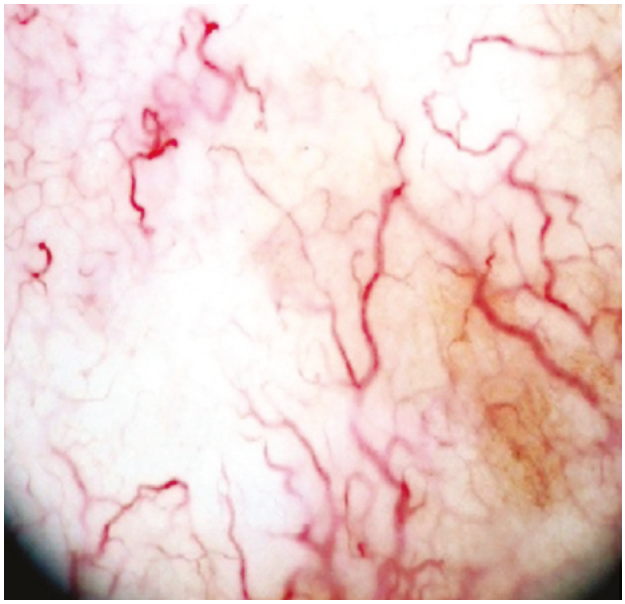


Fig. 18. Tree-shaped vessels in the focus of radiation atrophy

3. Vessels in the form of small glomeruli (glomerular vessels). These vessels are so named due to their morphology resembling the tortuous capillaries that make up the glomerular apparatus of the kidney (Fig. 19). These vessels are larger than dot-shaped vessels and may be located in clusters throughout the lesion. They are characteristic for Bowen's disease (Fig. 20) [2, 15], may occur in papules of red squamous lichen planus (SLP) and in other inflammatory skin diseases [7]. Much less frequently, these structures can be found in melanoma (more often in metastatic melanoma) [2].

Fig. 19. Glomerular vessels

Fig. 21. Crown vessels

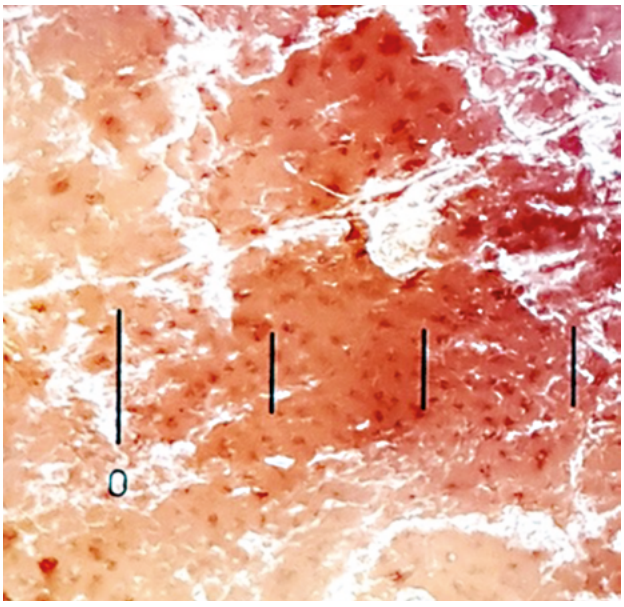


Fig. 20. Vessels in the form of small glomeruli in the focus of Bowen's disease

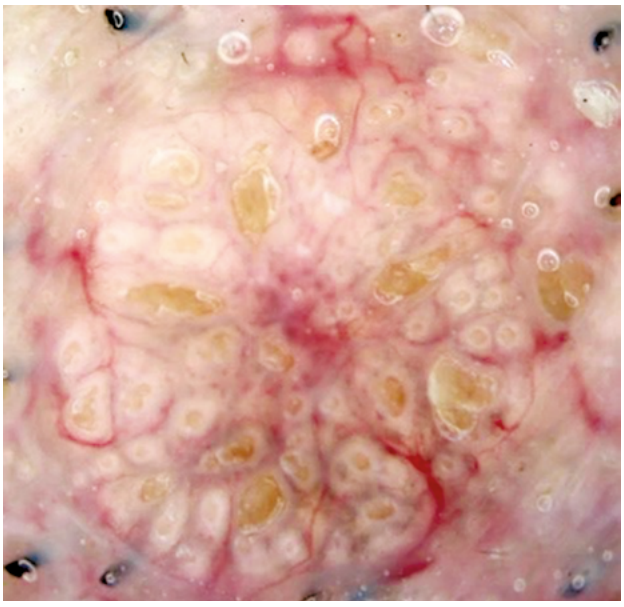


Fig. 22. Crown vessels in sebaceous hyperplasia

4. Crown vessels. These are homogeneously curved, thin tree-like vessels surrounding a yellowish-white central part (Fig. 21). They are usually found in sebaceous gland hyperplasia (Fig. 22), as well as in molluscum contagiosum [13]. On dermatoscopy, the crater-shaped sebaceous gland orifices are sometimes seen [16, 17].

5. String of pearls pattern. These dot-shaped or glomerular vessels are arranged in such a way that they resemble a string of pearls (Fig. 23). This structure is characteristic of a light-cell acanthoma (Fig. 24) [13, 18]. Also, these vessels can be found in psoriasis foci, SLP, chronic dermatitis, basaliomas and metastatic skin lesions [13].

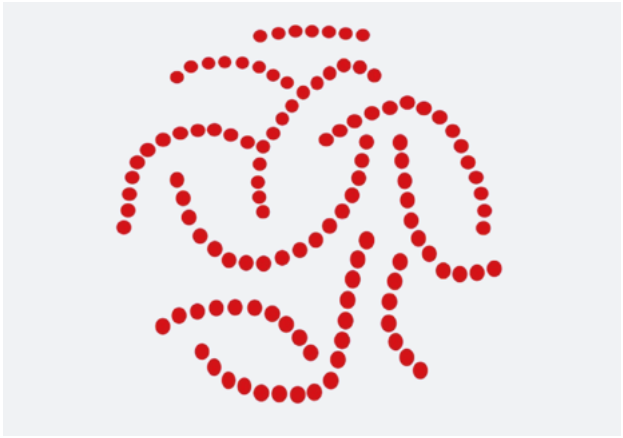


Fig. 23. String of pearls pattern

Fig. 25. Lacunar structure

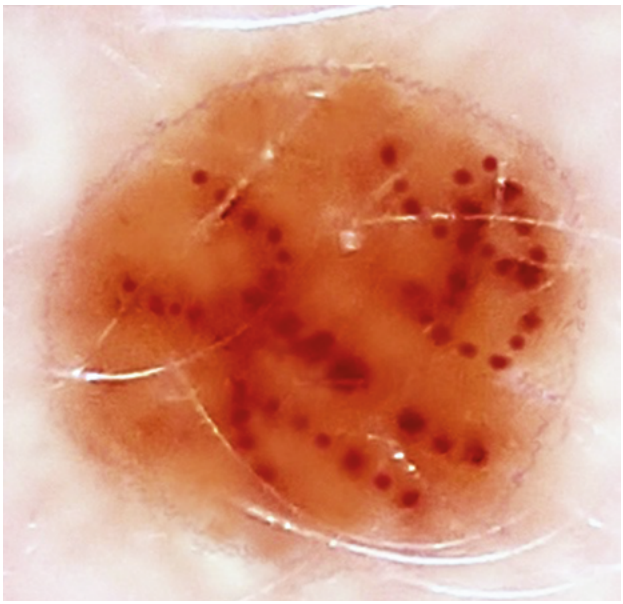


Fig. 24. Vessels in the form of a string of pearls in a light-cell acanthoma

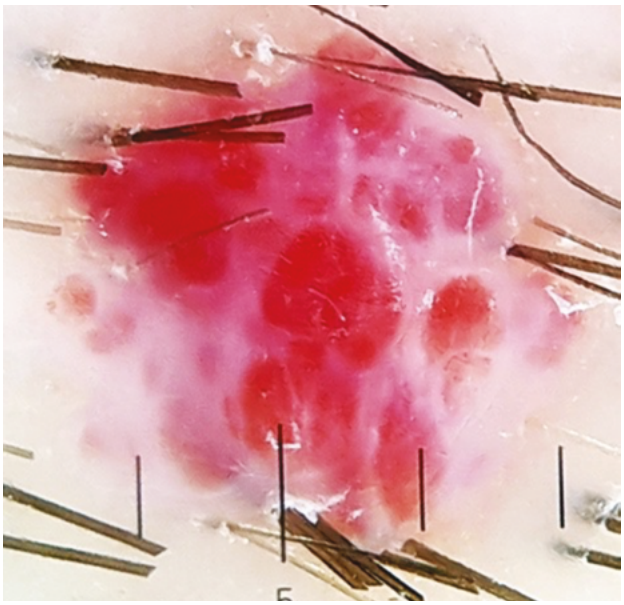


Fig. 26. Lacunar structure in cherry hemangioma

6. Vascular lacunae (Fig. 25). Vascular manifestations can completely form the dermatoscopic picture of tumors. This situation is most typical for hemangiomas and angiokeratomas. Specific feature of these benign neoplasms is vascular lacunae (Fig. 26) — they are of different size, clearly outlined, rounded or oval-shaped structures colored in red, burgundy or purple and blue. When hemangiomas are thrombosed, the vascular lacunae turn black [7, 9].

Using dermatoscopy, various vascular variants in skin neoplasms can be recognized and identified. This enables timely and more accurate diagnosis of various melanocytic and non-melanocytic skin tumors as well as differential diagnosis between benign and malignant neoplasms.
In melanocytic skin tumors, the following dermatoscopic vascular features are predominantly found: comma-shaped vessels, dot-shaped vessels, pink veils (milky red globules), senake-like (linearly twisted) vessels, corkscrew-like (tortuous) vessels, polymorphic vessels.
The following dermatoscopic vascular features are predominantly found in non-melanocytic skin tumors: hairpin-shaped vessels, small glomeruli (glomerular vessels), crown vessels, string of pearls pattern, vascular lacunas, tree-shaped vessels

Conclusions. Using dermatoscopy, various vascular variants in skin neoplasms can be recognized and identified. This enables timely and more accurate diagnosis of various melanocytic and non-melanocytic skin tumors as well as differential diagnosis between benign and malignant neoplasms.

In melanocytic skin tumors, the following dermatoscopic vascular features are predominantly found: comma-shaped vessels, dot-shaped vessels, pink veils (milky red globules), senake-like (linearly twisted) vessels, corkscrew-like (tortuous) vessels, polymorphic vessels.

The following dermatoscopic vascular features are predominantly found in non-melanocytic skin tumors: hairpin-shaped vessels, small glomeruli (glomerular vessels), crown vessels, string of pearls pattern, vascular lacunas, tree-shaped vessels.

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Information about the authors:

Igor A. Lamotkin — MD, DSc, professor, Head of the Skin and Venereology Department, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry; professor of the Department of skin and venereal diseases with the course of cosmetology, Medical Institute of Continuing Education, Russian Biotechnological University, Moscow, Russia — **responsible for contacts**, **ilamotkin@mail.ru**, ORCID: 0000-0001-7707-441X; ResearcherID: AAQ-4769-2021, eLibrary SPIN: 7153-3703

Daniil I. Korabelnikov — MD, PhD, Head of the department of preventive medicine, professor of the department of internal diseases, rector of Moscow Haass Medical and Social Institute, Moscow, Russia.

Elena G. Perevalova — MD, PhD, doctor of the highest qualification category, founder of the MDElena Dermatology and Cosmetology Clinic, Moscow, Russia.

Andrey I. Lamotkin — Specialist of departments of information and analytical, research and expert work of the Moscow Haass Medical and Social Institute, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored. Received 29.11.2023.

Sequential external osteosynthesis of gunshot fractures of limb bones at the stages of medical evacuation

UDK 616.71-001.5-089.227.84
DOI: 10.53652/2782-1730-2023-4-1-22-31

Artemev A.A.[1], Kerimov A.A.[1], Perekhodov S.N.[2], Grigoriev M.A.[3], Nelin M.N.[1], Torshina S.V.[1]

[1] Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia
[2] FSBEI HE A.I. Yevdokimov MSMSU MOH Russia, Moscow, Russia
[3] City Clinical Hospital No. 13 of the Moscow Healthcare Department, Moscow, Russia

Abstract. Staged treatment of the patients with gunshot fractures of long bones implies a differentiated approach to the choice of different methods and means of extremity immobilization taking into account their peculiarities and functional capabilities. The frequency of different types of osteosynthesis in specialized care of 212 wounded patients with 276 gunshot fractures of long bones who were immobilized with external fixation devices (EFD) at the stage of advanced care was analyzed. It was revealed that when performing sequential osteosynthesis, preference for internal constructions was given — 122 (44.2%) observations. External osteosynthesis with Ilizarov apparatus (IA) was second most frequently used — 87 (31.5%). EFD was used as the definitive method of treatment in 67 (24.3%) cases. We studied and compared the constructive and functional capabilities of EFD and IA.
The main advantage of the Ilizarov apparatus is the ability to control the position of the fragments and influence the process of regeneration by creating compression and distraction forces. The advantage of the EFD is the simplicity of use and, accordingly, the possibility of rapid fixation of the limb in resource-poor conditions with the simultaneous admission of a considerable number of wounded patients. Application of IA implies complex reconstructive interventions with prolonged subsequent treatment and rehabilitation. It should be taken into account when organizing staged treatment and use the type of osteosynthesis that corresponds to a particular stage. When providing qualified care, the use of EFD is absolutely indicated; when performing complex reconstructive operations of specialized trauma care, it is advisable to use the capabilities of the Ilizarov method.

Keywords: Ilizavov apparatus, gunshot fracture, war surgery, acute shortening.

Introduction. In modern battlefield surgery (BS) external osteosynthesis (EO) is one of the most effective methods of treatment of gunshot fractures of limb bones. Immobilization with devices of different designs ensures rest of the injured limb, reduces pain afferentation, provides gentle transportation of the injured, diagnostic procedures and therapeutic measures. The distinctive features of EO are: low traumatism, no need for additional manipulations in the fracture area, access to the injured tissues [3, 6, 7, 9, 10].

Owing to the research of G.A. Ilizarov and his followers, Russian traumatology has accumulated a huge experience in the use of EO, the basis of which was the Ilizarov compression-distraction spoke apparatus (IA). However, the diversity of various designs of modern external and internal fixators, new technologies of their manufacture and application have greatly changed the doctors' attitude towards the Ilizarov method.

The last three decades were characterized by the introduction into clinical practice of external fixation devices (EFD) as a means for both final (CITO device) and temporary immobilization (combined trauma kit — CTK), which replaced the plaster cast and skeletal traction [4]. For some time, this method of fixation was considered as an element in the system of damage control in the treatment of patients with polytrauma. Immobilization of limb bone fractures with EFD ensured early activation of patients and facilitated diagnostic and therapeutic procedures.

In the treatment of isolated open fractures, EFD osteosynthesis is used as the first step to create favorable conditions for wound healing and subsequent internal osteosynthesis [8]. Such therapeutic tactics gradually led to the replacement of classical IA and, to a large extent, to the loss of skills in its application. The main feature — external load-bearing construction — contributed to the fact that the modern generation of traumatologists perceives EFD and IA as identical in their functional capabilities, with the only difference being that AI is bulkier and more inconvenient. However, the EFD and IA should occupy completely different positions in the trauma care system.

That is especially evident in emergency situations, when there is a need to introduce a system of staged treatment of the wounded and injured. The difficulties of the first months of a special military operation (SMO) made us recall the experience accumulated by military surgeons in Afghanistan (1979–1989), when the principles of EO in the treatment of wounded limbs were developed and IA was introduced into the wide clinical practice of military traumatologists [1, 2]. The principles of external fixation techniques for gunshot fractures in the modern sense were developed later in the Russian BS on the base of the experience of medical provision for anti-terrorist operation in the North Caucasus [4].

Currently, the medical service of the Russian Armed Forces is sufficiently provided with both EFD and IA. However, the lack of experience in their application in the real situation of SMO causes some difficulties in determining the indications for this or that type of EO, in assessing the sequence and volume of reconstructive interventions. The presented work is aimed at overcoming these difficulties.

Objective. Evaluation of possibilities and determination of indications for the use of different variants of EO in the system of staged treatment of the wounded and injured under the conditions of SMO.

Material and methods. The work is based on the analysis of the treatment experience of 212 wounded with gunshot fractures (276) of long limb bones, fixed by EFD at the frontline stages of medical evacuation.

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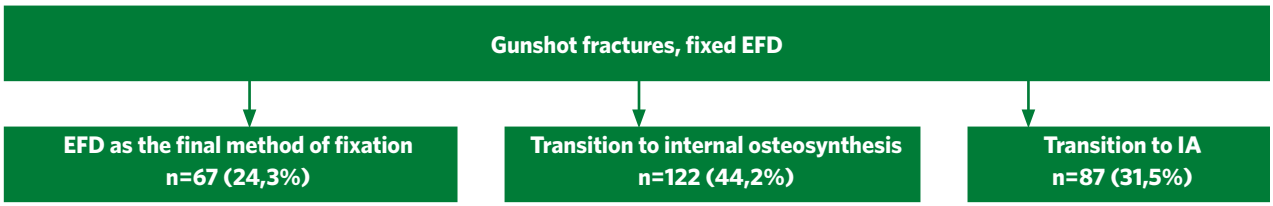


Fig. 1. Distribution of the patients according to the type of osteosynthesis

Depending on further treatment tactics, they were distributed as follows (Fig. 1).

The data presented in Fig. 1 demonstrate the structure of different types of final fixation of gunshot fractures at the stage of specialized medical care (SMC) after therapeutic transport immobilization with EFD performed at the previous stages. Transition to internal osteosynthesis in 122 (44.2%) cases reflects the established practice of treatment of gunshot fractures aimed at possible early and comfortable activation of the wounded [7-9]. This group of patients is of undoubted interest, but its analysis was not included in this study.

Thus, 125 wounded patients with 154 gunshot fractures of the long bones of the limbs were selected from the total group and became the object of study and analysis. All the wounded were men aged 18 to 51 years (mean age 29.2+8.1 years). The wounds were distributed by segments as follows: shoulder — 17 (11.0%), forearm — 23 (14.9%), thigh — 46 (29.9%), shin — 68 (44.2%).

In spite of the considerable number of observations, this article does not present such indicators of interest as the time of healing, the number of complications, etc. The final analysis will likely require several years of thorough research work. At present, the first practical experience in the use of well-known osteosynthesis constructions in such an unfamiliar area of surgery for many doctors as military traumatology is no less valuable.

Results. One of the first EFDs introduced into widespread practice in the care of the wounded was the rod device from "combined trauma kit (CTK-1)". Later, beginning in 2017, it was replaced by the rod device from the "military-type rod kit (MTRK)". The latter is currently included in the equipment of military medical institutions (MMI) and is used most frequently [4, 5].

A distinctive feature of MTRK for large segments is that the connecting rods are made of lightweight x-ray-transparent material. The CTK-1 and MTRK are primarily used in the MMI, while other, similar devices are widely used in civilian treatment facilities. The universal multifunctional fixation knots (clamps) of the MTRK ensure its compatibility with other types of EFD. By the type of devices in the observation (154 in total, 100%) were distributed as follows: MTRK — 106 (68.8%), CTK-1 — 23 (14.9%), hybrid based on MTRK — 13 (8.4%), other models — 12 (7.8%).

The MTRK is the most advanced in its functionality. Among its advantages are the low weight of the construction, ease of assembly, the use of self-drilling self-tapping rods [5]. With the help of universal clamps, you can easily form hybrid structures consisting of parts of other models. The most convenient options for fixation of Schanz rods in IA are shown in Fig. 2.

When changing from one type of external fixator to another, you can use the previously installed threaded rods as shown in Figure 2. However, in some circumstances this should not be done. When Schanz rods are arranged in different planes, attempts to attach them to the IA rings by using multiple brackets will make the structure heavier and significantly increase the duration of surgery. With osteolysis around Schanz rods, the stability of fixation decreases, which is detected after removal of the external device. In such cases, these rods should be removed during the insertion of the IA and replaced with standard screw rods.

The experience with external fixators replacement allowed us to develop a method that seems useful and rational. In order to reduce the surgery time and in cases of satisfactory positioning of the bone fragments in the EFD, the EFD rods and clamps can be gradually removed prior to surgery (in the ward), replacing them with external IA nodes in the same time (Fig. 3).

In Figure 3, replacement of the EFD with an IA in the ward prior to surgery took approximately 1.5 hours, which reduced the duration of the surgery itself by the same amount of time. The goal of the surgery was to provide compression in the arthrodesis area and to increase the stability of the structure. The previously installed EFD did not provide compression and was not stable enough for the patient to fully step on his leg.

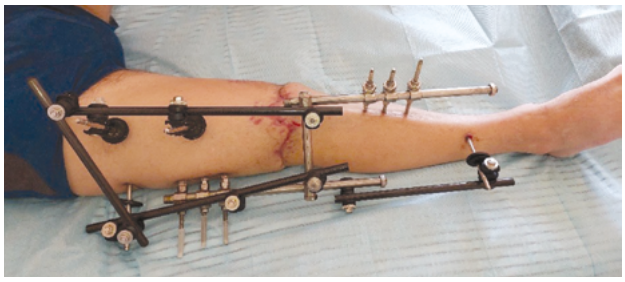
Experience with the use of EO devices made it possible to determine their capabilities and compare them according to the most important indices, which are shown in Table 1. The MTRK was taken as the baseline EFD as the most functional and frequently used one.

It is appropriate to comment on the data given in the table.

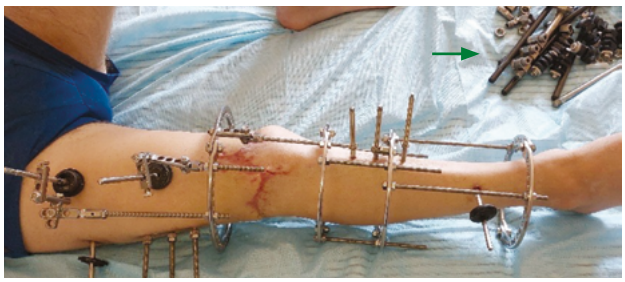
A

B

Fig. 2. Methods of fixation of Schanz rods from MTRK to the IA ring: A — with a rod fixator (angle clamp) from IA for rods of 5 and 6 mm diameter; B — using brackets with holes from IA for rods of any diameter



A



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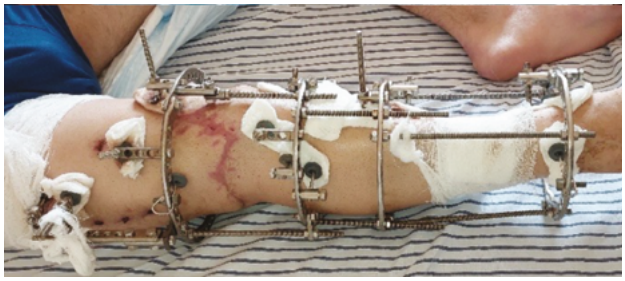

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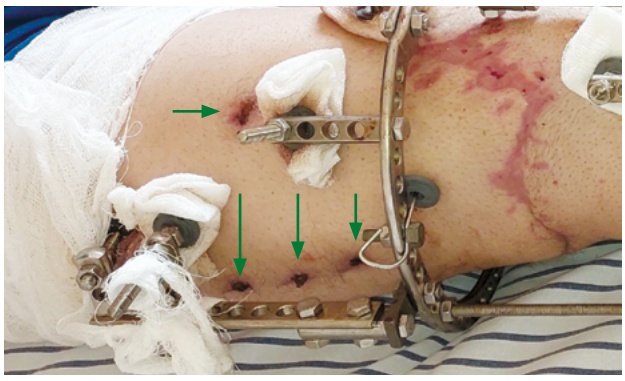


D

Fig. 3. Appearance of the limb of a wounded after resection of the knee joint due to a gunshot wound (3 months ago) and failed arthrodesis: A — limb fixed with hybrid EFD; B — disassembly in the ward before surgery of hybrid EFD with gradual replacement of its parts with IA parts and their attachment to Schanz rods (arrow shows parts of the removed rod apparatus); C — appearance of the same IA after surgery, which was to replace Schanz rods with IA screw rods; D — close-up at hip level (arrows show wounds in places of extracted Schanz rods).

The stability of the fixation is determined by the construction of the devices. The closed contour of the IA ring provides greater stability compared to the EFD frame. Threaded bars and manipulation with transosseous elements allow the degree of stability to vary depending on the phase of fracture healing. Therefore, when providing reduced specialized care, the task of the trauma surgeon is to ensure maximum stable fixation of the fracture while minimizing the use of time and EFD parts for safe patient evacuation. This requirement is fully met by the MTRK.

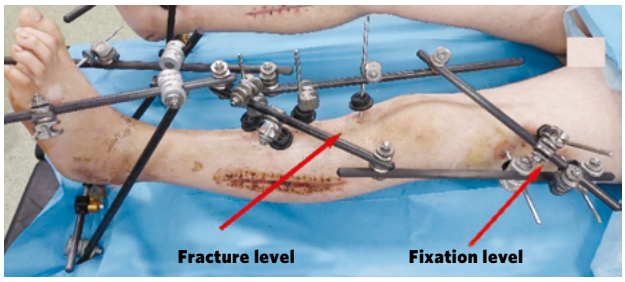
Preservation of motion in the adjacent joints. In periarticular fractures, adequate fixation of the MTRK requires blocking the joint with the same structure to fix the injured segment and the adjacent segment. Stability cannot be achieved in any other way. Prolonged immobilization of the joint during EFD treatment (sometimes over a period of several months) with the periarticular nature of the fracture can lead to the development of permanent contractures. IA allows mobilization of the joint without compromising the stability of the fixation, even if the fracture line is close to the joint (1.5–2 cm), by inserting 3–4 crossed spokes (Fig. 4).

Ensuring supportability in lower limb wounds directly depends on stability. IA for fractures allows walking with a full load in the early postoperative period. In the case of fixation of isolated hip fractures with MTRK, the wounded usually use crutches, limiting the load.

The patient's quality of life with any external fixator is rather low. However, at the initial stage, this aspect of the treatment process plays a minimal role. However, it becomes more important later on if further external fixation is necessary. IA has a higher value due to its ability to provide motion in adjacent joints, limb loading, and smaller size.

Since modern rod-type EFDs are designed for short-term fixation of fractures, their construction does not provide for dynamic control of the fragment location for the purpose of precise repositioning. If there are indications for continuation of treatment with an external apparatus, it is advisable to perform IA reosteosynthesis. If one-stage reposition is not possible, which is often the case with old displaced fractures, it is possible to achieve a perfect closed reposition in the postoperative period by manipulating spokes with thrust pads, screw rods, or external supports.

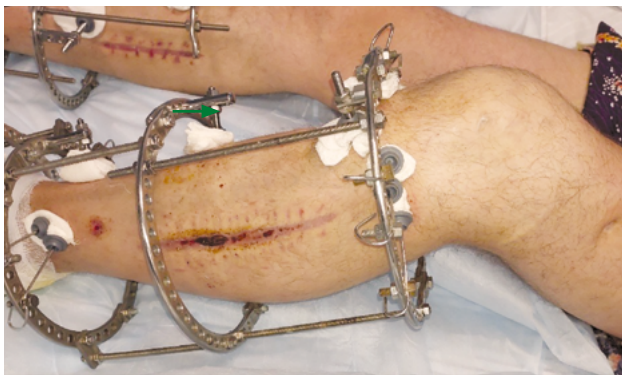
The management of the regeneration process by creating compression-distraction forces is one of the main options of IA. It is closely related to the previous one, the option of management of fragment position. The only thing worth adding is that, besides a given direction, certain, sometimes significant compression or distraction forces need to be applied. EFDs only provide fixation in a neutral position (Fig. 5).



A

B

C

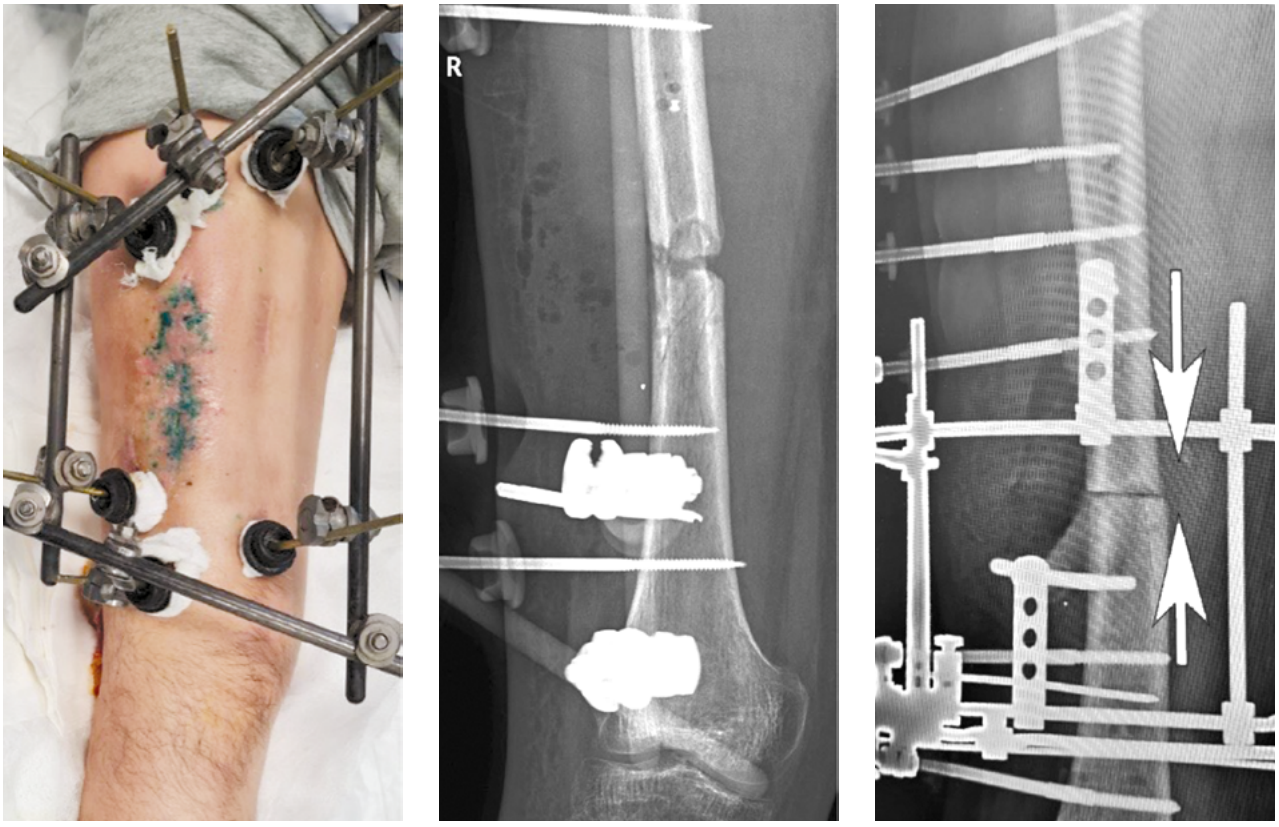


D

Fig. 4. Appearance and radiographs of a limb of a wounded person with a fracture in the upper third of the tibia: A, B — in the MTRK device, the knee joint is blocked; C, D — in IA device, movement in the knee joint is possible

Table1. Technical parameters and application of the MTRK and IA apparatuses

Main parameters	MTRK	IA
Stage of care	Qualified (reduced specialized) surgical care	Specialized care
Main purpose	Temporary therapeutic transport immobilization	Definitive method of fixation of the most severe fractures, reconstructive and restorative treatment
Main functional indicators*		
Static fixation stability	++++	++++
Ability to control the stability of the fixation	-	++++
Preservation of motion in adjacent joints	+	+++
Ensuring the supportability	++	++++
Quality of life	+	++
Fragment position management	-	++++
Management of regeneration processes	-	++++
Wound access	++++	++++
*Marked with "–" and "+" signs, where: "–" — no option; "+" — minimum feasibility; "++" — limited feasibility; "+++" — medium feasibility; "++++" — high feasibility		



A B C

Fig. 5. Wounded man with a gunshot fracture in the middle third of the femur. Appearance and radiographs 6 months after injury: A — appearance of the limb fixed with a MTRK; B — radiograph of the femur, there is an unrecoverable diastasis of 7 mm between the fractures, which excludes consolidation; C — radiograph of the hip fixed with IA after resection of the fracture edges and creation of axial compression

Access to soft tissue wounds for surgical treatment or vacuum dressing is equally convenient with almost all types of external fixators.

Discussion. Given the significant functional differences between IA and EFD, it should be kept in mind that these types of devices have different purposes. EFD is designed to provide emergency care in conditions of resource shortage — time, equipment, experience. The last factor is important, since in the case of mass influx of injured people, doctors of related surgical specialties are involved in providing traumatological care.

The simplicity of the use of various EFDs, in particular MTRK, provides an adequate amount of qualified (reduced specialized) care. However, it should be understood that simplicity has certain limits and requires knowledge of anatomy, general surgical experience, and certain skills. A manual on external fixation for orthopedic traumatologists can be recommended as a methodological aid [5].

The speed of EFD application, which is noted as an advantage of the method, is determined by the simplicity of the construction. In a real combat situation on the front lines, the time factor is of fundamental importance, and rod structures are quite reasonably the method of choice.

Despite the fact that the external fixation rod device can be used as a therapeutic immobilization for fractures in some cases [5], the functional indicators presented in Table 1 make it in favor of the limited use of EFD as the definitive type of osteosynthesis.

The presented 67 (24.3%) cases of MTRK use reflect the therapeutic approach typical for the initial period of SMO with relatively large admission of the wounded and the need to avoid additional complex interventions in the acute period. Currently, there is a tendency to decrease the proportion of this type of osteosynthesis in the overall structure of specialized surgical care.

It is reasonable to use the type of fixation that corresponds to the patient's condition and the place of medical care in order to reduce the number of intermediate interventions. When providing skilled (reduced specialized) care, a rod-type EFD should be used in a layout that ensures safe evacuation. Further, if there are indications for continuation of external fixation, conversion to IA should be performed.

Gunshot wounds are often accompanied by the development of local infectious processes, including bone lesions at a significant distance from the wound channel. The most effective method of treatment of such conditions is resection of fragment ends. In this case extended defects of long bones are formed. The above-mentioned functional capabilities of IA allow performing directed traction of bone fragments for defect replacement in polylocal osteosynthesis and providing compression of fragments in acute shortening.

The constructive features of modern external fixators, which in one or another modification are used in the treatment of the wounded with gunshot fractures of the extremities, have significant differences that affect their functional capabilities. Rod apparatuses, being as stable as fixation, have less functional capabilities compared to apparatuses with a closed circular contour At the same time, EFDs are easier to use and, accordingly, require significantly less time for their application. The use of IA implies complex reconstructive interventions with prolonged follow-up treatment and rehabilitation. This should be taken into account when organizing staged treatment and use the type of osteosynthesis that corresponds to a particular stage. When providing qualified care, the use of EFD is absolutely indicated; when performing complex reconstructive operations of specialized trauma care, it is advisable to use the capabilities of the Ilizarov method

Considering the possibility of wider implementation of the Ilizarov method in the care of the wounded, it is necessary to take into account the challenges encountered: the duration of fracture healing, the need for multistage and sequential reconstructive-restorative treatment, the shortage of specialists. Overcoming these difficulties is a promising task aimed at optimizing the provision of specialized trauma care for the wounded.

Conclusion. The constructive features of modern external fixators, which in one or another modification are used in the treatment of the wounded with gunshot fractures of the extremities, have significant differences that affect their functional capabilities. Rod apparatuses (CTK-1, MTRK, etc.), being as stable as fixation, have less functional capabilities compared to apparatuses with a closed circular contour (Ilizarov type). At the same time, EFDs are easier to use and, accordingly, require significantly less time for their application. The use of IA implies complex reconstructive interventions with prolonged follow-up treatment and rehabilitation. This should be taken into account when organizing staged treatment and use the type of osteosynthesis that corresponds to a particular stage. When providing qualified care, the use of EFD is absolutely indicated; when performing complex reconstructive operations of specialized trauma care, it is advisable to use the capabilities of the Ilizarov method.

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Information about the authors:

Aleksandr A. Artemev — MD, ScD, orthopedic traumatologist at Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts**, **alex_artemiev@mail.ru**, eLibrary SPIN: 3124-2701; ORCID: 0000-0002-0977-805X

Artur A. Kerimov — MD, PhD, orthopedic traumatologist, Head of the Center of traumatology and orthopedics, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Sergej N. Perehodov — MD, ScD, professor, corresponding member of the Russian Academy of Sciences, Head of the Hospital Surgery Department of the Medical Faculty of FSBEI HE A.I. Yevdokimov MSMSU MOH Russia, Moscow, Russia.

Maksim A. Grigoriev — MD, PhD, orthopedic traumatologist, Head of trauma department at City Clinical Hospital No. 13 of the Moscow Healthcare Department, Moscow, Russia.

Maksim N. Nelin — MD, orthopedic traumatologist at Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Svetlana V. Torshina — clinical resident at Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 22.02.2023

Features of examination of patients with kidney and ureter injuries

UDK 616-71/61-003.215
DOI: 10.53652/2782-1730-2023-4-32-38

Egorova E.A.[1], Magomedova Z.M.[2]

[1] *Federal State Budgetary Educational Institution of Higher Education "A.I. Yevdokimov Moscow State University of Medicine and Dentistry" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia*

[2] *FSBI «Clinical Hospital №1» Administrative office of the President of the RF, Moscow, Russia*

Abstract. The aim of the study was to assess the capabilities of magnetic resonance imaging (MRI) in the diagnosis of complications in patients with combined kidney and ureteral injuries during different periods of traumatic disease. The observation group included 139 patients aged from 18 to 72 years with renal and ureteral injuries, who were injured in traffic accidents. Complications of renal trauma occurred in 74 of 128 patients with isolated and combined injuries (59.2%), strictures were observed in 9 of 11 patients with ureteral trauma in the late period, and 1 of them had a failure of vesicoureteral anastomosis. The most common complication in the early and late periods of traumatic disease, occurring in 25.0% of cases, was pyelonephritis; patients with abscesses (12.5%) and acute renal failure (11.7%) were also common. The methods of choice for the diagnosis of combined injuries in the acute period were: ultrasound examinations according to the eFAST protocol and multislice computed tomography according to the "Polytrauma" protocol. Multiparametric magnetic resonance imaging (mpMRI) of the kidneys and ureters was indicated in the periods of early and late manifestations of traumatic disease to detect renal complications when there is a discrepancy between clinical data, ultrasound and multislice computed tomography (MSCT) findings, and there are contraindications for MSCT with intravenous contrast.

Keywords: magnetic resonance imaging, multislice computed tomography, kidney, ureter, traumatic, traumatic disease.

Introduction. According to the literature, individuals who received combined injuries as a result of road traffic accidents (RTAs) have renal and ureteral injuries in more than 80.0% of cases [5].

Difficulties of early diagnosis of this type of injuries and determination of the necessary volume of emergency care are the subject of study and discussion in practical medicine [2, 3].

The sequence and volume of therapeutic and diagnostic procedures depend on the nature of the injury and the consequences or complications occurring at different time intervals, which have their own features in different periods of traumatic disease (TD) [1].

The periods of TD are defined by the time elapsed since the injury:

- period of acute reaction of the body — up to 2 days;
- period of early manifestations — within 12–14 days;
- period of late manifestations — from 2 weeks to 2 months;
- rehabilitation period — more than 2 months, the duration depends on the severity and localization of injuries, the severity and nature of complications.

Objective. To assess the capabilities of MRI in the diagnosis of complications in patients with combined kidney and ureteric injuries during different periods of TD.

Material and methods. The results of clinical and radiological examination of 139 patients with combined and isolated kidney and ureteric traumas (Table 1) aged from 18 to 72 years old were analyzed.

The data in the table indicate that renal and ureteral injuries differed in their combination because of their location and relationship with surrounding structures (abdominal and retroperitoneal organs, ribs, spine, pelvic bones).

General clinical and biochemical blood tests were performed on all patients with suspected renal and ureteral trauma. Attention was paid to the total number of erythrocytes and leukocytes, hemoglobin and hematocrit levels, increased erythrocyte sedimentation rate (ESR), for biochemical analysis the levels of total protein, urea, creatinine. In general urine analysis the color and total amount of urine, the presence of signs of leukocyte and hematuria were taken into account.

Then an ultrasound examination (ultrasound) was performed according to the eFAST (extended Focused Assessment with Sonography for Trauma) protocol to detect peritoneal and pericardial fluid, pneumothorax and/or hemothorax [4]. When a patient was admitted in the acute period after trauma, preference was given to MSCT according to the «Polytrauma» protocol [6].

The scanning area included native scanning of the skull, brain and cervical spine with capturing of the upper thoracic region (up to ThIV level). Then, in order to reliably determine the condition of parenchymatous organs and vessels, the thoracic and abdominal cavities were examined with intravenous contrast enhancement (CE) (from the tops of the lungs to the ischial tuberosities), with postcontrast images in arterial, venous and delayed phases. In addition, a split-bolus technique was used in 85 (61.2%) cases, in which a dose of contrast agent (CA) (100–120 ml) was divided into portions, injected intravenously at a rate of up to 4 ml/s. The first portion of CA was 65–80 ml, followed by 50 ml of physiological NaCl solution. A pause of 10–15 s was made, after which the second portion of the CA bolus was administered in the volume of 35–40 ml and then 30–40 ml of physiological NaCl solution. Post-contrast scanning of the abdominal and thoracic cavities was performed 60 s after the first administration of CA. With this technique of contrasting, a clear image of the main vessels (arterial phase of contrasting) and parenchymatous organs is obtained simultaneously, i.e., a single post-contrast scan is performed, thereby reducing by half the radiation dose.

Contraindications for MSCT-study with intravenous contrasting were: impaired renal function with glomerular filtration rate (GFR) less than 30 ml/min, history of allergic reactions to iodine-containing drugs, polyvalent drug and food allergies, pregnancy, unstable hemodynamic parameters and ongoing massive bleeding (internal or external) [3].

Indications for mpMRI: ambiguous ultrasound results requiring clarification and impossibility to perform MSCT with intravenous CE.

However, in patients with combined trauma, MRI was possible using an optimally short protocol, which included pulse sequences with fat signal suppression - coronary T2 STIR (scan area — from diaphragmatic cupolas to ischial tuberosities). After detection of MR signal areas corresponding to renal parenchyma lesions, hematomas, infiltrative-liquid changes in the adipose tissue of the abdominal cavity and retroperitoneal space, was complemented by obtaining T1-, T2-WI in the area of interest in 3 planes, diffusion-weighted images (DWI) with construction of measured diffusion coefficient (MDC) maps.

Duration of the study using this MR protocol reached 15–20 min, which is comparable to the time spent on MSCT studies with intravenous contrast (including time spent on peripheral vein puncture and catheterization, preparation of the injector, native and post-contrast scans).

The severity of renal damage can be established reliably only on the basis of the above-mentioned radiological examinations, which were performed in various combinations in all the victims.

The severity of renal injury was determined according to the AAST (American Association for Surgery and Trauma) classification:

Grade I — contusion or non-growing subcapsular hematoma, trauma without rupture;

Table 1. Characteristics of upper urinary tract (kidneys and ureters) injuries in the examined patients (n=139)

Types of injuries	Number	
	abs.	%
Combined kidney injuries	125	89,9
Acute ureteric injuries	11	7,9
Isolated kidney damage	3	2,2
TOTAL	139	100,0

Table 2. Combined injuries detected in patients with renal and ureteric trauma (n=139)

Types of injuries	Number	
	abs.	%
Isolated kidney injury	3	2,4
Combined injuries of kidneys and ureters, of which:	136	97,6
– acute ureteric injuries	11	8,1
– rib fractures, bruises, and lung lacerations	42	30,9
– traumatic brain injury	30	22,1
– bones of the limbs	24	17,6
– abdominal organs	17	12,5
– spinal cord injury	12	8,8

Grade II — small peri-renal hematoma, cortical tear <1 cm deep, no urinary extravasation;

Grade III — cortical tear >1 cm deep, no urinary extravasation;

Grade IV — rupture through the corticomedullary junction into the collecting system or vessel damage, segmental artery damage, vein damage with hematoma formation, partial vessel wall damage or vessel thrombosis;

Grade V — multiple tears of the kidney, damage to the renal pedicle vessels, or detachment of the kidney from the vessels.

Excretory urography (EU) was not used in the acute period of trauma; it was performed mainly to determine the adequacy of drainage and stent placement.

Results and discussion. When examining the patients in the study group, it was found that most of the patients were those with I and II grade of kidney damage (Fig. 1).

It was noted that combinations of kidney and ureter injuries with craniocerebral and thoracic injuries were the most frequent (Fig. 2, Table 2).

According to the results of the complex examination, we found that complications of renal trauma occurred in 74 (59.2%) out of 128 patients with isolated and combined injuries; strictures were observed in 9 out of 11 patients with ureteral trauma in the late period, and 1 of them had a failure of vesicoureteral anastomosis.

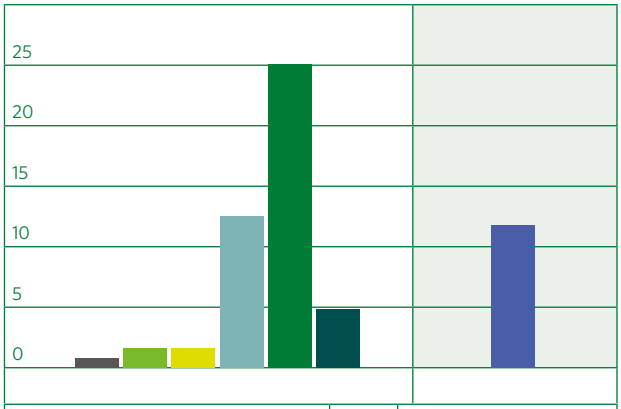
Figure 2 demonstrates that the most common complications in the early and late periods of TD were pyelonephritis (25%), renal abscesses (12.5%), and acute renal failure (ARF) (11.7%).

The greatest difficulty was represented by renal trauma in the acute and early periods of TD, which manifested as an erased clinical picture against the background of shock. Reliable characteristics of the suffered renal trauma were determined by the results of MSCT, which allowed us to determine the severity of the injury (Fig. 3).

When the ultrasound and MSCT data were ambiguous and did not correspond to the clinical and laboratory indicators, we performed mpMRI, which had a high potential in the diagnosis of renal and urinary tract injuries during different periods of TD and allowed obtaining images of the urinary tract, comparable to MSCT in its informative value. This referred to determination of perirenal hematomas, assessment of the depth of damage and viability of the renal parenchyma, visualization of pre-existing pathological changes in the

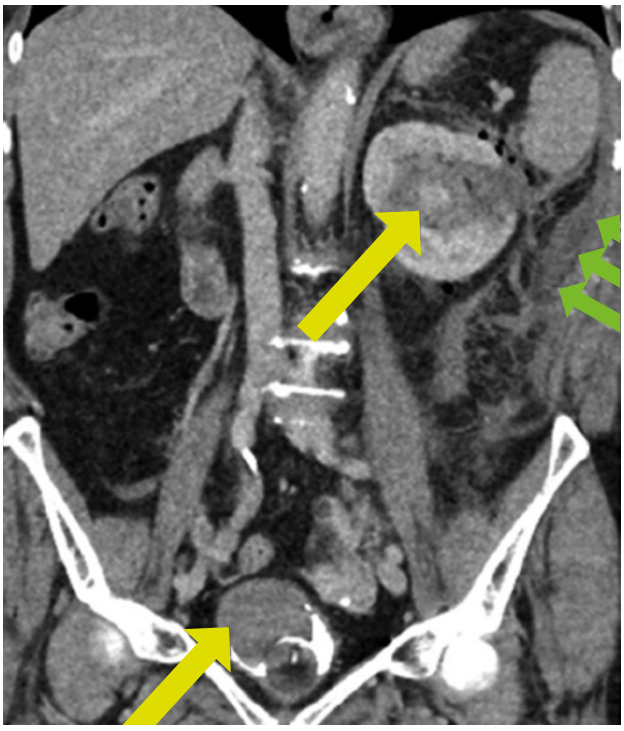
I grade	32,4%
II grade	38,8%
III grade	14,4%
IV grade	6,5%
V grade	7,9%

Fig. 1. Diagram of the distribution of injured patients according to the severity of renal trauma (n=128)



Urosepsis	0,8%	Periods of early (2 days–2 weeks) and late (2 weeks–2 months) manifestations
Peritonitis	1,6%	
Purulent retroperitoneal hematoma	1,6%	
Renal abscesses	12,5%	
Pyelonephritis	25,0%	
Urinoma	4,8%	
ARF	11,7%	At different periods of TD

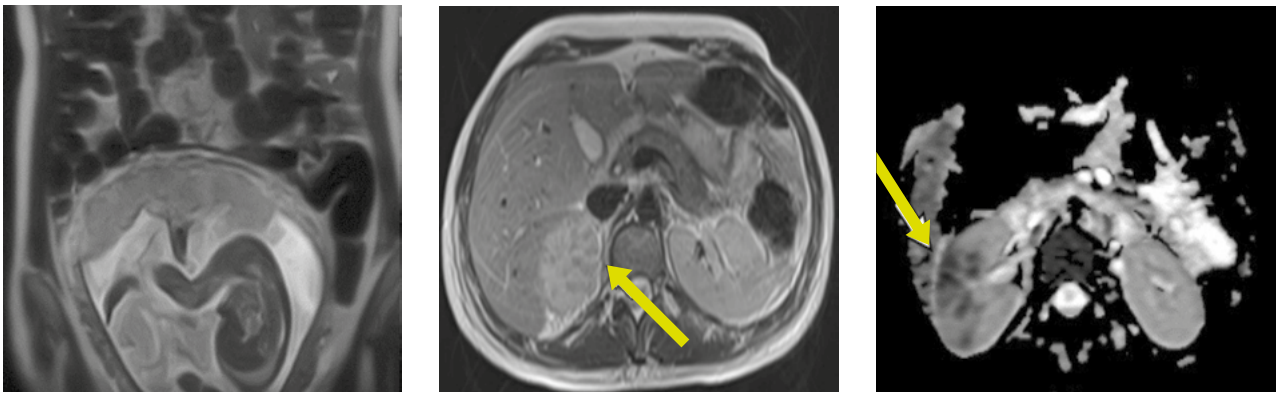
Fig. 2. Diagram of the distribution of complications in patients with isolated and combined kidney injuries (n=128) during different periods of TD



A

B

Fig. 3. CT scan of patient I., 45 years old, with intravenous contrast enhancement (A, B) of the abdomen and retroperitoneal space (multiplanar reconstructions) 3 h after injury — renal vein rupture, increasing hematoma in the renal portal area with hemotamponade of pelvis and bladder (yellow arrows), retroperitoneal hematoma (green arrows) — grade V AAST renal injury



A B C

Fig. 4. MRI of patient K., 32 years old (pregnancy 21-22 weeks): A — T2-WI in coronal plane, uterus enlarged according to gestational age, one fetus in cephalic presentation in the uterine cavity; B — parenchymal thickening with apostemes in cortical layer; C — DWI and MDC, diffusion restriction foci correspond to multiple apostemes

Table 3. Effectiveness of methods of clinical-laboratory and radiological examination of patients with kidney and ureteric injuries in different periods of traumatic disease

Methods of diagnostics	Periods of traumatic disease	Indices of diagnostic efficiency, %		
		Se	Sp	Ac
Clinical-Laboratory	acute reaction	61,2	56,1	57,5
	early manifestations	66,4	61,2	64,1
	late manifestations	86,3	82,7	85,6
EU	acute reaction	—	—	—
	early manifestations	13,7	15,9	13,1
	late manifestations	17,8	44,7	25,2
Ultrasound	acute reaction	68,3	35,9	46,7
	early manifestations	71,9	64,7	72,0
	late manifestations	89,9	82,7	86,3
MSCT with CE	acute reaction	92,0	84,9	89,2
	early manifestations	92,7	86,3	88,8
	late manifestations	94,2	84,8	89,5
MRI	acute reaction	—	—	—
	early manifestations	88,5	80,6	87,5
	late manifestations	92,1	87,8	89,9

urinary tract organs. There was no radiation load on the patient during MRI, however, images characterized by natural tissue contrast, were obtained without the need for mandatory use of intravenous contrast (Fig. 4).

Improvement of MRI technology and software made it possible to eliminate many of the previously existing drawbacks associated with respiratory artifacts.

Optimization of protocols with reduction of total examination time to 10-15 minutes using a necessary and sufficient set of programs, combined with high differentiation of soft tissues, changed the place of MRI in the diagnostic algorithm in patients with renal trauma.

Based on the results of statistical analysis, we compared the efficacy rates of radiological methods in the diagnosis of renal and ureteral injuries and their complications during different periods of TD (Table 3).

The only technique with low diagnostic efficacy was EU, due to the limitation of being a projection technique characterized by summation effects. Its data cannot be used to determine direct signs of infiltrative-fluid changes, hematomas both in renal parenchyma and in surrounding cellular tissue, and the study is accompanied by radiation and drug load.

From the data presented in the table, it follows that all methods of investigation are characterized by an increase in accuracy in detecting traumatic changes in the kidneys and ureters from the period of acute reaction to trauma to the period of late manifestations of TD.

Conclusion. The use of clear working algorithms for the use of tomographic methods of diagnosing complications of kidney and ureteral injuries in different periods of TD will allow to visualize more clearly the location of the injury and the extent of hematoma, as well as to use as an alternative method in case of contraindications for MSCT (in pregnant patients, patients with signs of renal failure and the presence of allergic reactions to iodine-containing preparations).

Conclusions. Multislice computed tomography (with intravenous CE, followed by multiphase scanning) has high diagnostic efficacy in the evaluation of complications of kidney and ureteral injuries in different periods of TD (acute reaction — 89,2%, early manifestations — 88,8%, late manifestations — 89,5%).

Magnetic resonance imaging of the kidneys and ureters is indicated in the periods of early and late manifestations of TD to reveal renal complications when there is a discrepancy between the clinical manifestations and the results obtained by ultrasound and MSCT (at early manifestations — 87.5%, at late manifestations — 89.9%).

The developed protocol of MRI study due to inclusion of short pulse sequences with fat signal suppression — coronary STIR-sequence — allows to achieve high rates of diagnostic efficacy of MRI.

Excretory urography can be excluded from the algorithm of examination of patients with renal and ureteric traumas, given its low rates of diagnostic efficiency, if MSCT with CE is available.

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Information about the authors:

Elena A. Egorova — MD, ScD, professor of radiation diagnostics department, Federal State Budgetary Educational Institution of Higher Education "A.I. Yevdokimov Moscow State University of Medicine and Dentistry" of the Ministry of Healthcare of the Russion Russian Federation, Moscow, Russia — **responsible for contacts**, **tylsit@mail.ru**, ORCID: 0000-0003-2580-5692; eLibrary SPIN: 3771-3676; AuthorID: 662902; ResearcherID (WOS): O-7304-2017; Author ID (Scopus): 57196761433

Zavazhat M. Magomedova — MD, radiologist, FSBI «Clinical Hospital № 1» Administrative office of the President of the RF, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 10.02.2023.

Peripheral cerebral aneurysms: clinical picture and diagnostics

UDK 616.13 002.2-007.64
DOI: 10.53652/2782-1730-2023-4-1-39-47

Shitov A.M.[1], Sazonov I.A.[2], Belousova O.B.[2], Eliava S.S.[2]

[1] *Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia*
[2] *National Medical Research Center for Neurosurgery named after academician N.N. Burdenko, Ministry of Health of the Russian Federation, Moscow, Russia*

Abstract. The article is devoted to the clinical manifestations and diagnosis of peripheral cerebral aneurysms. The clinical course of this disease was analyzed in 139 patients depending on topographic and anatomical features (106 patients with hemorrhagic stroke, 33 without a history of aneurysm rupture). The study included patients with peripheral aneurysms of the anterior cerebral, middle cerebral arteries, posterior cerebral, posterior inferior cerebellar arteries. A high incidence of seizures was noted in case of rupture of distal aneurysms (up to 10%). Quite typical for hemorrhage from peripheral aneurysms was the formation of an intracerebral hematoma (43.1%). A comparison of diagnostic methods for detection of this vascular pathology was performed: cerebral angiography (informative in 93.3%), CT angiography (CTA) (90.9%) and magnetic resonance imaging in the vascular mode (12.2%). CTA is a highly effective method for diagnosing peripheral cerebral aneurysms and in most cases does not require additional invasive angiographic examination.

Keywords: peripheral, distal cerebral aneurysms, diagnostics, clinic, hemorrhagic stroke.

Introduction. The incidence of spontaneous subarachnoid hemorrhage (SAH) is 8-12 cases per 100,000 people per year in the population [9]. In 75-80% of cases the cause is an arterial aneurysm rupture [2, 6]. In Russia (140 million people), about 14 thousand non-traumatic SAH occur annually [5]. It is well known that 40–50% of the patients with SAH die, and 1 out of 8 transported patients dies on the way to the hospital [9]. Those who survive become disabled in 75% of cases, with about 10% of such patients being bedridden [10].

Among the variety of arterial aneurysms, peripheral aneurysms [6, 8], located distal to the cranial base arteries, form a special group. The analysis of the world experience in the treatment of peripheral aneurysms of cerebral vessels showed the lack of a unified view on the features of clinical course of the disease due to different characteristics of peripheral aneurysms, and so far there has been no analysis of localization, morphological features, clinical course and treatment results of the whole set of peripheral aneurysms observed in one clinic [4]. In addition, the peculiarity of clinical course of peripheral aneurysms often becomes a source of errors both in diagnosis and management [3, 7].

Objective. To identify the main clinical symptoms and assess the informativity of modern methods of neuroimaging of peripheral aneurysms based on the analysis of the course of the disease in patients with peripheral aneurysms depending on topographic and anatomical features.

Material and Methods. The study included 139 patients (49 retrospective and 90 prospective cases) with peripheral aneurysms of cerebral vessels. All patients were underwent treatment at the Research Institute of Neurosurgery named after N.N. Burdenko from 2002 to 2011. The retrospective group included the patients treated from January 2002 till August 2007. The prospective part of the study was performed from September 2007 till December 2011 (64.7% of patients).

Results and discussion. The most frequent peripheral aneurysms of cerebral vessels manifested as acute cerebral circulation disorder (ACCD) of hemorrhagic type. Among 139 patients, 106 (76.3%) had aneurysms of hemorrhagic character, 33 (23.7%) patients had peripheral aneurysms without traces of a previous hemorrhage, including 18 (12.9%) with pseudotumor-like course, 10 (7.2%) aneurysms were incidental, and 5 (3.6%) had ischemic stroke in the artery basin where the peripheral aneurysm was located (Fig. 1).

A group of patients with verified peripheral aneurysm rupture was chosen to analyze the clinical picture of hemorrhage. In addition to 106 hemorrhagic stroke patients, it included 90 patients in both cold and acute hemorrhage periods with aneurysms of different vascular basins (Table 1).

General hemorrhage symptom in the form of acute headache were observed in 71 patients. Hemorrhage in 55 (61,1%) cases was accompanied by loss of consciousness, among them there were 14 patients in whom the disease manifested itself as a sudden loss of consciousness without prior pain syndrome. In 5 cases there were no data on the onset of the disease.

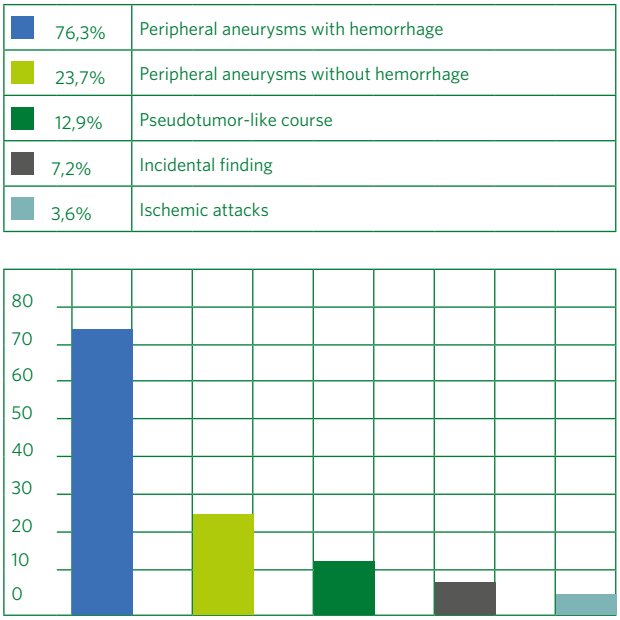


Fig. 1. Distribution of patients with peripheral aneurysms by clinical manifestation of the disease

Table 1. Number of patients with peripheral aneurysms that caused hemorrhage in different cerebral vascular basins (abs.)

Basin			
Anterior Cerebral Artery (ACA)	Middle Cerebral Artery (MCA)	Posterior Cerebral Artery (PCA)	Posterior Inferior Cerebellar Artery (PICA)
46	31	7	6

Table 2. Distribution of patients with loss of consciousness depending on peripheral aneurysm localization (abs. number/%)

Clinic of hemorrhage	Distal			
	ACA	MCA	PCA	PICA
With loss of consciousness	31/67,4	15/48,4	5/71,4	4/66,7
Without loss of consciousness	15/32,6	16/51,6	2/28,6	2/33,3

Table 3. Dependence of severity of patients' condition at the time of admission on the type of hemorrhage (abs. number/%)

Variant of hemorrhage	MRS-0	MRS-1	MRS-2	MRS-3	MRS-4	MRS -5
SAH	17/32,7	20/38,5	6/11,5	7/13,5	2/3,8	0
SAPH	3/33,3	2/22,2	3/33,3	1/11,1	0	0
IH	10/30,3	5/15,1	4/12,1	1/ 3,0	9/27,3	2/6,1
IH + IVH	0	1/11,1	2/22,2	2/22,2	3/33,3	1/11,1
IVH	2	1	0	0	0	0

49%	by SAH type
31%	with the formation of intracerebral hematoma (IH)
9%	SAH with parenchymal component (SAPC)
8%	with the formation of ICH in combination with intraventricular hemorrhage (IVH)
3%	isolated IVH

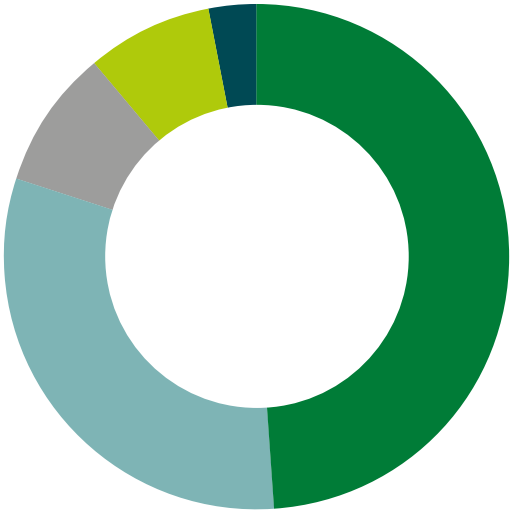


Fig. 2. Distribution of hemorrhage types in peripheral cerebral vascular aneurysms

Thus, loss of consciousness was most frequently observed in the rupture of peripheral aneurysms of the posterior (PCA) and anterior (ACA) cerebral arteries: 71.4% and 67.4%, respectively, whereas in the rupture of distal aneurysms of the middle cerebral artery (MCA) it was observed in 48.4% (Table 2).

Quite often peripheral aneurysm hemorrhage was accompanied by a seizure. There were 9 (10%) such cases among the patients who suffered hemorrhage, of which 7 (15.2%) patients of this localization were patients with aneurysms of ACA basin, 2 (6.5%) — with aneurysms of distal segments of MCA basin, including one case with aneurysm located in the M3 segment, and another — in M4 segment.

As for the localization of the ACA basin aneurysms the rupture of which caused episyndromes, 2 of them were A2 segment aneurysms (13.3% of them), 4 were A3 segment aneurysms (15.3%), and 1 was an A4 segment aneurysm (6.6%). In 8 of 9 cases, an epileptic seizure occurred as a grand mal seizure with loss of consciousness and limb convulsions. In 1 case (M4 segment aneurysm), it was a visual disturbance followed by loss of consciousness. Electroencephalography (EEG) showed epileptic activity in the occipital area of the corresponding hemisphere.

Peripheral aneurysm rupture resulted in different types of hemorrhage. Thus, among 106 patients who suffered hemorrhage, in 52 of them it was of SAH type, in 9 — of SAH type with parenchymatous component (SAPH), in 33 — with the formation of intracerebral hematoma (IH),

in 9 — with the formation of IH combined with intraventricular hemorrhage (IVH). An isolated IVH was detected in 3 patients (Fig. 2).

In order to assess the extent to which the type of hemorrhagic ACCD affected the severity of the condition, we analyzed data on admission according to the modified Rankin Scale (MRS) (Table 3).

To objectify the assessment of the dependence of the condition on the type of hemorrhagic stroke, the patients (regardless of the time when hemorrhagic stroke occurred) were divided into three groups according to the severity of the condition: Group 1 patients with MRS-0 and MRS-1; Group 2 patients with MRS-2 and MRS-3; Group 3 patients with MRS-4 and MRS-5.

Among patients with SAH, 37 (71.1%) had a mild condition, 13 (25%) had a moderate condition, and 2 (3.8%) had a severe condition. In SAPH, 5 (55.5%) patients' condition corresponded to a mild, and 4 (44.4%) patients' condition corresponded to a moderate severity. In isolated IVH (in the cold period) the condition of all 3 patients corresponded to a mild severity.

At hemorrhage with the formation of IH combined with IVH, the condition of only 1 (11.1%) patient corresponded to a mild severity, the condition of 4 (44.4%) — medium and another 4 (44.4%) — severe. Among patients with IH, 15 (45.4%) patients had a mild, 5 (15.1%) had a moderate, and 11 (33.3%) had a severe condition.

Thus, the dependence of patient's condition severity on the type of hemorrhagic stroke is determined: the more pronounced and more massive the hemorrhage, the more severe it is, which is typical for aneurysms of any localization.

Among 46 peripheral aneurysms of the ACA basin that were the origin of hemorrhagic stroke, there were aneurysms of the following localizations: A2 segment — 15 cases, A3 segment — 26, A4 segment — 1, distal parts of the callus-marginal artery — 3, frontal-polar artery — 1. As a result of hemorrhage, IH was detected in 23 (50%) patients, of which 7 (15%) had a combination of IH and IVH (15%), including 18 (39%) patients with SAH and 5 (11%) with SAPH.

Focal symptomatology was detected in 16 (35%) patients and was represented by motor disorders in 10 (22%), intellectual and mental disorders in 8 (17,4%), with sensory disorders in 2 (4%) and aphasic disorders in 2 (4%).

While comparing different types of hemorrhages and focal symptoms, it appeared that the most frequent cause of neurological deficit was IH (both with and without ventricular component): among 16 patients with focal neurological deficit, 11 (68, 75%) patients with IH were identified, including 4 — with IVH, SAH caused focal symptoms in 4 (25%) cases, SAPH — in 1 (6%). At the same time, it was reliably determined that in 2 cases (SAH and SAPH) a vascular spasm developed, which led to an extensive ischemic stroke, which was subsequently the cause of focal symptomatology.

All 46 patients (during both cold and acute periods of hemorrhage) were assessed according to MRS on admission. The majority (54.3%) were classified as mild severity and corresponded to MRS-0 and MRS-1, less frequently (34.8%) there were patients whose condition was rated as moderate severity and corresponded to MRS-2 and MRS-3, the proportion of patients in severe condition MRS-4 and MRS-5 was 10.9%.

The severity of patients depended on the type of hemorrhage that developed after peripheral aneurysm rupture. Thus, the patients who suffered SAH without a parenchymatous component were mostly (77.8%) of mild severity. In case of SAPH, the proportion of patients with mild severity was 60%. When IH developed, only 50% of patients had a mild degree of severity, and when IH was combined with IVH, there were no patients in a mild condition.

Thus, the most severe consequences of hemorrhage were in the case of IH with IVH.

The group of patients with MCA aneurysms that manifested with hemorrhage included 31 patients. The aneurysms had the following localization: M2 segment — 22 patients, M3 segment — 7, M4 segment — 1 patient. 15 (48%) patients had SAH type hemorrhage, 3 (10%) aneurysm rupture caused SAPH, 13 (42%) patients had IH, 1 (3%) of them had IH combined with IVH.

Hemorrhage from peripheral aneurysms of the distal MCA segments always manifested with generalized cerebral symptoms. In 14 (45%) people (nearly half of the patients) there were focal symptoms of varying severity. In contrast to the clinic of ruptured distal ACA aneurysms, there were no cases of severe intellectual and mental disorder. Focal symptomatology of ruptured distal MCA aneurysms manifested itself as motor disorders in 12 (39%) patients, aphasic disorders — in 10 (32%) patients. Epileptic seizures were observed in 3 (9.7%) patients who had hemorrhage, and in 2 cases an epileptic syndrome developed: in one patient — as rare

While comparing different types of hemorrhages and focal symptoms, it appeared that the most frequent cause of neurological deficit was IH (both with and without ventricular component)

generalized seizures, in another — as partial seizures (the focus of epileptic activity, according to EEG, coincided with the localization of aneurysm). No hydrocephalus development was observed in this group of patients.

When assessing the severity of this group of patients using MRS, it was found that 61% were patients of mild (MRS-0 and MRS-1), 26% of medium (MRS-2 and MRS-3) and 12% of severe condition (MRS-4 and MRS-5).

From the assessment of hemorrhage outcome, it follows that, as in the group in general, hemorrhages without IH and ventricular component formation are more easily tolerated (Fig. 3).

In cases when aneurysm rupture leads to IH formation, the risk of focal neurological deficit increases. Thus, when IH developed, 9 (69%) out of 13 patients had motor or aphasic abnormalities or their combination. Patients (18 patients in total) with SAH or SAPH were two times less likely to form focal symptoms, and their proportion was 33% (6 patients with focal symptoms).

There were 7 patients with verified hemorrhage with peripheral PCA aneurysm as the source, including 4 with P2 segment PCA aneurysms, 2 with P3 segment aneurysms, and 1 with P4 segment aneurysm. All patients were admitted during the cold period of hemorrhage. In this group, in most cases hemorrhage proceeded with general cerebral symptoms in the form of headache with nausea and vomiting. Loss of consciousness was noted in 4 patients, one patient had an epileptic attack. The severity of condition at the time of admission in 3 of them was rated on MRS as 0, and in 4 — as 1.

Thus, there were no patients with focal neurological symptoms in this group. All 4 patients whose condition was rated as MRS-1 suffered SAH-type hemorrhage, 3 patients with MRS-0 severity had IVH, SAH with ventricular component and hemorrhage with IH formation in the parietal region.

Of the 8 patients with PICA aneurysms, 6 had aneurysmal hemorrhage. Aneurysm rupture resulted in SAH in 4 cases, IH formation in the cerebellum in 1 case, and IH formation with a ventricular component in another 1. In the acute period of hemorrhage 2 patients were admitted. Their condition was assessed according to the Hunt-Hess scale, which corresponded to the second and third grade of severity. In assessing the severity of condition of 6 patients admitted during the cold period of hemorrhage, 4 patients corresponded to MRS-2 and 2 patients corresponded to MRS-1. General cerebral symptomatology (headache, nausea, vomiting) was the most common in the clinic of peripheral PICA aneurysm rupture. Loss of consciousness was observed in half (3 patients). In one patient with a ruptured distal PICA aneurysm a paresis of the VI nerve developed on the side of the aneurysm, another patient had cerebellar symptoms in the form of shakiness when walking, impaired swallowing and hiccups. The presence of vascular spasm (verified by Doppler imaging) was detected in both patients in the acute period of hemorrhage: in one of them the hemorrhage was of SAH type, and in the other - with the formation of IH and a ventricular componen.

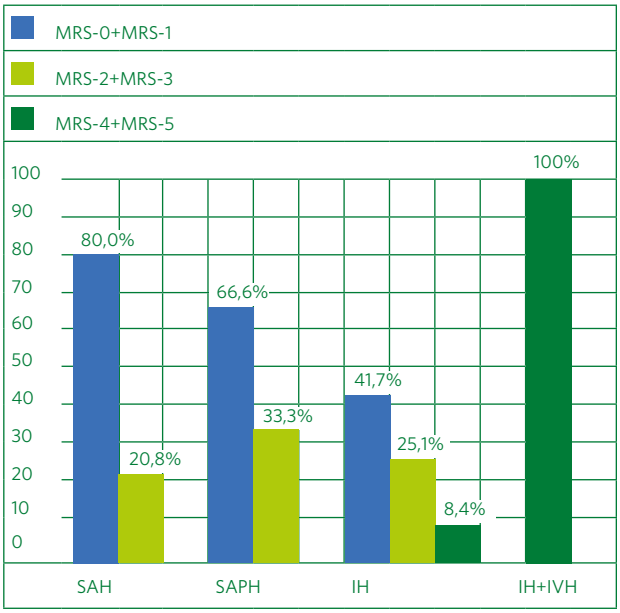
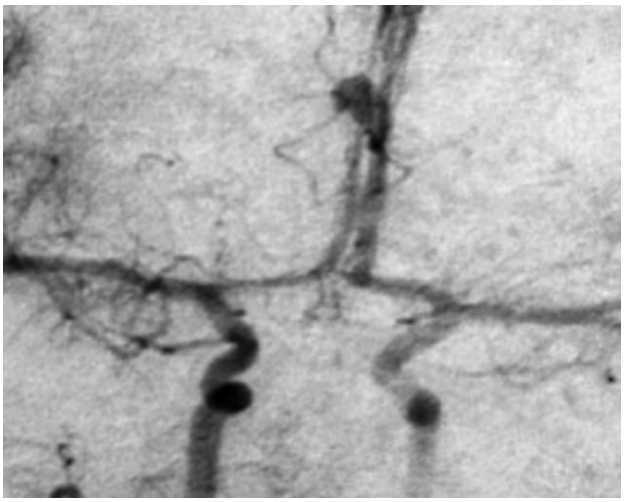


Fig. 3. Relationship of condition severity according to MRS and hemorrhage type

Vasospasm was detected in 16 (64%) patients. In most cases — 12 (48%) patients had moderate vasospasm with increased linear velocity of blood flow in MCA up to 230 cm/s, in 4 (16%) patients — severe vasospasm with increased linear velocity of blood flow in MCA above 230 cm/s. Two of these patients had aneurysm rupture with IH formation: in 1 patient the hemorrhage was of SAH type, in another — of SAPH type. These findings are consistent with those obtained when assessing the severity of vasospasm in aneurysms of typical localization in the acute period of hemorrhage. According to O.B. Belousova [1], the signs of vasospasm in transcranial ultrasound Doppler imaging (TC USDG) were detected in 72.3% of patients, and severe angiospasm - in 17.6%.

Thus, based on the data obtained, we can state that despite the distal location of peripheral aneurysms, the risk of development and severity of potential vasospasm is comparable to the risk of angiospasm in patients with proximal aneurysm rupture.

Among 139 examined patients with peripheral aneurysms we detected 25 (17.9%) patients with pseudotumor-like (17 patients) and ischemic (8 patients) types of clinical picture. In all 8 patients ischemic cerebral circulation disorders were localized in the aneurysm basin — the latter was either partially (5 patients) or completely (3 patients) thrombosed. Among the aneurysms that



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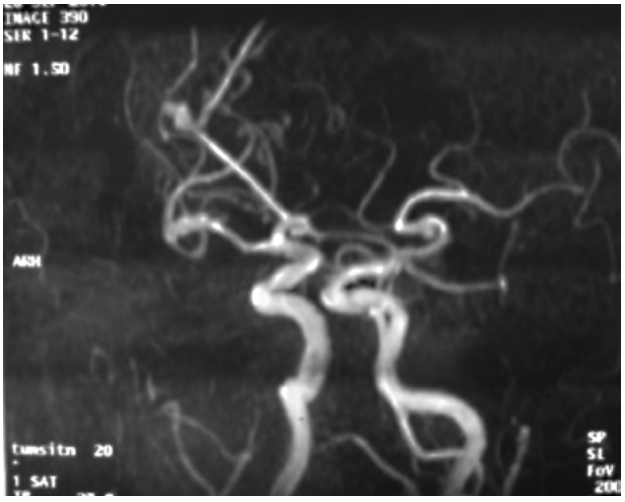

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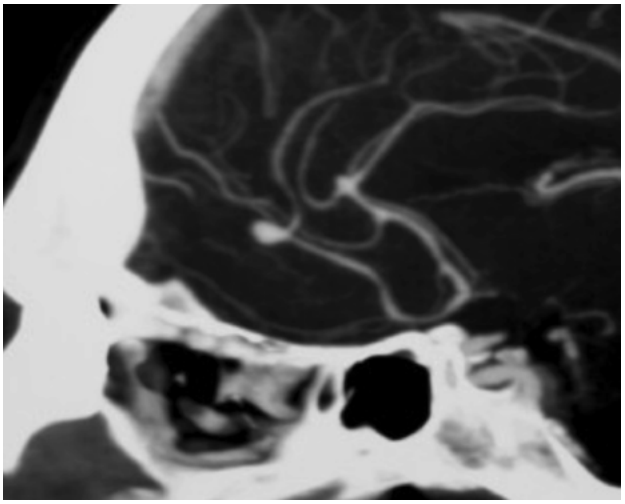

C

Fig. 4. Diagnostic techniques for peripheral cerebral vascular aneurysms
Examples of distal aneurysms in the ACA basin: A — selective carotid angiography; B — MRI-AG; C — sCT-AG

manifested with ischemic circulatory disorders, 4 were in the MCA basin and two in the ACA and PCA basins each. Clinical manifestations such as aphasic disorders, decreased sensitivity, limb movement impairment, facial asymmetry (aneurysms of MCA and ACA basins), brainstem symptoms (PCA aneurysms), both transient disorders (2 patients) and persistent focal symptomatology (6 patients) were detected.

Peripheral aneurysms with pseudotumor-like course most frequently (10 patients) had cephalgia clinic, at the same time headache could be combined with epileptic seizures (5 patients), dizziness and coordination disorders (3 patients), visual impairment (2 patients), oculomotor disorders (2 patients), disruption of V, VII, VIII, IX craniocerebral nerves functions (2 patients). In 3 (17.7%) patients with peripheral aneurysms and pseudotumor-like course an aneurysm at the stage of preoperative preparation was considered as a tumor, and aneurysm detection was an intraoperative finding.

These were partially thrombosed aneurysms of distal MCA, PCA and PICA segments. It should be noted that all 3 patients underwent preoperative magnetic resonance imaging (MRI) of the brain, which revealed a round-shaped neoplasm, at that, the patient with M3 segment aneurysm also underwent cerebral angiography (CAG), which did not reveal any vascular pathology.

Among the entire cohort of 139 examined patients with peripheral cerebral vascular aneurysms, 6 (4.3%) had hydrocephalus requiring bypass surgery, however, it should be noted that in only 3 (2, 16%) of this group the source of hydrocephalus was a peripheral aneurysm, while the rest had either a proximal aneurysm, or it was impossible to differentiate the bleeding aneurysm among other aneurysms (in a patient with multiple aneurysms).

Overall, out of 87 patients with verified hemorrhagic stroke, where the source of hemorrhage was specifically a peripheral aneurysm, 3 (3.5%) patients required liquor bypass surgery, in one of them (distal right PICA aneurysm) aneurysm rupture led to SAH, in another (A2 segment aneurysm) — to IH, in the third one (A2 segment aneurysm) — to IH with IVH.

Thus, patients with peripheral cerebral vessel aneurysms are 5 times less likely to develop aresorptive hydrocephalus than patients with typically localized aneurysms. This is most likely due to the lower subarachnoid component of hemorrhage in peripheral aneurysm rupture.

Selective AG (total and subtotal) was performed to diagnose peripheral cerebral vessel aneurysms. This examination was performed in 104 (74.8%) patients. For the same purpose, magnetic resonance imaging angiography (MRI-AG) was performed in 41 (29.5%) patients, and sCT-AG was performed slightly less frequently in 33 (23.7%) patients (Fig. 4).

IH formation is typical for hemorrhage from peripheral aneurysms (43.1%). Aaresorptive hydrocephalus in patients with bleeding peripheral aneurysms develops significantly less frequently than in aneurysms of typical localization.
sCT-AG is a highly effective method of diagnosing peripheral cerebral vessel aneurysms and in most cases does not require additional angiographic examination (selective cerebral AG). In this case differential diagnosis with volumetric masses — tumors, cavernomas, spontaneous IH — is required more often than in case of aneurysms of typical localization

The informative value of these methods was different and assessed as follows:

1. informative: aneurysm is visualized, it is possible to assess correctly the aneurysm location and its relationship with arteries;
2. poorly informative: aneurysm is visualized, but it is impossible to correctly assess its location and relationship with arteries;
3. not informative: it is impossible to visualize an aneurysm.

Among 104 patients who underwent angiographic examination, it was informative in 97 (93.3%) patients, unsatisfactory informative in 1 (0.9%), and not informative in 6 (5.8%). Among 41 patients in whom MRI-AG was performed as the first step, this method was informative and allowed no further examination in only 5 (12.2%) cases. Among 33 patients in whom sCT-AG was performed, this method of diagnosis and neuroimaging was informative in 30 (90.9%) cases, poorly informative in 1 (3%) case and not informative in 2 (6.1%) cases.

Thus, in case of suspecting peripheral aneurysm, direct AG and sCT-AG are the methods of choice. The latter is practically as effective as AG, moreover, sCT-AG is a safer and more cost-effective method of investigation, therefore it should be preferred. MRI is not an adequate method for diagnosis of peripheral aneurysms.

Conclusions. IH formation is typical for hemorrhage from peripheral aneurysms (43.1%). Aaresorptive hydrocephalus in patients with bleeding peripheral aneurysms develops significantly less frequently than in aneurysms of typical localization.

sCT-AG is a highly effective method of diagnosing peripheral cerebral vessel aneurysms and in most cases does not require additional angiographic examination (selective cerebral AG). In this case differential diagnosis with volumetric masses — tumors, cavernomas, spontaneous IH — is required more often than in case of aneurysms of typical localization.

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Information about the authors:

Andrey M. Shitov — MD, neurosurgeon, Head of the neurovascular department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts**, **shitovandrew@inbox.ru**, ORCID:0000-0002-6024-255X

Il'ja A. Sazonov — MD, PhD, neurosurgeon, Head of the Medical management unit with the teams, Head of the reception department of National Medical Research Center for Neurosurgery named after academician N.N. Burdenko, Ministry of Health of the Russian Federation, Moscow, Russia.

Ol'ga B. Belousova — MD, ScD, Professor of the Department of Neurosurgery with courses in neuroscience, leading researcher, neurologist of the 3th neurosurgery department (vascular neurosurgery) of National Medical Research Center for Neurosurgery named after academician N.N. Burdenko, Ministry of Health of the Russian Federation, Moscow, Russia.

Shalva S. Eliava — corresponding member of the Russian Academy of Sciences, MD, ScD, professor, neurosurgeon, Head of the 3th neurosurgery department (vascular neurosurgery), leading researcher of National Medical Research Center for Neurosurgery named after academician N.N. Burdenko, Ministry of Health of the Russian Federation, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 29.01.2023.

A case of successful treatment of a patient with splenic artery aneurysm, splenic vein malformation and splenomegaly

Chuprina A.P.[2], Polushin S.Yu.[1], Zamskiy K.S.[1], Vinogradov E.V.[1]

[1] *Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia*
[2] *Main Military Medical Directorate of the Ministry of Defense of the Russian Federation, Moscow, Russia*

UDK 612.412
DOI: 10.53652/2782-1730-2023-4-1-48-54

Abstract. The clinical picture, diagnosis and selected option of surgical treatment of splenic artery aneurysm with splenic vein malformation and splenomegaly in a 30-year-old patient are discussed.

Keywords: splenic artery aneurysm, angiography, thrombocytopenia.

Introduction. Aneurysm of the splenic artery (ASA) is not common, yet is a serious vascular disease, its diagnosis is rather complicated and poorly studied, despite the fact that it was first described back in 1745 by G.M. Lancisii, and then in 1770 by M. Beaussier [1–3].

The frequency of in vivo detection of ASA has increased with the appearance of modern high-resolution imaging technologies. Usually ASA detection is an incidental finding during an examination prescribed for other indications. The "gold standard" of diagnosis is angiography (AG), which due to its high spatial resolution enables to assess the condition of small vessels, and further, if necessary, to perform therapeutic intervention.

ACA is the third most frequent among all intraabdominal aneurysms after abdominal aortic and iliac artery aneurysms [1, 4–7]. Pancreatitis, pregnancy (especially multiple pregnancies) and childbirth, portal hypertension, hepatic cirrhosis, atherosclerotic degenerative changes of the splenic artery, trauma, connective tissue fibrosomuscular dysplasia are among the factors contributing to ASA formation. In addition, arterial hypertension is among the risk factors of ASA development in 40% of cases [2, 3, 5, 7–9]. 95% of splenic artery aneurysms detected during pregnancy burst, leading to a disproportionately high (70%) rate of maternal mortality and fetal mortality (75%) [8]. Nevertheless, the cause of ASA in a large proportion of cases remains unknown. About 40% of patients have multiple aneurysms [2].

In most cases, ASA can be asymptomatic for a long time. Its clinical manifestations include pain in the epigastrium, left subcostal area, feeling of stomach fullness, loss of appetite, nausea, vomiting. In aneurysm rupture there is a classical picture of "double rupture" described by R. Brockman, with primarily developing tamponade of omental sac, followed by intra-abdominal bleeding through Winslow hole and hemodynamic collapse [2, 4].

One of the most serious complications of visceral abdominal aortic branch aneurysms is spontaneous intra-abdominal bleeding [2]. The risk of spontaneous ruptures (according to different authors) varies from 2 to 10% and is accompanied by lethality in 10–40% of cases, including patients who underwent urgent surgical intervention [1, 10, 11]. The lethality rate in ASA rupture is particularly high in patients with portal hypertension. Splenic artery aneurysms are more common in women, but ruptures are more common in men [1, 2, 4, 7].

The treatment of ASA can only be surgical. The high risk of rupture and high mortality rate in ASA make it necessary to perform surgical intervention in all patients as soon as possible. Laparotomy, laparoscopic and endovascular operations, as well as their combinations are used. The choice of treatment method depends on aneurysm localization, patient's age, risk of surgical intervention and clinical status of the patient. Aneurysms of the proximal and middle third of the splenic artery are well treated by simple excision with proximal and distal ligation of the artery. For aneurysms located in the distal third, resection with splenectomy is most frequently performed.

Recently, percutaneous endovascular interventions: embolization of aneurysm cavity and/or proximal segment of the splenic artery using special spirals or embolizing agents have been increasingly used to treat ASA [10, 11]. Nevertheless, the use of spirals for ASA occlusion has shown unsatisfactory results due to high recanalization rate [12]. It is also worth noting that postoperative mortality is close to 1% [4].

Malformation of the splenic vein in isolation is extremely rare [13]. Only in isolated cases there is an association of arteriovenous malformations (AVMs) in the spleen with the development of ASA [6].

Despite the fact that domestic and foreign literature periodically reviews clinical cases of patients with ASA, the lack of comprehensive information on splenic vascular malformations, especially in combination with splenomegaly, aneurysmal dilation of splenic and bilateral carotid arteries determines the value of describing surgical tactics in such clinical observations.

The surgical treatment of patient with this pathology was performed at MMCH named after N.N. Burdenko. Treatment results and tactics could be of interest for practicing surgeons.

Objective. To determine the treatment tactics for a patient with splenomegaly, splenic vein malformation and aneurysmal dilation of the splenic and both internal SA.

Material and methods. Clinical case. Patient P., 30 years old, was admitted from a distant region of the country to the surgical department of the hospital with complaints of periodic pain and discomfort in epigastrium, mesogastrium, as well as in the left lateral abdominal area. She considers herself ill for the last 5 years, when the feeling of discomfort and heaviness in the epigastrium appeared, on examination since 2017 splenomegaly (spleen size 15.4 cm) was revealed. Repeatedly examined in various hospitals, where an increase in the size of the spleen was noted, however, she refused the proposed splenectomy. In 2020, due to increased pain syndrome and deformation of the anterior abdominal wall due to the enlarged spleen, as well as her desire to become pregnant, she had consultations at medical institutions of St. Petersburg, including a hematological center. The patient was denied surgical treatment (splenectomy) on the reason of a high risk of complications due to severe leukocytopenia and thrombocytopenia. At the end of 2020, the patient sought medical help at the MMCH named after N.N. Burdenko. Given the large size of the spleen and the high risk of its rupture, the patient was advised

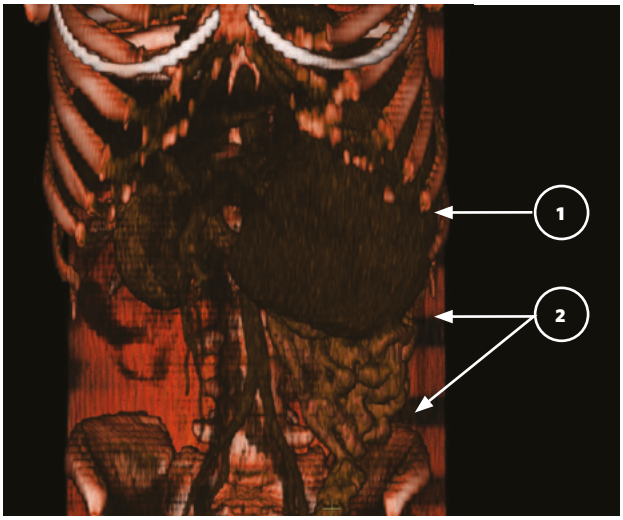

Fig. 1. 3D modeling of aneurysmal changes in the splenic vein. 1 — spleen, 2 — splenic vein malformation

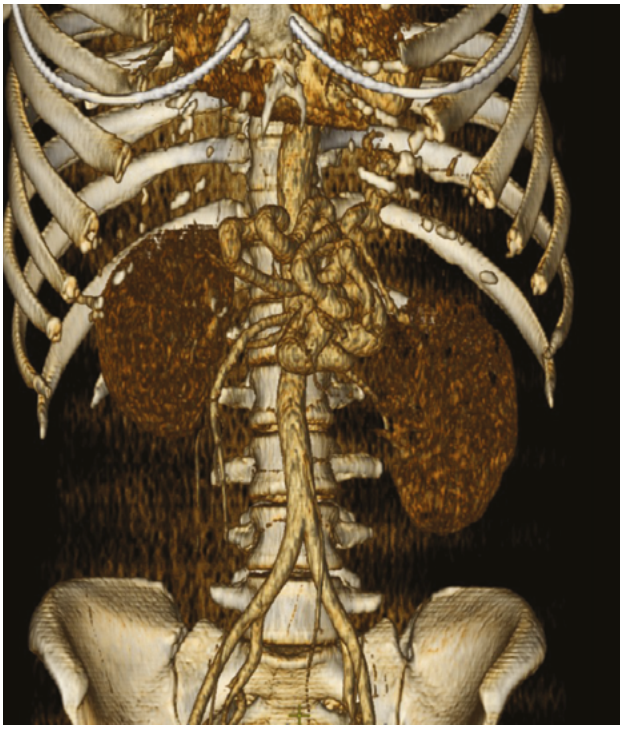

Fig. 2. 3D modeling of aneurysmal changes in the splenic artery. 1 — aneurysmal changes in the splenic artery

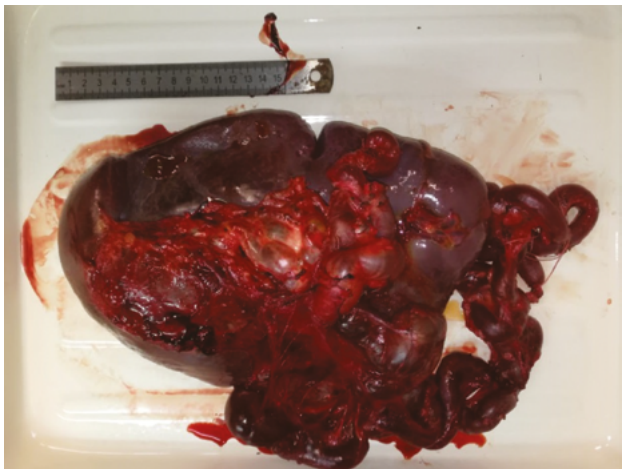

Fig. 3. Removed spleen with altered vessels

to undergo surgical treatment. On 22.01.2021 the patient was routinely admitted to the 2nd surgical department of the hospital by referral.

The patient's condition on admission was satisfactory. Color of the skin was normal. Hemodynamics was stable. Examination of the abdomen and palpation revealed an enlarged spleen.

Clinical blood test: red blood cells 4.4×1012/l, hemoglobin 108 g/l, platelets 32×109/l, leukocytes 0.55×109/l, platelets according to Fonio 40000. Biochemical blood test was within the reference values. Coagulogram showed fibrinogen 1.6 g/L, Quik prothrombin percentage 60, activated partial thromboplastin time (aPTT) 52 s, international normalised ratio (INR) 1.39. Abdominal ultrasound examination (ultrasound) showed decreased size of the diffusely altered liver, signs of periportal fibrosis, splenomegaly, AVM of the splenic vessels. Computed tomography (CT) revealed focal thickening of the left lung up to 0.5 cm of unclear genesis, liver formations 9.2×8.8 mm (probably small hemangiomas), splenomegaly 166×112 mm (vertical size up to 202 mm), a pathological network of dilated venous and arterial vessels is detected in the portal area, diameter of veins up to 16 mm, arteries up to 23 mm, conglomerate of veins traceable to the pelvis, left renal vein dilated up to 18 mm. Lymph nodes of the abdominal cavity and retroperitoneal space were not enlarged. There was no free fluid in the abdominal cavity.

CT scan of the abdomen, pelvis and retroperitoneal space in 3D modeling (Fig. 1 and 2) revealed an enlarged spleen and significant splenic vein malformation.

Elastometry of the liver was performed (ARFI-1.25 m/s), which corresponds to F1 on Metavir scale, spleen — 3.07 m/s, which means no pathological changes

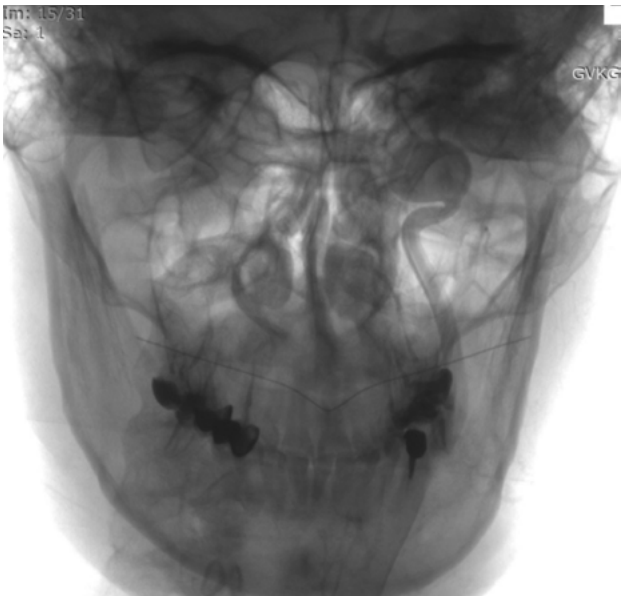

Fig. 4. Angiography demonstrating aneurysmal dilation of the left internal carotid artery. 1 — fusiform aneurysm of the left ICA (C1 segment according to Krylov V.V. classification) 4.5×30 mm in size

in the examined organs. When performing fibrogastroduodenoscopy (FGDS), varicose esophageal veins of 1–2 grade, insufficiency of cardia, superficial gastritis are determined.

Ultrasound examination of extracranial brachiocephalic arterial vessels revealed initial manifestations of atherosclerosis, deformation of the internal carotid arteries (ICA), on the left — pronounced complex local S-shaped tortuosity before the ICA entering the cranial cavity, linear blood flow rate (LBFR) increase up to 216 cm/s was registered, on the right — pronounced local S-shaped tortuosity of the medial segment of ICA, the increase in LBFR up to 228 cm/s was registered, the LBFR at the level of entrance into the cranial cavity was 85 cm/s, moderate curvature of vertebral arteries in the channels of the transverse processes of cervical vertebrae (Fig. 4–6).

Thus, the examination of the patient revealed three pathological conditions requiring surgical correction: splenomegaly with hypersplenism (thrombocytopenia, leukopenia), risk of rupture and bleeding, ASA with AVM and risk of aneurysm rupture, and left ICA aneurysm.

A multidisciplinary consilium with the participation of leading hospital specialists determined the neces-

Fig. 5. Angiography demonstrating aneurysmal dilation of the left internal carotid artery. 1 — fusiform aneurysm of the left ICA (C1 segment according to Krylov V.V. classification) 4.5×30 mm in size

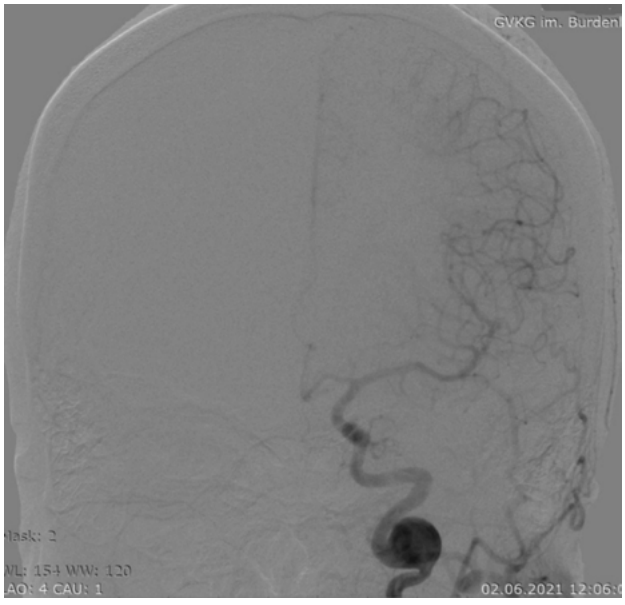

Fig. 6. Angiography demonstrating aneurysmal dilation of the left internal carotid artery. 1 — fusiform aneurysm of the left ICE (C1 segment according to Krylov V.V. classification) 4.5×30 mm in size

sity of surgical intervention for vital signs. Splenectomy was the first stage, taking into account the high risks of spleen rupture and intra-abdominal bleeding; the second stage was reconstruction of the left ICA.

Laparotomy and proximal splenic artery ligation were determined to be the optimal surgical treatment tactics. The idea of embolization was rejected due to the high risk of pancreatic necrosis and necessity of corpuscular resection of the pancreas, which could have been fatal. A vascular surgeon was included in the surgical team, and a CellSaver device was prepared for use.

On February 17, 2021 the patient underwent surgical intervention. Intraoperatively the presence of the enlarged spleen was confirmed, the venous vascular plexuses and pathological tortuosity from the spleen gate to the small pelvis were traced. In the area of the splenic artery branching from the tail of the pancreas to the spleen's gates there were two saccular arterial aneurysms up to 1.5 cm in diameter, the artery was ligated and stitched proximal to the aneurysms. Primary ligation of the splenic artery resulted in partial reduction of the spleen, thus reducing the total blood loss. It was determined that blood discharge from the splenic vein was carried out not only into the portal vein system, but also into the left renal and left iliac vein system due to portocaval communicants, which were ligated. The spleen weighing 2.5 kilograms with altered vessels was removed from the abdominal cavity (Fig. 3). Intraoperatively, 2 doses of thromboconcentrate were transfused, blood loss was 600 ml with the preparation.

Results. There were no peculiarities in the early postoperative period. The patient was discharged on the 9th day after the operation. Blood tests on the 2nd day showed normalization of the thrombocyte level (172×10^9/l) and leukocyte level (10.9×109/l), normocoagulation was registered.

According to the histological report, there was a pronounced plethora of the spleen, sharply pronounced plethora, dilation of arteries and veins with thinning of the vascular wall, cirrhosis of the liver.

In 3 months we performed surgical treatment (the second stage) of aneurysm of the left ICA. The right femoral artery was punctured. Catheterization and AG in the straight, lateral and oblique views of the left ICA were performed consecutively. The presence of a fusiform aneurysm of the left ICA (C1 segment according to Krylov V.V. classification) measuring 4.5×30 mm was confirmed. Endovascular implantation of a Leo+ flow-guiding stent at the level of the fusiform aneurysm of the left ACA was performed.

The control AG determines complete opening of the stent in the lumen of the left ICA with overlapping of the aneurysm. The intracranial arteries were traced throughout.

The patient was discharged in satisfactory condition on the 5th day after the operation. Thus, the chosen tactics appeared to be optimal.

Conclusion. Splenic artery aneurysms combined with splenic vein malformation and splenomegaly are extremely rare. High risk of aneurysm or splenic aneurysm rupture requires surgical intervention, and although this is a challenging task for the doctors, safe surgical treatment is possible with a carefully planned approach based on adequate exposure and control of the proximal and distal arteries.

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Information about the authors:

Alexandr P. Chuprina — MD, PhD, Chief surgeon of Main Military Medical Directorate of the Ministry of Defense of the Russian Federation, Moscow, Russia.

Sergei Yu. Polushin — MD, PhD, Head of the 2th surgery department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts**, **spolushin1@gmail.com**, ORCID: 0000-0001-9588-2701; eLibrary SPIN: 4973-1590; AuthorID: 875734

Kirill S. Zamsky — Head of the 26th surgery department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Evgeni V. Vinogradov — doctor of the 26th surgery department of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 31.01.2023

Mixed type plasmacytoma with multiple myeloma: therapy and prognosis

UDK 616.71-018.46-006.447
DOI: 10.53652/2782-1730-2023-4-1-55-62

Tutaeva V.V., Rukavitsyn O.A., Ignatieva E.V.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. Extramedullary and paraskeletal plasmacytomas are not common and are usually one of the possible complications of multiple myeloma. This variant of the disease is more aggressive, less responsive to therapy, and recurs more often than conventional multiple myeloma. In our work, we described two cases of aggressively ongoing multiple myeloma with a mixed plasmacytic variant diagnosed at the time of setting the diagnosis. In both cases, a rapid progressive course was observed despite the wide range of both the newest drugs and the classical chemotherapy drugs used during treatment. Thus, this variant of the disease remains most often resistant to the therapy, with an unfavorable prognosis, and requires further study and improvement of the treatment approach to improve outcomes.

Keywords: paraskeletal, extramedullary, plasmacytoma, multiple myeloma, therapy.

Introduction. In the population, multiple myeloma (MM) accounts for 1% of all cancers and 15% of hematologic malignancies. This disease is characterized by the proliferation of a clone of plasma cells whose growth and proliferation are regulated by the microenvironment. However, in about 1/3 of cases plasma cells manage to minimize the impact of the microenvironment, which leads to the formation of plasmacytomas. Despite the importance of the problem at the moment there are no data in the literature on control studies on MM in combination with plasmacytomas.

In this work, the data on two clinical cases of the onset, course, therapy and outcome of the disease in patients with highly aggressive MM combined with mixed types of plasmacytomas have been presented.

Clinical case № 1. A 38-year-old male patient started to experience pain in the cervical spine and numbness of the upper and lower extremities in August 2021. Magnetic resonance imaging (MRI) revealed a pathological fracture of the 7th cervical vertebra with almost complete replacement of bone tissue by a soft tissue component.

On September 01, 2021, the patient underwent surgery to remove the tumor with installation of telescopic prosthesis. According to histological and immunohistochemical (IHC) tests, the soft tissue mass was identified as a plasmacytoma.

On September 29, 2021 the patient was admitted to MMCH named after N. N. Burdenko. On admission he had intense pain in the cervical and lumbosacral spine, right shoulder and impaired mobility. Computed tomography (CT) revealed multiple soft tissue masses in all parts of the spine of varying sizes with sprouting into the spinal canal and compression of the spinal cord. The maximum size of the mass was that of the pelvis with sprouting into the gluteal region and retroperitoneal space.

X-ray of the right shoulder showed a pathological fracture in the growth of the soft tissue component. Radiation therapy was performed on the body of the 4th lumbar vertebra and the left iliac bone (total focal doses (TDF) of 30 Gy) in order to reduce the intensity of the pain syndrome. The myelogram showed 7.4% plasma cells. Immunochemical analysis of proteins revealed monoclonal secretion of Gκ (9.3 g/L) in serum and Bence-Jones protein κ (excretion with urine is 0.35 g/day, serum 3.1 g/L), β2-microglobulin 2.93 mg/L. No genetic abnormalities were detected by FISH test.

Final diagnosis: MMGκ, BJκ, grade IIIA, multiple plasmacytomas and bone-destructive lesions. From October to December 2021, 2 cycles of VCD-Dara (daratumumab, Cyclophosphan, Velcade, dexamethasone) were administered. After the 1st cycle, there was a positive effect in the form of decreased intensity of pain in the right shoulder and lumbosacral spine, and improved mobility. However, by the end of the 2nd cycle, a pronounced negative dynamics was observed. A CT scan showed an increase in the soft tissue component at the level of the 7th cervical vertebra up to 60×35 mm with compression of the spinal cord at this level. Radiation therapy was performed on the mass, and the 2nd line therapy was started according to the KRD scheme (carfilzomib, lenolidamide, dexamethasone). Against the background of the therapy, there was further negative trend, so in January 2022 we started the 1st cycle of the 3rd line D-PACE therapy (dexamethasone, doxorubicin, Cyclophosphan, etoposide, cisplatin). At the time of the first 2 cycles, positive dynamics in the form of decreased pain intensity, resolution of neurological symptoms, and recovery of mobility were observed. Before the start of the 3rd cycle, 2 soft tissue neoplasms were found growing subcutaneously on the patient's head in the parietal region. From March to June 2022, 3 more cycles of D-PACE with pomalidomide (4 mg/day, days 1 to 21) were done. Against the background of which, the condition with pronounced positive dynamics, resolution of the scalp plasmacytomas, reduction of the intensity of pain syndrome were noted. In July 2022, immunochemical analysis of blood and urine proteins was performed, full immunochemical remission was stated, however according to PET/CT (PET — positron emission tomography) the reduction of plasmacytomas size did not exceed 50%.

Thus, according to the criteria of IMWG therapy efficacy evaluation, only stabilization of the process was achieved. The patient clinically completely resolved neurological symptoms, restored mobility, the pain syndrome occurred only during prolonged physical activity. Due to the development of grade III-IV neutropenia after multiple cycles of polychemotherapy, autologous bone marrow transplantation was not an option at the end of the last D-PACE + pomalidomide cycle. In October 2022, the patient received PD maintenance therapy (pomalidomide 4 mg/day, dexamethasone). In November, the patient's condition abruptly deteriorated, with appearance of massive soft tissue masses in the sternum, supraclavicular areas and fracture area of the right shoulder. Blood leukopenia (1.9×10^9/l), anemia (75 g/l), thrombocytopenia (70×10^9/l). A CT scan showed progressive growth of soft tissue masses of the spine, pelvis, and skull. Taking into account the history of therapy, since December 2022, the therapy with pomalidomide (4 mg/day, days 1-21) and Venclexta (100 mg/day for one week, then the dose was increased to 200 mg) was started. After three weeks of therapy, there was a 50% reduction in the size of soft tissue conglomerates in the manubrium of sternum and supraclavicular areas, the size of the conglomerate in the right shoulder fracture area — without dynamics. According to immunochemical analysis, complete immunochemical remission was maintained. Blood anemia and thrombocytopenia of grade I, leukocyte level was normal. After 6 weeks of therapy (February 2023), the condition with

negative dynamics: growth of soft tissue masses, increase of three-lineage cytopenia, bilateral massive hydrothorax. Pleural puncture was performed, pleural fluid contained a large number of plasma cells. Progression of the disease was stated. The prognosis is unfavorable.

Clinical case №2. A female patient, 51 years old, who was diagnosed with ovarian masses of 110×95×100 mm on the left and 110×80×90 mm on the right during a physical examination in April 2021.

On May 13, 2021, a puncture biopsy was performed at the gynecological department of MMCH named after N. N. Burdenko. Histological and IHC tests revealed a plasmacytoma. On May 12, 2021, the patient fell down and was diagnosed with a comminuted fracture of the upper third of the humerus. On May 18, 2021, osteosynthesis surgery was performed. CT scan revealed volumetric masses in both ovaries; no other pathological foci were detected. Plasma cells in myelogram were 15.3%. Immunochemical analysis of proteins: serum monoclonal Gκsecretion 43.2 g/l, Bence-Jones protein κsecretion not detected, ι2 microglobulin 9.7 mg/l.

FISH examination revealed the following genetic abnormalities: monosomy of the TR53 gene locus, t(4;14), t(2;8)(p11;q24). Diagnosis: MM, Gκ grade IIIA.

In June-July 2021, 3 cycles of chemotherapy on the VCD regimen were administered. Immunochemical testing revealed a 25% decrease in paraprotein, which corresponds to a minimal response to the ongoing therapy. After the end of the 3rd cycle, negative dynamics in the form of intense pain and swelling of the right shoulder due to growth of the soft tissue component. Radiation therapy was administered to plasmacytoma area of the right humerus (TDF 40 Gy). Pain syndrome resolved.

In August-September 2021, 2 cycles of 2nd line KRD therapy were administered. After 2 cycles, further negative dynamics in the form of right shoulder enlargement and increase of pain syndrome was observed. Radiation therapy was performed on the right shoulder (8 Gy) for pain relief. In October-November 2021, a third line of therapy, 2 cycles of Darzalex-DCEP (daratumumab, dexamethasone, cisplatin, Cyclophosphan, etoposide) was administered. According to immunochemical study, very good partial remission was achieved, however, soft tissue masses decreased in varying degrees depending on localization: less than 50% — plasmacytoma of the shoulder and more than 50% — plasmacytomas of the pelvic region.

Dara-DCEP Cycle 4 was completed in February 2022. According to the immunochemical analysis, a very good partial remission was maintained. During the recovery period after the end of the 4th cycle, negative dynamics in the form of growth of a soft tissue mass of the right shoulder and the appearance of a pronounced pain syndrome were observed.

In March 2022 the therapy was started: isatuximab, pomalidomide, dexamethasone, bendamustine. In April, radiation therapy was carried out for plasmacytoma of the right shoulder (TDF 30 Gy). Despite the conducted therapy, negative dynamics intensified in the form of increased pain in the lumbar spine, right shoulder, appearance of multiple soft tissue foci in the subcutaneous fatty tissue of the anterior abdominal wall, back, plasmacytoma growth of the right shoulder with transition to the scapula area.

The first cycle of HyperCVAD was performed in May 2022 to control progression. No effect. Pain syndrome, growth of soft tissue masses, and multiple organ failure increased.

In June 2022 the patient died as a result of the progression of the main disease.

Discussion and literature review. According to the literature, there are 2 types of soft tissue neoplasms (plasmacytomas) combined with MM: extramedullary (with hematogenous cell spread and formation of new foci exclusively in soft tissues) and paraskeletal (characterized by tumor spread from foci of bone lesions) [1].

There are several modifications of these definitions in different sources, but it should be noted that in clinical practice, if a patient has both types of plasmacytomas, it is often difficult to understand whether a given paraskeletal plasmacytoma is an extramedullary cutoff or an independent entity that has appeared, so this classification is somewhat relative.

The detection rates of extramedullary and paraskeletal plasmacytomas in patients at the time of diagnosis are 1.7–4.5 and 7–34.4%, respectively [2]. When the disease recurs, the incidence of extramedullary plasmacytomas increases from 3.4 to 10%, while the incidence of paraskeletal plasmacytomas remains unchanged.

The most frequently involved areas in the development of extramedullary plasmacytomas: skin (single or multiple subcutaneous tumors), liver, pleura, mammary glands, lymph nodes, central nervous system (CNS). Paraskeletal plasmacytomas mainly affect the vertebrae, ribs, sternum, and skull.

Extramedullary plasmacytomas are associated with cytogenetic abnormalities, resistance to ongoing therapy, and a worse prognosis compared to the paraskeletal variant.

Tumor characterization in extramedullary plasmacytoma. Typically, plasma cells of extramedullary plasmacytoma show immature or plasmoblast-like morphology. In contrast, cells from parasternal plasmacytomas are more mature and morphologically are plasmocytes. Various studies have been described in the literature comparing cytogenetic abnormalities in the cells that make up plasmacytomas and bone marrow plasma cells in patients with MM. The data from these studies is inconsistent, yet it has not been reliably demonstrated that there are more neg-

Extramedullary plasmacytomas are associated with cytogenetic abnormalities, resistance to ongoing therapy, and a worse prognosis compared to the paraskeletal variant

ative genetic abnormalities detected in extramedullary plasmacytoma cells compared with plasma cells in bone marrow or in paraskeletal plasmacytomas. In 2020, the study of Paiva B. et al. was published, where the genetic heterogeneity of cells from patients with MM and extramedullary plasmacytomas was investigated using the latest methods. The idea of the study was as follows: although MM is characterized by proliferation of clonal plasma cells in the bone marrow, there are circulating tumor cells that managed to avoid interaction with the tumor microenvironment and separated from the pool of cells in the bone marrow or extramedullary plasmacytoma. By isolating these cells and comparing their cytogenetic characteristics with bone marrow plasma cells and extramedullary plasmacytomas, it was planned to find differences that would help in understanding the reasons for the aggressive course of the disease associated with extramedullary soft tissue masses. Samples from 53 patients (37 initially diagnosed and 16 at the time of disease recurrence) were used. Methods such as next-generation flow cytometry and whole-genome sequencing were used to analyze the cells. According to the study, the mutations detected in circulating tumor cells were 92% consistent with those found in bone marrow plasma cells and plasma cells. The genetic characteristics of the 3 samples obtained from three different anatomical regions were similar.

Thus, no additional changes in the genome of tumor cells circulating in the bloodstream were identified that could explain their ability to detach from the pool of bone marrow or plasmacytoma cells and form new distant metastases, making the disease course associated with extramedullary plasmacytomas aggressive and resistant to therapy.

In our clinical cases, we performed only FISH tests to determine the presence of prognostically unfavorable mutations in patients. No such mutations were found in the 1st case, whereas they were present in the 2nd case. The study of B. Paiva et al. suggests "genetic uniformity" of pathological cells in the bone marrow, plasmacytes and bloodstream, however, during therapy we observed asymmetrical growth of masses at recurrence and their asymmetrical reduction in different anatomical areas in case of a positive response to therapy. In our cases in both patients the most resistant were plasmacytomas in the area of humeral bone fractures. While other soft tissue masses decreased on therapy, in this area the reduction process was either absent or extremely poor (according to the literature, the trigger for the development of extramedullary plasmacytomas may be surgery or trauma/fracture). This may be due to the presence of as yet unidentified genetic differences or the existence of different tumor clones with varying degrees of sensitivity to therapy in different anatomical areas of the body.

Evaluating the effectiveness of therapy. Unified criteria for evaluating the effectiveness of therapy have been developed by IMWG. The percentage of reduction of paraprotein levels in the blood and urine necessary to achieve partial remission and very good partial remission is defined. Soft tissue masses (plasmacytomas) must decrease by more than 50% to achieve partial remission. The criterion for achieving a very good partial remission has not been defined. Blade J. et al. suggested defining the achievement of a very good remission as a combination of immunochemical criteria and complete resolution of the plasmacytomas. It is recommended to evaluate the effectiveness of therapy after 3 months from its initiation. In the absence of achieving a partial remission (immunochemical parameters, the size of the plasmacytes) it is necessary to change the line of therapy or conduct radiation therapy. After remission is achieved, control instrumental examinations (MRI, PET/CT, CT) should be performed at least once a year.

It is important to note another feature that makes it difficult to assess the effectiveness of the therapy in patients with soft tissue masses. There is evidence that the achievement of complete, very good or partial remission according to immunochemical criteria often does not coincide with the degree of remission achieved based on the size of soft tissue masses. This phenomenon has been described in patients treated with carfilzomib, thalidomide, and bortezomib.

In both cases described, the achievement of complete and very good partial immunochemical remission in patients was combined only with stabilization and then progression of soft tissue masses. This situation occurred after therapy with different drugs: daratumumab, bortezomib, ixosumib, carfilzomib. Based on the IMWG response criteria for the size of plasmacytomas, none of our patients achieved even partial remission during the entire period of therapy.

Thus, questions arise: what indicator in these patients should be taken as the main criterion for evaluating the response to the ongoing therapy, and what exactly is the main prognostic criterion in this kind of patients?

Prognosis of the course of the disease. The presence of a soft tissue component at any stage of the disease has been shown to be associated with a pronounced reduction in progression-free survival and overall survival. Studies have found that patients with paraskeletal plasmacytomas who have undergone autologous stem cell transplantation have the same duration of progression-free survival and overall survival as patients without the presence of plasmacytomas. Based on these data, we can assume that the high-dose melphalan used in autologous stem cell transplantation can overcome the negative factor introduced by soft tissue masses in the prognosis of the disease course. Patients with extramedullary type of plasmacytoma even after performing autologous stem cell transplantation have a much shorter 3-year recurrence-free incidence and overall survival compared to patients without plasmacytoma. According to the literature, tandem autologous stem cell transplantation does not increase overall survival in patients with both types of plasmacytoma. The lowest survival rate is in patients with CNS involvement (less than 3 months).

Principles of therapy. As already mentioned, the course of the disease with soft tissue masses has a more aggressive character and is associated with a lower overall survival rate. These facts certainly influence the choice of therapy. Unfortunately, most published studies include both types of plasmacytomas, describing them with the single term "extramedullary lesions", thus not allowing for a more accurate analysis of the effectiveness of the therapy.

In spite of this, certain conclusions can be made. First, alkylating agents are an effective first-line therapy, especially high-dose melphalan in the presence of paraskeletal plasmocytes. Varettoni M. et al. [4] showed that after treatment with melphalan 72% of primary patients with plasmacytomas achieved at least partial remission. Similar data were presented by Wu R. et al. [3], although the percentage of those who achieved partial remission was lower — 50-52%. Secondly, the data on the efficacy of therapy with the latest drugs are contradictory. Carfilzomib has shown limited efficacy in patients with recurrent MM and plasmacytomas, especially in the extramedullary variant of soft tissue masses. The efficacy of ixazomib is unclear. At the same time, marizomib is able to penetrate the blood-brain barrier, which makes it effective in cases of CNS lesions. Data on the effectiveness of immunomodulatory drugs (thalidomide and its derivatives) is also limited. The Mayo Clinic [5] published findings that 4 (31%) of 13 patients with extramedullary plasmacytomas achieved complete (2 patients) and partial (2 patients) remission after therapy with pomalidomide and low-dose dexamethasone. The opposite data were obtained by Catalan Myeloma Group [6]. After providing similar therapy to 21 patients with extramedullary plasmacytomas, only 2 achieved partial remission. Adding isatuximab to pomalidomide and dexamethasone (Isa-Pd) increases the total number of patients responding to therapy up to 50 percent, compared with 10 percent for dexamethasone and pomalidomide therapy [7]. Data on the efficacy of daratumumab is also limited, with only one study showing an overall response rate of 17% to monotherapy with the drug in patients who had not previously used monoclonal antibodies. Recently, findings suggesting ineffectiveness of daratumumab monotherapy in patients with relapsed myeloma, including variants with plasmacytic development, have been published.

Interestingly, the use of meflufen achieves a good response in patients with both types of plasmacytomas. According to the literature, the overall response with meflufen therapy is 23%, the duration of the effect obtained is similar in patients with and without plasmacytomas [14]. Selinexor and dexamethasone showed efficacy in 31% of cases, but in this study only 16 of 27 patients with MM had plasmacytomas [8].

Venetoclax can be added to therapy if recurrence develops in patients with a soft tissue component and the presence of t(11;14).

Thus, the therapy of choice in patients with paraskeletal plasmacytomas is a combination of bortezomib, melphalan, prednisolone and daratumumab (Dara-VMP) or Revlimid, bortezomib and dexamethasone (RVD) [9]. Autologous stem cell transplantation is recommended to consolidate the effect. Urgent radiation therapy should be indicated in case of spinal cord compression or patients with severe pain syndrome against the background of massive soft tissue lesions, as well as those with persisting plasmacytomas after completion of systemic therapy. For patients with extramedullary form of plasmacytomas, the 1st line therapy is the so-called lymphoma-like cycles of PACE, DCEP, in combination with which the use of new drugs such as lenalidomide, carfilzomib, bartizar, pomalidomide followed by tandem transplantation or allogeneic transplantation with reduced doses of conditioning (Allo-RIC) is recommended.

Despite the fact that it is possible to obtain a response, early progression is typical for these patients. Therefore, a short intensive induction is recommended — 2–3 cycles followed by tandem autologous transplantation or Allo-RIC at short intervals. In case of tandem transplantation, the interval between procedures should be as short as possible. However, the EBMT Registry recently provided data suggesting that there is no advantage in performing tandem transplantation over single transplantation in patients with extramedullary variant plasmacytomas. Further studies are needed to determine the best approach to therapy in these patients.

The prognosis of patients with recurrence accompanied by progressive plasmacytoma growth is usually

The variant of multiple myeloma with soft tissue components (plasmacytomas) over the last decade is occurring more and more often. The problem of therapy of this variant of the disease, evaluation of the effectiveness of current therapy, the search for new combinations of drugs, both the latest and classical chemotherapy, capable of leading to a maximum effect in the treatment, is more relevant than ever. Further clinical and laboratory basic research is required to better understand the nature of the disease and approaches to its therapy

extremely unfavorable [10, 11], since before disease progression patients usually received 2–3 lines of therapy including immunomodulators, the most effective therapy options being DCEP, PACE, Dexa-BEAM. The response rate is about 50%, with a short duration of response of no more than 4 months. If possible, high-dose therapy (autologous or allogeneic bone marrow transplantation) is suggested [13, 15]. In the case of recurrence in patients who had a good response to bortezomib, the use of proteasome inhibitors is recommended [12].

In the cases we described, each patient had at least 3–4 lines of therapy. Relatively long-term positive effect in the first case was achieved only after adding pomalidomide to the D-PACE regimen. It is also interesting to note the moment of stabilization and even improvement of the patient's condition within 6 weeks on the background of pomalidomide in combination with venetoclax, despite the absence of a formal indication for its use in the form of translocation [11, 14]. In the second case there is a highly aggressive course of the disease with the use of 5 lines of therapy. Only the Dara-DCEP therapy achieved a very good partial remission according to the immunochemical analysis. However, the absence of reaching even a partial remission when assessing the size of the plasmacytomas and the rapid progression of the disease indicate, in general, the ineffectiveness of the therapy.

Conclusion. The variant of multiple myeloma with soft tissue components (plasmacytomas) over the last decade is occurring more and more often. The problem of therapy of this variant of the disease, evaluation of the effectiveness of current therapy, the search for new combinations of drugs, both the latest and classical chemotherapy, capable of leading to a maximum effect in the treatment, is more relevant than ever. Further clinical and laboratory basic research is required to better understand the nature of the disease and approaches to its therapy.

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Information about the authors:

Oleg A. Rukavitsyn — MD, ScD, professor, Head of Haematology Center of Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Viktorija V. Tutaeva — MD, PhD, haematologist, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, perestroika-1@yandex.ru**, ORCIDID: 0000-0002-2840-2963

Elena V. Ignatieva — MD, haematologist, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 08.02.2023.

Neoadjuvant immunotherapy in the treatment of squamous cell carcinoma of the head and neck

UDK 616.71-018.46-006.447
DOI: 10.53652/2782-1730-2023-4-1-63-71

Tsapir A.V.[1], Pitkevich M.Yu.[1], Smolin A.V.[1], Kosyrev V.Yu.[2,3], Vologdin A.A.[4]

[1] *Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia*
[2] *Department of Oncology at the N.V. Sklifosovskiy Institute of Clinical Medicine of the Sechenov University, Moscow, Russia*
[3] *Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia*
[4] *Branch of the Federal State Budgetary Military Educational Institution of Higher Education "Kirov Military Medical Academy" of the Ministry of Defense of the Russian Federation, Moscow, Russia*

Abstract. Head and neck tumors are among the ten most common neoplasms both in the world and in Russia [1]. In 64% of cases, squamous cell carcinoma of the head and neck is first diagnosed at the stage of a locally spread process. The emergence of new equipment for radiation therapy, new irradiation techniques such as VMAT, IMRT, better visualization, positioning of the patient and the emergence of new methods of drug treatment have allowed to increase the duration and quality of life of patients. However, even with such treatment approaches, the 5-year overall survival rate is only 50% [11]. The effectiveness of immunotherapy in patients with advanced squamous cell carcinoma of the head and neck and unsatisfactory results of surgical treatment of operable stages have set the ground for active study of neoadjuvant therapy [11]. In the available literature, we found that neoadjuvant immunotherapy for squamous cell carcinoma of the head and neck has already demonstrated its effectiveness in preliminary clinical studies, which makes it a promising direction for further study and implementation in the daily practice of an oncologist

Keywords: squamous cell carcinoma, head and neck cancer, immunotherapy, neoadjuvant therapy, HPV, P-16, PD-1, PD-L1.

Introduction. Head and neck tumors (HNT) are in the top ten most common neoplasms both in the world and in Russia. In Russia in 2020, the incidence of HNT was (per 100 thousand people): for diseases of the oral cavity — 30.7, for diseases of the pharynx — 13.1, for diseases of the larynx — 30.8 [1].

Histologically the majority (90%) of diagnosed HNT are squamous cell tumors. The main risk factors for the development of squamous cell carcinoma of the head and neck (SCCHN) are tobacco and alcohol abuse, and human papillomavirus (HPV) infection.

Smoking tobacco products remains a major risk factor for SCCHN, and there is a clear increase in risk in patients with a higher frequency and longer duration of tobacco use [2, 3, 4]. Various studies have shown that 26% to 56% of patients smoke at the time of SCCHN diagnosis, especially patients with laryngeal cancer [5, 6, 7, 8]. It is important to note that smoking history, in addition to tumor stage and localization, is one of the most relevant prognostic clinical factors in patients with SCCHN. Tobacco use is associated with a greater history of comorbidities and other possible types of malignancy, which leads to higher mortality among these patients. Several studies have shown that the risk of mortality is approximately twice as high in smokers or former smokers compared to nonsmokers [5, 7, 9]. In addition, it has long been known that patients with SCCHN who continue to smoke while receiving radiation therapy have a worse prognosis compared with patients who quit smoking before treatment [10, 11]. Smoking also worsens prognosis in HPV-associated patients; they have higher rates of recurrence and distant metastases compared to nonsmokers [12, 13]. Also, tobacco use may have some immunosuppressive effect on the tumor microenvironment in patients with SCCHN and therefore reduces the possible efficacy of checkpoint inhibitor (CI) drugs [14]. In the CheckMate-141 study, which led to approval of nivolumab in patients with platinum-resistant disease, the effect of treatment with the anti-PD-1 inhibitor was less in the smoker subgroup compared with the nonsmoker subgroup. Another retrospective analysis also showed that the outcome of patients-smokers who received checkpoint inhibitors was worse compared with those who never smoked. It is important to note that this was true only for HPV-negative patients, and there was no statistically significant difference between smokers and nonsmokers with HPV-positive tumors [15].

The latest version of TNM classification divides oropharyngeal tumors into p16-positive and p16-negative due to significant differences in prognosis in these groups of patients.

For T1-2N0-1M0 p16-positive tumors stage I is defined, for T1-2N2M0 and T3N0-2 spread — stage II, for T1-3N0-3M0 and T4N0-3M0 — stage III. For p16-positive tumors, stage IV disease is defined only if distant metastases are present [16]. Such division of classifications is caused by a significant difference in prognosis of the disease in these two groups of patients. HPV-associated head and neck squamous cell carcinoma differs in several parameters [17, 18]. These patients tend to be younger, without smoking or alcohol abuse.

The overall incidence of HPV-positive oropharyngeal cancer is increasing, while the incidence of HPV-negative cancer is decreasing. Presumably 45-90% of cases of oropharyngeal squamous cell carcinoma are HPV-positive [19].

Patients with locally spread HPV-positive SCCHN have better overall survival (OS) and progression-free survival (PFS) compared with HPV-negative tumors. A meta-analysis of 18 studies involving 4,424 patients with SCCHN showed that patients with both HPV-positive and p16-positive tumors had better 5-year survival and recurrence-free survival compared with patients with HPV-negative/r16-negative, HPV-positive/r16-negative and HPV-negative/r16-positive tumors. However, patients who were HPV-negative/p16-positive had a better 5-year OS compared with p16-negative (regardless of HPV status) patients [20].

HPV-16 accounts for approximately 90% of SCCHN cases in HPV-positive patients. HPV-associated squamous cell carcinoma of the head and neck is localized in the lingual and palatine tonsils, which are the lymphoepithelial organs that represent the first line of defense against oral infections. Oncogenic HPVs express foreign viral antigens, but have learned to avoid the body's immune response. The defense mechanisms of HPV have been studied by many authors. Lyford-Pike S. and his research team evaluated PD-L1 expression in the tonsil tissue of patients not infected with HPV and found localized PD-L1 expression in the reticular epithelium of the deep crypts.

Interestingly, PD-L1 expression was not detected in the superficial epithelium of the tonsils. This suggests that the reticular epithelium of the tonsillar crypts may represent a different immune microenvironment compared to the superficial epithelium. The deep invagination of the crypts of the tonsils makes them susceptible to the accumulation of bacteria and foreign bodies.

Thus, during HPV infection, resident lymphohistiocytes are chronically exposed to high concentrations of a foreign antigen. Therefore, it is possible that even in the absence of overt chronic tonsillitis, basal immunity activation controlling PD-L1 expression continues in the crypts. Given the selective expression of PD-L1 in the deep crypts, this region may represent an immune-privileged area in which the effector function of virus-specific T cells is suppressed, thereby facilitating evasion of the immune response during initial HPV infection and subsequent malignant transformation induced by the virus [21].

Neoadjuvant immunotherapy for SCCHN is promising for a number of reasons. Incorporating immunotherapy into the treatment process may reduce the risk of local recurrence and distant metastasis, thereby improving PFS and OS. The possibility of potentially de-escalating adjuvant therapy and reducing the amount of surgical treatment required is also of interest. The investigational use of neoadjuvant immunotherapy also offers an ideal platform for correlational studies to assess whether predictors of response to immunotherapy can be found

The tumor suppressor P16INK4A (p16) regulates the cell cycle by binding to cyclin D1 CDK4/CDK6 and thereby blocking phosphorylation of the Rb protein.

Expression of the HPV E6 and E7 oncogenes inactivates the tumor suppressor proteins p53 and pRb, respectively, which are frequently mutated in mucosal squamous cell carcinoma associated with tobacco. Inactivation of p53 and pRb promotes genomic instability and cancer development and is responsible for up-regulation of p16 protein expression, a reliable surrogate marker for the presence of HPV DNA in these tumors [22]. Genetic profiling of HPV-positive cancers has demonstrated that they are genetically distinct from HPV-negative SCCHN. The efficacy of checkpoint inhibitors in HPV-positive patients with SCCHN has been demonstrated in many clinical trials [22].

Checkpoint inhibitors are antibodies that target cytotoxic T lymphocyte antigen 4 (CTLA-4), PD-1, and programmed cell death receptor ligand-1 (PD-L1) and thereby block inhibition of the immune response by the tumor and its microenvironment. These drugs have improved outcomes in patients with numerous different tumor types and have the potential to improve survival rates in patients with metastatic disease [23, 24, 25, 26)]. The results of some phase I trials have shown that higher PD-L1 expression in tumor cells or tumor cells and immune cells together correlates with a higher frequency of response to checkpoint inhibition [27, 28]. This has made PD-L1 the most important and widely used prognostic biomarker for immunotherapy [29, 30, 31].

Studies have shown that the PD-1:PD-L1 axis is strongly associated with HPV-positive rather than HPV-negative PRGS [32, 33]. PD-1 is expressed on effector T cells in both HPV-positive and HPV-negative tumors, but the level of expression appears to be elevated in HPV-positive SCCHN, suggesting that PD-1 expression on cytotoxic T cells is relevant and may play an important role, especially in HPV- SCCHN.

In 64% of cases, SCCHN is first diagnosed at the stage of locally disseminated process. For this type of dissemination, the optimal treatment option is independent radiotherapy (RT)/chemoradiotherapy (CRT) or extensive surgery followed by adjuvant RT/CRT [11]. However, even with this aggressive approach, the 5-year OS is only 50% [34].

The effectiveness of immunotherapy in patients with disseminated SCCHN and unsatisfactory results of surgical treatment of operable stages have set the stage for an active study of neoadjuvant therapy for SCCHN [11].

The established efficacy of immune checkpoint inhibitors in recurrent and metastatic diseases has generated widespread interest in their neoadjuvant use.

In the available literature, we found multiple justifications for prescribing anti-PD-1 drugs in the neoadjuvant regimen for the treatment of SCCHN.

Neoadjuvant immunotherapy for SCCHN is promising for a number of reasons. Incorporating immunotherapy into the treatment process may reduce the risk of local recurrence and distant metastasis, thereby improving PFS and OS. The possibility of potentially de-escalating adjuvant therapy and reducing the amount of surgical treatment required is also of interest. The investigational use of neoadjuvant immunotherapy also offers an ideal platform for correlational studies to assess whether predictors of response to immunotherapy can be found [35].

Liu J. and colleagues have suggested that neoadjuvant immunotherapy may contribute to systemic immunity, which may be effective in eliminating potential residual tumor cells after surgical removal of the primary tumor. Their studies in mice proved that neoadjuvant immunotherapy in combination with surgery is superior to surgical treatment in combination with adjuvant immunotherapy in the treatment of locally spread tumor process [36, 37].

KEYNOTE-048: OB (**CPS≥20**) Pembrolizumab vs EXTREME				
	Events	HR (95% CI)	p	Median OS, months (95% CI)
Pembro mono	62%	0,61	0,0007	12,3 (10,8-14,9)
EXTREME	78%	(0,45-0,83)		10,3 (9,0-11,5)

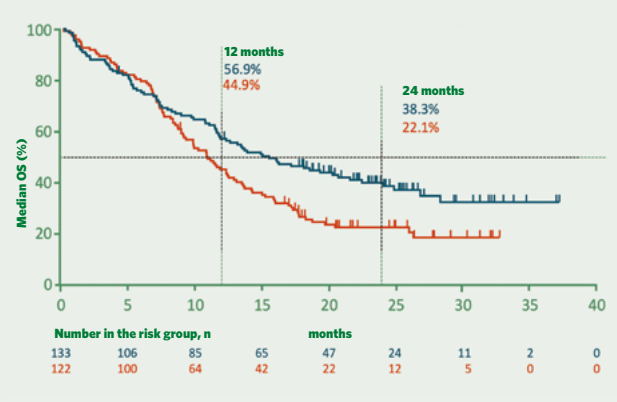


Fig. 1. Overall survival rates in patients with CPS≥20

KEYNOTE-048: OB (**CPS≥1**) Pembrolizumab vs EXTREME				
	Events	HR (95% CI)	p	Median OS, months (95% CI)
Pembro mono	69%	0,78	0,0086	12,3 (10,8-14,9)
EXTREME	81%	(0,64-0,96)		10,3 (9,0-11,5)

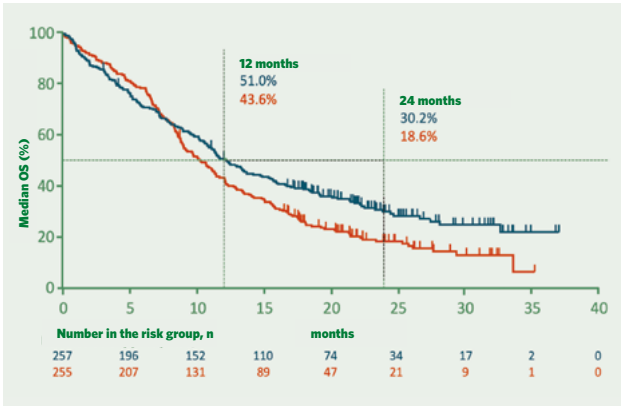


Fig. 2. Overall survival rates in patients with CPS≥1

Blockade of PD-1 immune checkpoints has become the standard first- and second-line palliative therapy for recurrent or metastatic SCCHN regardless of PD-L1 status [38–42].

In the Keynote-048 phase 3 clinical randomized trial, in which participants were stratified by PD-L1 expression, p16 status, and general medical status, they were randomly assigned (1:1:1) into several groups: pembrolizumab in monotherapy; pembrolizumab plus a platinum drug and 5-fluorouracil (pembrolizumab with chemotherapy (CT)); and cetuximab plus a platinum drug and 5-fluorouracil (cetuximab with CT).

Between April 20, 2015, and January 17, 2017, 882 participants were randomized: to receive pembrolizumab alone (n=301), pembrolizumab with CT (n=281), and cetuximab with CT (n=300); of these, CPS≥1 occurred in 754 (85%) and CPS≥20 occurred in 381 (43%).

In a second interim analysis, pembrolizumab in monotherapy improved OS compared with cetuximab with CT in the CPS≥20 (median 14.9 months versus 10.7 months [HR] 0.61 [95% CI 0.45-0.83], p=0.0007) and CPS≥1 (median 12.3 versus 10.3 months [HR] 0.78 [95% CI 0.64-0.96], p=0.0086) groups. Pembrolizumab with CT improved the OS compared with cetuximab with CT in the general population (13.0 months vs. 10.7 months [HR] 0.77 [95% CI 0.63-0.93], p=0, 0034) at the second interim analysis in the CPS≥20 group (median 14.7 vs 11.0 [HR] 0.60 [95% CI 0.45-0.82], p=0.0004), CPS≥1 (median 13.6 vs 10.4 [HR] 0.65 [95% CI 0.53-0.80], p<0.001) at the final analysis.

Based on observed efficacy and safety, pembrolizumab both in monotherapy (at CPS≥20) and in combination with platinum and 5-fluorouracil proved to be a suitable first-line treatment for recurrent or metastatic SCCHN (Figure 1-3) [39].

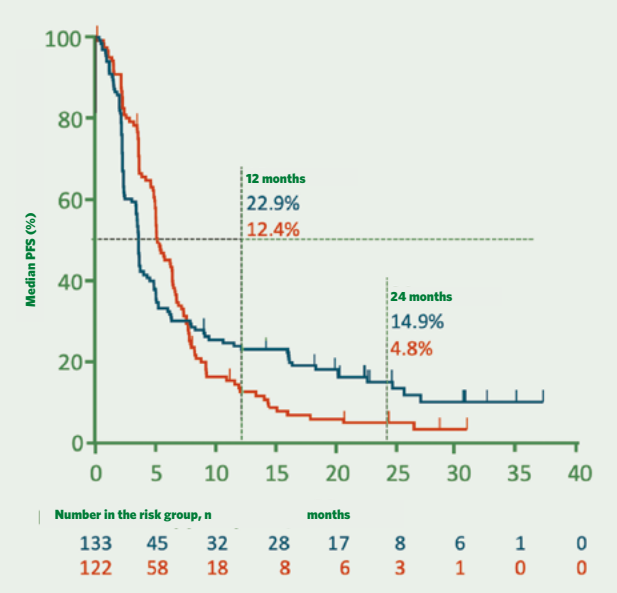
Uppaluri R. and a research team studied the effect of neoadjuvant therapy with pembrolizumab in patients with operable SCCHN. The authors reported a 44% pathomorphologic response rate after a single injection of pembrolizumab and a 16.7% recurrence rate in the first year after surgery [43].

The study conducted by the researchers included 36 patients. Pembrolizumab (200 mg) was administered to patients in neoadjuvant mode 2-3 weeks before surgery. Postoperative RT/CRT was also planned. Patients with risk factors (positive resection margin and/or extranodal spread) received pembrolizumab in the adjuvant regimen.

One of the criteria for the effectiveness of neoadjuvant treatment was the evaluation of the degree of pathologic tumor response (pTR), which was quantified as the ratio of residual tumor bed, necrosis, horny masses and giant cells/histiocytes to total tumor bed area: pTR-0 (<10%), pTR-1 (10-49%) and pTR-2 (≥50%). Additional primary endpoints were pTR-2 among all patients and one-year recurrence rate in patients with high-risk factors. Correlations of baseline PD-L1 and T-cell infiltration with pTR were assessed.

No grade 3-4 adverse events were noted during neoadjuvant therapy. There were also no surgical treatment delays. pTR-2 was detected in 8 (22%) patients, pTR-1 in 8 (22%) patients. The one-year recurrence rate among the 18 patients with high-risk pathology was 16.7% (95% CI: 3.6-41.4%). pTR≥10% correlated with baseline PD-L1 tumor levels, immune cell infiltration, and IFN-γ activity.

KEYNOTE-048: ВБП (**CPS≥20**) Pembrolizumab vs EXTREME				
	Events	HR (95% CI)	p	Median OS, months (95% CI)
Pembro mono	86%	0,99	0,5	3,4 (3,2-3,8)
EXTREME	91%	(0,75-1,29)		5,0 (4,8-6,2)



KEYNOTE-048: ВБП (**CPS≥1**) Pembrolizumab vs EXTREME				
	Events	HR (95% CI)	p	Median OS, months (95% CI)
Pembro mono	88%	1,16	0,5	3,2 (2,2-3,4)
EXTREME	91%	(0,96-1,39)		5,0 (4,8-5,8)

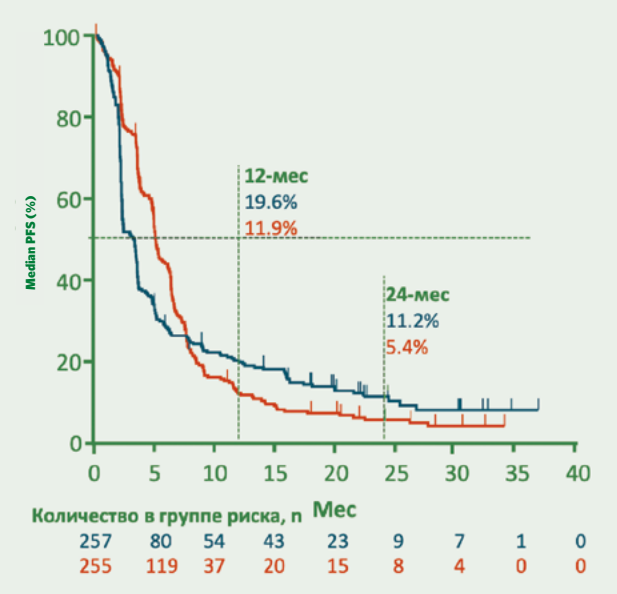


Fig. 3. Progression-free survival rates in patients with CPS≥20 and CPS≥1

The combination of nivolumab and ipilimumab as neoadjuvant therapy was studied by a research group led by Vos J.L. The authors of the study documented a significant pathomorphologic response (Major Pathological Response (MPR), a 90-100% tumor cell response) in 35% of patients who received the drug combination (nivolumab + ipilimumab) and in 17% of patients who received nivolumab monotherapy. None of the 9 patients with MPR had recurrence of SCCHN within 2 years after surgical intervention [22].

Today, not only the efficacy, but also the safety of neoadjuvant immunotherapy is being actively studied worldwide. The prescription of an additional treatment option increases the time to surgical intervention.

The result of a study conducted by van Harten M.C. investigating the relationship of survival to treatment waiting times, which included a total of 13,140 patients, showed that longer waiting times for surgery, RT or CRT are a significant negative prognostic factor for patients with SCCHN. In this regard, the time frame available for the use of neoadjuvant checkpoint inhibitors in SCCHN in phase I/II studies is limited, because surgery performed later than 6 weeks after diagnosis worsens long-term treatment outcomes, namely recurrence-free and overall survival [44].

Conclusions. Analyzing many years of experience in providing medical care to patients with SCCHN, significant progress in the development of treatment methods in this cohort of patients can be noted.

The introduction of new RT equipment, new radiation techniques such as VMAT, IMRT, better imaging, patient positioning, and new drug therapies have increased the duration and quality of life of patients.

The high recurrence rate and still relatively low overall life expectancy require improvements in treatment methods.

Neoadjuvant immunotherapy for SCCHN has already demonstrated its efficacy in preliminary clinical trials, making it a promising area for further study.

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Information about the authors:

Aleksej V. Tsapir — MD, radiotherapist of the 32th department of the Center for radiology, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, tsapir.mo@mail.ru**, ORCID: 0000-0003-4554-8937

Maria Yu. Pitkevich — MD, radiotherapist of the 32th department of the Center for radiology, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Aleksej V. Smolin — MD, PhD, Chief of the Center for radiology, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia. ORCID: 0000-0002-3023-0515

Vladislav Ju. Kosyrev — MD, ScD, assistant professor of oncology department at N.V. Sklifosovskiy Institute of Clinical Medicine of the Sechenov University; leading researcher of the Interventional radiology department at Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia.

Andrej A. Vologdin — MD, PhD, department of emergent surgery, Branch of the Federal State Budgetary Military Educational Institution of Higher Education "Kirov Military Medical Academy" of the Ministry of Defense of the Russian Federation, Moscow, Russia.

The authors declare no conflicts of interest.
The study was not sponsored.
Received 15.02.2023

ISSN: 2782-1730 (PRINT) / ISSN: 2713-0711 (ONLINE) / DOI:10.53652/2782-1730-2023-4-1
MEDICAL BULLETIN OF THE MAIN MILITARY CLINICAL HOSPITAL NAMED AFTER N.N. BURDENKO.
Scientific and practical edition.
Circulation 1000 copies. Format: 60—90 1/8. Sertificate of registration of mass media PI number FS77-78674 on July 10, 2020. The Bulletin is published quarterly. Signed for printing 20.03.2023.
Founder: The Main Military Clinical Hospital named after N.N. Burdenko.
Editorial board: The Main Military Clinical Hospital named after N.N. Burdenko. Gospital sq. 3105229, Moscow, Russia. Phone: +7 499 263 5555, +4509, +4512,+4513; e-mail: gvkg.300@mail.ru
Scientific editing and proofreading: Tatiana Ursegova, Karina Peryanova.
The journal's articles are included in the independent database of the complete list of scientific papers — the Russian Science Citation Index (RSCI). Free access policy.
The journal is included in the List of peer-reviewed scientific publications recommended by the Higher Attestation Commission under the Ministry of Education and Science of Russia for the publication of the main scientific results of dissertations for the degree of Candidate of Sciences and Doctor of Sciences.
Electronic versions of the published issues of the journal are available online: hospitalburdenko.com.
Target audience: doctors of various clinical disciplines, health care organizers, doctors of related specialties, residents, postgraduates.

Journal production "Medical Bulletin of the Main Military Clinical Hospital named after N.N. Burdenko": Publishing house "Opinion Leader". 125183, Moscow, Likhoborskie Bugry st., 6, # 30. Tel.: +7 926 317 4445; e-mail: opinionleaderph@gmail.com
Director of the publishing house: Anna Gurchiani. Issuing editor: Svetlana Episeeva. Design & layout: Elena Mappyrova. Corrector: Elena Travkina. Photographer: Natalia Vremyachkina. Translator: Petr Radaev.