

**Analytical review of scientific theses defended in 2018
with the Dissertation Board D 999.063.03
at the Russian Ilizarov Scientific Center for Restorative Traumatology and Orthopaedics
of the Ministry of Health of Russia,
FSBEI of higher education "South Ural State Medical University"
of the Ministry of Health of Russia and
FSBEI of higher education "Tyumen State Medical University"
of the Ministry of Health of Russia**

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The Dissertation Board D 999.063.03 has the right to accept dissertations for the candidate and doctor of medical sciences degrees in the specialties 14.01.15 (traumatology and orthopedics) and 14.03.02 (pathological anatomy) according to the order of the Ministry of Education and Science of the Russian Federation No. 53n/k of January 16, 2016.

In 2018, seven dissertations were defended with the Board, including one doctoral and two candidate theses in specialty 14.03.02 (pathological anatomy), four candidate theses in specialty 14.01.5 (traumatology and orthopedics).

Semenova Anna Borisovna from the South Ural State Medical University of the Ministry of Health of Russia presented her doctoral dissertation **"Morphological and functional characteristics of the cellular component of the microenvironment of breast carcinomas of various grades of malignancy and molecular genetic subtypes"** in the specialties 14.03.02 (pathological anatomy) and 14.03.03.02 (clinical immunology, allergology). Scientific consultants were professor Kazachkov Evgeny Leonidovich, doctor of medical sciences, and doctor of medical sciences, professor, honored scientist of the Russian Federation Ilya Ilyich Dolgushin. The work stresses that timely identification and complete information about the localization and sizes, sources of blood supply, histostructure and relationships with surrounding tissues is necessary for the effective treatment of malignant neoplasms.

A.B. Semenova outlined the goal of her study as morphological and functional characteristics of the cellular components of the microenvironment

of invasive carcinomas of the mammary gland of a nonspecific type, depending on the malignancy grade and molecular genetic subtypes to improve the intravital morphological diagnosis of these neoplasms.

The work contains clinical and experimental sections.

The applicant showed the formation of extracellular traps by peripheral blood neutrophils after interacting with the cell lines of tumor cells HEP-2 (human, epidermoid laryngeal carcinoma), RD (human, rhabdomyosarcoma) and evaluated their effectiveness; the cell composition of the microenvironment in the intratumoral, peritumoral and distant zones of invasive breast carcinomas of a non-specific type was studied depending on the malignancy grade and molecular genetic subtypes. For the first time, the formation of extracellular DNA networks by neutrophils of the microenvironment in the intratumoral, peritumoral and distant zones in the surgical material was compared.

A method for detecting neutrophilic extracellular traps in the peritumoral zone of breast carcinoma was developed as an additional criterion for tumor malignancy identification, which was used in intraoperative morphological diagnosis for early determination of the prognosis of the disease. The results obtained do not contradict the data presented in independent sources on this topic. The dual role of neutrophilic granulocyte in interacting with tumor cells was shown for the first time, its antitumor effect at the first stage, and the pro-tumor effect at the stage of the neutrophilic trap formed.

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The practical significance of the research results obtained by the applicant is that the way of morphological diagnosis of epithelial carcinomas of various localizations was optimized depending on the biological characteristics and the degree of their malignancy, due to the ability of autologous neutrophils as significant components of the tumor microenvironment, to form extracellular DNA networks. The study of the characteristics of antitumor immunity, new properties of immunocompetent cells and mechanisms of "evasion" or screening of tumor cells opens up prospects for developing a prognosis of the disease, creating treatment regimens to maximize overcoming the blockade of immunocompetent cells.

The main statements of the dissertation were presented in scientific publications and reports at scientific and practical events by the applicant personally and in collaboration. Twenty-eight scientific papers devoted to the topic of the dissertation were published, including 15 in the journals recommended by the High Attestation Board for publishing dissertation materials, one publication from the list of Web of Science, Scopus, and one teaching aid was issued.

The dissertation **"Endometrial dysfunction in women with uterine myoma and chronic endometritis in infertility in married women"** for the degree of candidate of medical sciences in specialty 14.03.02 (pathological anatomy) was presented by **Miroshnichenko Larisa Evgenievna** from the South Ural State Medical University of the Ministry of Health of Russia (supervisor, doctor of medical sciences, associate professor Voropaeva Ekaterina Evgenievna).

The applicant published 17 papers on the topic of the dissertation, including 7 articles in journals and publications recommended by the Higher Attestation Board for presenting main scientific results of dissertations, one work in a scientific journal, 8 works in materials of all-Russian and international conferences and symposia, one teaching aid for students of postgraduate and continuing education in the specialty 14.03.02 (pathological anatomy) and 14.01.01 (obstetrics and gynecology).

The dissertation substantiates the concept of the development of endometrial dysfunction in patients with uterine myoma, which does not require surgical treatment, and chronic endometritis in infertility in marriage. It has been proven that endometrial dysfunction is almost exclusively associated with a chronic inflammatory process in the uterine mucosa. It is proposed to consider the activity of the chronic inflammatory process in the endometrium when assessing the nature of endometrial dysfunction. New concepts of clinical-anamnestic and morphological determinants of endometrial dysfunction were introduced.

The author substantiates the provisions contributing to the expansion of ideas about the morphological determinants of significant endometrial dysfunction in patients with uterine myoma and chronic endometritis in infertility in marriage.

The applicant has developed and introduced into the work of medical institutions of the city of Chelyabinsk technologies for studying endometrial dysfunction. The results of the study are used in the pedagogical process at the Department of Pathological Anatomy and Forensic Medicine of the Federal State Budgetary Educational Establishment of Higher Education "South Ural State Medical University" of the Ministry of Health of Russia. The prospects of using theoretical principles in practice to optimize diagnostic and rehabilitation technologies for pregravid preparation and enhancement of the implantation potential of the endometrium in women with infertility were determined. A system of practical recommendations was proposed.

The thesis covers the main issues for solving the scientific task of defining clinical, anamnestic and morphological determinants of endometrial dysfunction in women with uterine myoma, which does not require surgical treatment, and chronic endometritis in infertility in marriage, and meets the criteria established by the "Regulation on awarding scientific degrees" approved by the Government of the Russian Federation of September 24, 2013 No. 842 (as amended), applicable to dissertations for the degree of the candidate of sciences.

Shamanova Anna Yurievna, also from the Federal State Budgetary Educational Institution of Higher Education "South Ural State Medical University" of the Ministry of Health of the Russian Federation, presented her candidate of sciences thesis **"Morphological features of local antitumor protection in carcinomas of the larynx of various clinical stages"**, specialty 14.03.02 – pathological anatomy. The dissertation was conducted at the Department of Pathological Anatomy and Forensic Medicine (supervisor: professor Kazachkov Evgeny Leonidovich, doctor of medical sciences).

The work was aimed at studying the morphological and functional features of the components of the peritumoral zone in laryngeal carcinomas depending on the clinical stages and properties of the tumors (differentiation grade, growth pattern, ability to metastasize, radiation pathomorphosis of the tumor).

The applicant published 20 scientific papers on the topic of the dissertation, including 10 papers in leading peer-reviewed scientific journals and publications recommended by the Higher Attestation Board. The applicant also published 9 works in the materials of all-Russian and international conferences and symposia, and issued one teaching textbook. The

works reflect the main content of the dissertation.

The author gives a comparative complex morphological characteristics of the cellular and fibrous-vascular components of the peritumoral zone in laryngeal carcinomas and in laryngeal carcinomas in the state of radiation pathomorphism; immunophenotyping of the components of the cellular infiltrate of the peritumoral zone with laryngeal carcinomas was carried out with the determination of its features depending on the clinical stages and properties of the tumor (differentiation degree G, growth pattern, metastasis ability, radiation tumor pathomorphosis), including qualitative and quantitative features of the formation and distribution of extracellular neutrophilic DNA networks of the peritumoral zone. The concepts of "peritumoral zone", "degree of inflammation activity in the peritumoral zone" are introduced; a semi-quantitative method for assessing the activity and severity of inflammation in the peritumoral zone using the surgical material of laryngeal carcinomas (granulocytic (neutrophilic granulocytes), lymphocytic, plasma cell infiltration) was proposed.

Additional morphological criteria for the degree of differentiation (G) of squamous cell carcinoma of the larynx, the presence of metastatic lesions of the cervical lymph nodes, and radiation pathomorphism of the tumor were established and characterized. It was shown that the cellular component of the peritumoral zone in laryngeal carcinomas has morphological features characteristic of various degrees of tumor differentiation (G), radiation pathomorphism, and also depends on the presence of metastases in the cervical lymph nodes. It was established that the number of neutrophilic extracellular DNA networks is a morphological marker of the activity of neutrophilic granulocytes in the cellular infiltrate of the peritumoral zone, depending on the degree of differentiation of the tumor and its ability to metastasize. It was shown that primary laryngeal carcinomas of various degrees of differentiation (G) and laryngeal carcinomas in the state of radiation pathomorphism are characterized by structural features of the vascular-fibrous component of the peritumoral zone.

The established morphological features of the microenvironment of the squamous cell carcinoma of the larynx, their dependence on the clinical stages and properties of the tumor can be used in the intravital pathological study of the surgical material of the larynx cancer as additional morphological criteria for the degree of differentiation of squamous cell carcinoma of the larynx, the presence of metastatic lesions of cervical lymph nodes, radiation pathogens.

The results of the dissertation have been used in the educational process of the Department of Pathological Anatomy and Forensic Medicine of the Federal State Budget Educational Institution of Higher Education the South Ural State Medical University of the Ministry of Health of Russia, Chelyabinsk, and

have been introduced into the practice of medical institutions in Chelyabinsk. Based on the results of the study, a manual was published for additional professional education of doctors specializing in "pathological anatomy".

The work of **Dmitry Nikolaevich Efimov** "*Tactics of treating patients with fractures and nonunion of the femoral neck using reconstructive arthroplasty*" in the specialty 14.01.15 (traumatology and orthopedics) was conducted at the Russian Ilizarov Scientific Center for Restorative Traumatology and Orthopedics of the Ministry of Health of the Russian Federation (supervisor: Chegurov Oleg Konstantinovich, doctor of medical sciences).

The author of the dissertation stresses that the elimination of complications after conservative treatment and osteosynthesis of a femoral neck fracture is a challenging problem, since the percentage of unsatisfactory outcomes of treatment with conservative methods or osteosynthesis is high. They develop in half of the cases, and each subsequent surgical intervention is more traumatic than the previous one. Hip joint replacement has been increasingly used for the treatment of fractures and nonunion of the femoral neck, as well as for complications associated with the failure of osteosynthesis and impaired blood supply to the femoral head after organ-preserving operations. However, at present, the necessity and features of arthroplasty for fractures and nonunion of the femoral neck, the use of the Ilizarov apparatus in the complex treatment of nonunion of the femoral neck with reconstructive arthroplasty have not been sufficiently substantiated. The author did not find studies in the available literature on the treatment of pseudoarthrosis of the femoral neck with varying degrees of soft tissue rigidity, with a high proximal femur dislocation and a high risk of neuropathy of the main nerve trunks. There are no unified tactical approaches to the treatment of the pathology with the arthroplasty method depending on gender, age, presence of metal implants (complicating arthroplasty), on the time from the moment of injury, and rigidity of the soft tissues surrounding the fracture zone or nonunion.

The above unsolved problems of restorative orthopedics were the focus of the study.

Objective: to increase the effectiveness of surgical treatment of patients with fractures and nonunion of the femoral neck.

The results of reconstructive arthroplasty in patients with fractures and nonunion of the femoral neck were studied. The pathology was systematized according to symptoms depending on the grade of hip dislocation and soft tissue rigidity; anatomical and functional disorders affecting the tactics of surgical treatment were determined. Differentiated indications for reconstructive arthroplasty were developed. Intraosseous blood flow

was studied in the fracture and nonunion zone of the femoral neck, as well as in the paraarticular soft tissues. The assembly of the apparatus was developed depending on the anatomical and functional disorders. The application of this method allows for gradual reduction of the femur into a physiological position with the restoration of its offset. An algorithm was developed for the tactical and technical approach to differentiated indications in the treatment of patients depending on the nature of the fracture, age, condition of the soft tissue component, degree of hip dislocation, and presence of concomitant pathology.

The procedure for examining patients with these pathologies and the technology for implanting an artificial hip joint using reconstructive arthroplasty, including using the Ilizarov apparatus, were standardized. Procedures of preoperative examination, preoperative preparation and postoperative management of patients were optimized. Three types of pathology were identified in patients with pseudarthrosis of the femoral neck, depending on the severity of anatomical and functional disorders. A diagnostic technique was proposed to determine the safety of simultaneous bringing the femur down in different rigidity conditions of the hip joint. The causes of errors and complications were identified, and measures for their prevention were developed. New knowledge, the developed methods for the prevention of errors and complications in clinical practice, the standardization of preoperative examination procedures and postoperative management will contribute to improvement of anatomical and functional results of treating patients with fractures and nonunion of the femoral neck using the method of reconstructive arthroplasty.

Maksimov Alexander Leonidovich, also from the Federal State Budgetary Institution Russian Ilizarov Scientific Center for Reconstructive Traumatology and Orthopedics of the Ministry of Health of the Russian Federation defended his thesis ***“Treatment of patients with the consequences of injuries and diseases of the hip joint with the use of an endoprosthesis of increased primary fixation”*** in the specialty 14.01.15 (traumatology and orthopedics). His scientific adviser was Chegurov Oleg Konstantinovich).

The author states that there is a wide variety of methods for treating the pathology of large joints. In the recent decades, arthroplasty has become increasingly widespread. The development and spread of arthroplasty has led to the emergence of different designs of implants and their manufacturers. Arthroplasty systems use fixation with and without cement. The latter are fixed primarily during surgery, after which, over time, secondary fixation occurs when bone tissue grows over the implant surface. Thereby, some components have high primary stability (screwed cups), while the functioning of others involves secondary fixation.

Only a few publications on the use of cementless endoprostheses were found in the literature; there are no data on long-term functional results assessed according to generally accepted systems of evaluation as well as on the experience based on a large number of revision operations. Interesting might be the analysis of the causes of aseptic instability, as the main factor limiting the life of an implant, as well as the development of revision techniques.

The appearance of a large number of varieties of prostheses with different construction philosophies on the market, various methods of their implantation, experience in treating patients, errors and complications identified during the study of treatment results and measures being developed for their prevention indicate that the problem of choosing the optimal implant has not been solved yet and requires further study. As a result, a detailed study of each specific implant system is an urgent issue.

All this prompted the applicant to analyze the experience with an implant of increased primary fixation using the cementless SLPS system of Altimed CJSC as a sample.

The purpose of the study was to increase the efficiency of treatment of patients with the consequences of injuries and diseases of the hip joint using an implant of increased primary fixation.

The changes occurring in the area of the hip joint and in the body after arthroplasty, including the development of aseptic instability were studied. The experience of treating a sufficiently large number of patients with implants of increased primary fixation with an average follow-up of 10 years was studied. The causes of the development of total and one-component aseptic instability were analyzed; prognostic criteria for its development were identified. The structural merits and shortcomings of the studied system leading to a decrease in the effectiveness of the method were determined. A useful model was developed to remove the prosthesis cup during revision surgery. For the first time, the complex conditions for the optimal functioning of the implant of increased primary fixation were identified.

The prognostic criteria for the development of aseptic instability revealed during the study on the example of the system allowed the author to identify risk groups after primary arthroplasty, contribute to early detection of this complication, and find measures to prevent its development. As a result of the work, methods of revision arthroplasty for instability of the SLPS of ZAO Altimed system were proposed: a method of revision arthroplasty of the hip joint for wear of a polyethylene liner and a stable pelvic component, a method for removing a polyethylene insert of the pelvic component using the SLPS implant of Altimed CJSC, a method for

delimiting the bottom of a cavity during arthroplasty of a hip joint, a method for suturing a skin wound, a method of removing osteophytes around the gap of the hip joint implant.

A specific algorithm for conducting revision intervention for aseptic instability of this prosthesis design was developed. Using the developed algorithm, it was possible to reduce the number of fractures of the femoral and pelvic bones, reduce the time of surgery, reduce intraoperative blood loss, invasiveness of the operation, preserve bone tissue as much as possible, and reduce the number of postoperative complications.

One training manual was published for surgeons and a device for removing the pelvic component of the implant was proposed. The results of the study, the developed methods of revision were introduced and have been used in clinical practice at the Federal State Budgetary Institution Russian Ilizarov Scientific Center for RTO as well as during training at the Department of Traumatology and Orthopedics of the Tyumen State Medical University functioning on the basis of the RISC for RTO, courses of advanced training in arthroplasty of large joints.

The main provisions of the dissertation were presented and discussed at nine Russian congresses and conferences.

Sixteen papers were published on the topic of the dissertation, of which 9 were published in journals recommended by the Higher Attestation Board for publishing materials for candidate and doctoral dissertations.

Ilya Vladimirovich Stasenko from the Omsk State Medical University of the Ministry of Health of the Russian Federation presented and defended his thesis "**Treatment of patients with chronic osteomyelitis and long bone defects using osteoconductive materials (experimental and clinical study)**" in the specialty 14.01.15 of traumatology and orthopedics (supervisor: professor Reznik Leonid Borisovich, doctor of medical sciences,).

The applicant has 8 published scientific papers on the topic of the dissertation, including 3 papers in leading peer-reviewed scientific journals recommended by the Higher Attestation Board for the publication of dissertation materials, one of which is included in the SCOPUS bibliographic database; one patent was received. In the materials of all-Russian and international conferences and symposia, the applicant published 5 works. The works reflect the main content of the dissertation.

Based on the research conducted by the applicant in an animal experiment, high osteoconductive potential of the carbon nanostructured implant (CNI) for post-resection defects was confirmed with formation of bone regenerate. A biomechanical study

enabled to determine the resistance of the regenerate of the experimental bony conglomerates to rupture at the bone-to-implant interface, as well as to compare the data with the optical parameters of the regenerate obtained during the evaluation of the radiographs. New knowledge was gained about the process of bone tissue regeneration at the bone-to-implant border after the defect was managed with various osteoconductive materials. The author developed an algorithm for managing a bone defect in chronic osteomyelitis. The conditions of using CNI to achieve a positive treatment result were determined. An implant was developed that features antibacterial activity in the defect zone. For the first time, the supporting area necessary to maintain the strength of the implant was mathematically determined.

High osteoconductive activity of the CNI was proven experimentally. The defined mechanical resistance of the bone-to-implant block to rupture corresponded to the parameters of a healthy bone and amounted to 0.097 ± 0.013 N/m, which exceeded the similar characteristics of blocks with allogenic bone and ceramic implants by 45-50 %. The morphological study confirmed the presence of rearrangement of the sections of the cortical layer at the border with the carbon implant with the formation of lacunae of osteocytes and blood vessels in the remodeling bone matrix. The nanocarbon implant for segmental defects of long bones with antibiotic-bearing impregnation provided an antibacterial effect in the implantation zone; the minimum supporting area of the implant was mathematically determined, which should be at least 0.75 cm^2 .

It was confirmed in practice that the use of a carbon implant for a bone defect in the diaphysis of a long bone in osteomyelitis which is in the phase of persistent remission and extrafocal transosseous osteosynthesis provides complete consolidation with the formation of a durable bone-to-carbon block in a period of 20 weeks if the defect is bridged of no more than 10 % of segment lengths. Positive short- and long-term results of treatment of patients with the use of CNI for post-resection defects of long bone were obtained in 60 % of cases. The effectiveness of the proposed methodology for management of long bone defects in the stage of persistent remission of osteomyelitis allows us to recommend it in the clinical practice of specialized departments of regional hospitals, as well as at research institutes of orthopedic and traumatological profile.

The dissertation for a candidate of sciences degree "**Functional examination and differentiated treatment of patients with anterior instability of the knee joint**" in the specialty 14.01.15 (traumatology and orthopedics) was presented by **Chmutov Alexander Mikhailovich** from FSBEI "South Ural State Medical University" of the Ministry of Health

of Russia (supervisor: Astapenkov Danila Sergeevich, doctor of medical sciences).

“Injuries of the anterior cruciate ligament (ACL) of the knee joint are common lesions,” the author indicates. Untimely diagnosis and improper treatment of ACL tears lead to the development of chronic anterior instability of the knee joint, and subsequently to patient disability. The widespread introduction of arthroscopic methods in modern medicine has made it possible to qualitatively improve both the diagnosis of ACL ruptures and the treatment results. But a retrospective analysis by many authors has shown that there are a number of problems leading to unsatisfactory results.

Detection of anterior instability of the knee joint in a patient with common clinical methods does not quantify its magnitude and diagnosis of the anatomical conditions (destruction, tears) leading to it. And widespread instrumental techniques, such as magnetic resonance imaging and ultrasonography are able to reveal structural disorders of the anterior cruciate ligament but do not determine its functional failure along with other stabilizers of the knee joint. Improving the examination paths taking into account new economic, material and social conditions and trends forced the author to study these problems in-depth, to try to develop algorithms for diagnosing and treating patients with anterior instability of the knee joint.

The purpose of the study conducted by the applicant is to improve the treatment results in patients with anterior instability of the knee joint, taking into account the causes, genetic characteristics of the body, the degree and functional compensation of instability established during a comprehensive examination using the developed methodology of functional magnetic resonance imaging.

Justification of diagnostic and surgical treatment algorithms for ACL injuries considering its grade, functional compensation of knee joint instability, and genetic characteristics of the body, can improve the quality of examination of such patients and improve treatment outcomes.

The author developed a method for performing functional magnetic resonance imaging (MRI) of the knee joint with an open-type 0.25 T MRI HELPIC RENEX system. A technique was developed of quantitative determination of the magnitude of anterior instability of the knee joint under the physiological

tone of dynamic stabilizers. The indications for the operative restoration of the anterior cruciate ligament were clarified and determined. Recommendations were developed on the choice of material for the operative restoration of ACL, taking into account the magnitude of the instability of the knee joint and the genetic predisposition of own tissues to traumatic ruptures.

The developed method for determining the magnitude of anterior instability of the knee joint using functional magnetic resonance imaging under conditions of preserved muscle tone provides an adequate assessment of the compensatory capabilities of anterior stabilization of the knee joint. Better visualization of ACL increases the diagnostic capabilities of MRI in partial and complete ACL tears of the knee joint.

Comparison of the magnitude of anterior instability of the knee joint during functional MRI during treatment and recovery of patients after surgery allows assessment of compensation of dynamic stabilizers of the knee joint and the effectiveness of the treatment.

The use of functional MRI data when choosing material for the operative recovery of ACL enables to achieve good results in treating patients and reducing the number of instability recurrence.

Identification of the genetic risk of developing traumatic ACL tear allows predicting transplant failure harvested from one's own tissues during reconstruction of the cruciate ligament.

The research results were presented and reported at two conferences of the All-Russian level, conferences of regional and city the levels.

Eleven scientific papers were published on the topic of the dissertation, of which four articles were in the journals recommended by the Higher Attestation Board of the Russian Federation for the publication of the results of dissertation research, and one foreign publication. A patent on the invention entitled “Method of magnetic resonance imaging for determining anterior instability of the knee joint” was filed.

Clinical trials of the dissertation research with the developed medical technology took place at the traumatology department of the Hospital of the Chelyabinsk Railway Station of the Russian Railways which was introduced in the work of the department.

The main results of all dissertations that were defended with the Board are used in clinical practice and further scientific studies.

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