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ЕВРОПЕЙСКИ СЪЮЗ  
ЕВРОПЕЙСКИ СТРУКТУРНИ И  
ИНВЕСТИЦИОННИ ФОНДОВЕ



ОПЕРАТИВНА ПРОГРАМА  
НАУКА И ОБРАЗОВАНИЕ ЗА  
ИНТЕЛИГЕНТЕН РАСТЕЖ

## ИНФОРМАЦИОНЕН БЮЛЕТИН

Проект  
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**ЦЕНТЪР ЗА КОМПЕТЕНТНОСТ ПО  
ПЕРСОНАЛИЗИРАНА МЕДИЦИНА,  
ЗД И ТЕЛЕМЕДИЦИНА, РОБОТИЗИРАНА  
И МИНИМАЛНО ИНВАЗИВНА ХИРУРГИЯ**

*Леонардо да Винчи*



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**НАУЧНИ ПУБЛИКАЦИИ В НАЦИОНАЛНИ, ЕВРОПЕЙСКИ И  
СВЕТОВНИ МЕДИЦИНСКИ ИЗДАНИЯ**

**КНИГА С АБСТРАКТИ / ABSTRACT BOOK**

**SCIENTIFIC PUBLICATIONS IN NATIONAL, EUROPEAN AND WORLD  
MEDICAL EDITIONS**

### 1. HALL SENSOR WITH GEOMETRY ENHANCED SENSITIVITY

*Siya Lozanova; Avgust Ivanov; Chavdar Roumenin*

#### **ABSTRACT:**

A novel silicon Hall device with geometry-enhanced sensitivity was fabricated and characterized. The magnetosensitivity grows with the charge carrier density on the Hall sides. The shape of the edges on which the Lorentz force deflects the electrons has the form of isosceles acute triangles on whose corners the ohmic Hall contacts are formed. The sensors were realized based on n-Si wafers with  $\rho \approx 7.5 \Omega \cdot \text{cm}$ . The obtained transducer efficiency is by about 20 % higher than the sensitivity of the usual with orthogonal activation Hall element from the same material and with the same input conditions. The new Hall configuration is very promising for low-field magnetometry and robotized surgery.

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*Conference Location: Sozopol, Bulgaria*

### 2. RELEVANT PHENOMENA TO THE HALL EFFECT IN SENSOR DEVICES

*Siya Lozanova*

#### **ABSTRACT:**

The regularity in conducting materials, including semiconductors, with limited dimensions and arbitrary geometry form, within wide temperature range, which are placed in cross supply and magnetic field has been explained. It is expressed in arising, on the opposite surfaces of the devices, apart from the Hall voltage, of magnetically controlled surface currents, which are linear and odd functions of the supply and the magnetic field. The additional carriers, deflected by Lorentz force on the respective boundary of the structure are movable and not localized as it has been deemed so far, and they form the surface current. The individual potentials and the Hall voltage are generated simultaneously by the field of the additional charges on the opposite sides and by the voltage drop on the interfaces from the magnetically controlled surface currents flowing there.

**Key words:** *Hall sensors, Hall current, magnetically controlled surface current, Lorentz force deflection*

*Comptes rendus de l'Academie bulgare des Sciences, , No3, pp.422-4 DOI: 10.7546/CRABS.2021.03.14*

### 3. SENSOR WITH SUBSEQUENT MEASUREMENT OF X, Y AND Z MAGNETIC FIELD COMPONENTS

*Siya V. Lozanova; Martin L. Ralchev; Avgust J. Ivanov; Chavdar S. Roumenin*

#### **ABSTRACT:**

An original multidimensional magnetic-field sensor using subsequent measurement method based on a bipolar drift-aided magnetotransistor is presented. The device contains silicon substrate, emitter, two base contacts and four collectors. Using a new effect consisting of electrical control of magnetosensitivity polarity, the full information about all components is obtained by three collector pair arrangements. The measurement is carrying out with the same magnetotransistor, but at different time. The channel sensitivities reach  $S_x \approx 37.5 \mu\text{A/T}$ ,  $S_y \approx 75 \mu\text{A/T}$  and  $S_z \approx 98 \mu\text{A/T}$ , respectively.

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### 4. THREE CONTACT IN PLANE SENSITIVE HALL DEVICES

*Siya V. Lozanova; Martin L. Ralchev; Avgust J. Ivanov; Chavdar S. Roumenin*

*Institute of Robotics at Bulgarian Academy of Sciences, Sofia, Bulgaria*

#### **ABSTRACT:**

A new in-plane sensitive Hall configurations were suggested and tested. Each of them contains two identical rectangular n-type silicon slabs disposed in parallel. There are three elongated ohmic contacts on one of the surfaces of substrates. In one structure the contacts are asymmetrically arranged as output electrodes are outside the regions through which the currents flow. The other device is symmetrical, as contacts are at equal distances. Arrangements have low offset about 4mT, high sensitivity 36V/AT and operational volume  $110 \times 100 \times 40 \mu\text{m}^3$ .

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*Publisher: IEEE*

*Conference Location: Sozopol, Bulgaria*

### 5. TWO AXIS MAGNETIC FIELD SENSOR

*S. Lozanova, A. Ivanov, M. L. Ralchev, C. Roumenin,*

#### **ABSTRACT:**

This paper presents a 2-D vector microsensor that simultaneously and independently measures both planar magnetic field components. The configuration contains a supply in current mode of operation and n-type silicon substrate. An n-ring with p-type conductivity and shaped like a symmetric Maltese cross is embedded on one side. In the central n-region there is a square ohmic contact. One inner and one outer contact are formed relative to the sides of central electrode. The width of the outer contacts is about twice that of the inner ones. The sum of the areas of the inner electrodes is commensurate with that of the central one. The inner terminals are electrically connected and through the current source are fed to the central electrode. The measured magnetic field is in the plane of n-Si substrate. The pairs of external contacts opposite to the square are the outputs for the magnetic vector components. The magnetosensitivity of the channels is  $S_x=S_y\approx 31$  V/AT, the nonlinearity at  $B\leq\pm 0.5$  T is  $NL\approx 0.4$  %, and at  $B\leq\pm 1.0$  T it is 1.2%. The cross-talk at induction  $B\approx 0.8$  T consists about 3 % and metrology resolution reaches  $B_{min}\approx 15$   $\mu$ T. One of the actual applications of the new magnetometer is robotized surgery.

**Keywords:** 2D vector magnetometer; silicon in-plane sensitive Hall configuration; magnetic-field measurement; internal noise; channel cross-talk.

*Proc. Intern. Scient. Confer. UNITECH 2023", TU - Gabrovo, 2023, ISSN: 1313-230X, vol. I, pp.180-186*

## 6. DOUBLE HALL MICROSENSOR

*S. Lozanova, A. Ivanov, M. L. Ralchev, C. Roumenin*

### **ABSTRACT:**

In this paper, a novel microsensor configuration representing a double-Hall device is investigated. It contains a thin n-type silicon substrate with a parallelepiped shape. On its two long side, four pairs of ohmic contacts, first and second, third and fourth, fifth and sixth, seventh and eighth, respectively, are formed spaced and symmetrically opposite each other. The contacts with even numbers are on one side and with odd numbers on the other. The first and fifth contacts are fed to the power supply in current mode of operation. The first and fourth, and respectively the fifth and eighth contacts are connected. The second and third, and respectively the sixth and seventh contacts are coupled, too. The differential output of the new microsensor are the second and sixth contacts. The external magnetic field is perpendicular to the plane of the substrate. The sensitivity of the double-Hall device is 27 V/AT, the nonlinearity at  $B\leq\pm 0.5$  T is  $NL\approx 0.3$  %, and at  $B\leq\pm 1.0$  T it is 1.1 %. Significant minimization of the parasitic output offset is achieved. The lowest value of the detected magnetic field with a supply current of 2 mA reaches about 12  $\mu$ T.

### **Keywords:**

*Hall effect; vertical Hall device; double-Hall configuration; offset reduction, sensor characteristics.*

*Proc. Intern. Scient. Confer. UNITECH 2023", TU - Gabrovo, 2023, ISSN: 1313-230X, vol. I, pp.186-192*

## 7. A NEW HALL MICRODEVICE WITH MINIMAL COMPLEXITY

*S. Lozanova, A. Ivanov, M. L. Ralchev, C. Roumenin,*

### **ABSTRACT:**

A new Hall microdevice with minimal complexity and orthogonal magnetic field activation is suggested. The microsensor contains rectangular n-type silicon substrate. On the long sides three ohmic contacts are formed symmetrically and opposite each other. The first two opposite electrodes are connected and the second two are fed in the same way, third ones are the output. The increased sensitivity constituting 40V/AT is due to the reduced parasitic surface currents. Furthermore, output electrodes are moved out of the area where the supply currents flow. The spatial resolution of the sensor is  $80\times 135\times 30\mu\text{m}^3$ . This ensures detailed mapping of the magnetic-field topology.

### **Keywords:**

*Hall effect; vertical Hall element; orthogonal Hall configuration; sensor characteristics  
Proceedings 2023, in press*

Варна

## 1. TRANSFORMING SCIENTIFIC RESULTS INTO EDUCATIONAL MATERIALS ADDED VALUE OF A RESEARCH PROJECT

*Yanita Chernogorova , Turgay Kalinov, Nikolay Dukov , Kristina Bliznakova, Alexander Zlatarov , Nikola Kolev , Zhivko Bliznakov*

### **ABSTRACT:**

In recent years, there has clearly been a trend towards widespread dissemination of scientific results and achievements by sharing them in the form of educational materials. The application of the results of a research project in the education and knowledge development of students, young researchers and scientists, brings an added value to the outcomes of the scientific project. This work aims at contributing to the global process of free access to scientific materials by sharing the experience of a research group from the Medical University of Varna (MUV) in systematizing the results of three research projects, their transformation into educational resources and their application in innovative courses. The consolidated and systematized results of a research project are valuable assets for development of innovative educational materials. These resources, uploaded in a shared online repository, contribute to strengthen the international scientific community networking.

**Keywords** – *educational materials, educational methods, research projects, educational resources.*

*TEM Journal. Volume 11, Issue 1, pages 120-124, ISSN 2217-8309,*

*DOI: 10.18421/TEM111-14, February 2022.*

## 2. A FILAMENT 3D PRINTING APPROACH FOR CT COMPATIBLE BONE TISSUES REPLICATION

*Nikiforos Okkalidis , Kristina Bliznakova , Nikola Kolev*

### **ABSTRACT:**

### **Purpose**

The aim of this study is the development of a methodology for manufacturing 3D printed anthropomorphic structures, which mimic the X-ray properties of the human bone tissue.

### **Methods**

A mixing approach of two different materials is proposed for the fabrication of a radiologically equivalent hip bone for an anthropomorphic abdominal phantom. The materials employed for the phantom were polylactic acid (PLA) and Stonefil, while a custom-made dual motor filament extrusion setup and a custom-made software associating medical images directly with the 3D printing process were employed.

**Keywords:** *daVinciXi; opensurgery; rectalcancers; short-termclinicaloutcomes.*

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*. 2023 Feb;118(1):27-38. doi: 10.21614/chirurgia.2688.*

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### **3. FEASIBILITY AND SAFETY OF ROBOTIC-ASSISTED SURGERY FOR RECTAL CANCER: SHORT-TERM OUTCOMES OF A PILOT STUDY WITH DA VINCI XI PLATFORM DURING COVID-19**

*Kristina Bliznakova, Nikola Kolev, Alexandar Zlatarov, Turgay Kalinov, Tihomir Georgiev*

#### **ABSTRACT:**

Background: Colorectal cancer is a major cause of morbidity and mortality in the world. Approximately, one of three diagnosed colorectal cancers is a rectal cancer. Recent developments in the field of rectal surgery have promoted the use of surgical robots, which are of great need when surgeons face anatomical difficulties, such as a narrowed male pelvis, bulky tumor, or obese patients. This study aims to evaluate the clinical results of robotic rectal cancer surgery during the introduction period of a surgical robot system. Moreover, the period of the introduction of this technique coincided with the first year of the COVID-19 pandemic. Methods: Since December 2019, the Surgery Department of the University Hospital of Varna has become the newest and the most modern Robotic Surgery Center of Competence in Bulgaria, equipped with the most advanced da Vinci Xi surgical system. From January 2020 to October 2020 a total number of 43 patients have underwent surgical treatment, of which 21 had robot-assisted procedures and the rest - open procedures. Results: Patient characteristics were close between the studied groups. The mean patient age in robotic surgery was 65 years, as six of these patients were females, while in case of open surgery these values were to 70 and 6, respectively. Two thirds (66.7%) of the patients operated on with da Vinci Xi were with tumor stage 3 or 4 and approximately 10% had the tumor located in the lower part of the rectum. The median value of the operation time was 210 min, while the length of hospital stay was 7 days. These short-term parameters were not found to have a large difference in respect to the open surgery group. A significant difference is depicted for the number of lymph nodes resected and the blood loss, with both parameters demonstrating advantage for the robot-assisted surgery. The blood loss is more than twice less than the case of open surgery. Conclusions: The results confidently showed the successful introduction of the robot-

assisted platform in the surgery department despite the limitations caused by the COVID-19 pandemic. This technique is expected to become the main choice of minimally invasive technique applied to all types of colorectal cancer surgery in the Robotic Surgery Center of Competence.

**Keywords:** *daVinciXi; opensurgery; rectalcancers; short-termclinicaloutcomes.*

*Chirurgia (Bucur)*

*. 2023 Feb;118(1):27-38. doi: 10.21614/chirurgia.2688.*

*DOI: 10.21614/chirurgia.2688*

### **4. ASSESSMENT OF STUDENTS' SATISFACTION WITH VIRTUAL ROBOTIC SURGERY TRAINING**

*T. Kalinov, T. Georgiev, K. Bliznakova, A. Zlatarov, N. Kolev*

#### **ABSTRACT:**

##### **Objective**

Nowadays, in Bulgaria there is a trend of increasing entry into the surgical field of robot-assisted surgery operations, which suggests a need for the establishment of a large number of specialists in this field in a short period. Based on these arguments, the Medical University of Varna was the first university in the country to introduce a robotic surgery training program for medical students. The study aims to investigate the medical students' satisfaction on robotic surgery training provided at Medical University of Varna with da Vinci Skills Simulator.

##### **Design**

During the summer semester of the academic 2020/2021 and 2021/2022 years, a pilot training of robotic surgery was conducted with 5th year students in Medicine. Within one month, the students had the opportunity to get acquainted with the simulator of da Vinci Xi robotic system. The training was divided into two modules: a two-week theoretical module and a two-week practical module. After completing the training, students filled out a questionnaire dedicated to assess their satisfaction with the proposed training. Correlation between their responses and the objective parameters assessed on the simulator was calculated.

##### **Results**

Thirty participants (16 men and 14 women) shared their opinion on easiness of use and usefulness of the robotic simulator in training of surgery activities. Students' responses highly evaluated both aspects with average five-point Likert scale scores of 4.3 and 4.5, respectively. 93% of the participants would continue their further education and training in robotic surgery field. In addition, there was no correlation between objective evaluation by the simulator and students responses.

##### **Conclusions**

Training in robotic surgery proves to be a useful approach for training students to develop skills and profession in the field of surgery. The results suggest that training in this field may be accomplished even at the student level, by exploiting the robotic surgery in realistic scenario and thus, in a timely manner to find out the surgical direction they want to be further evolved.

#### **Keywords:**

*Robotic surgery Education Training da Vinci Survey Satisfaction*

*Heliyon*

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### 1. A STUDY ON TUMOUR INFILTRATING LYMPHOCYTES, PD L1 AND BRCA1 IMMUNOHISTOCHEMICAL EXPRESSION IN BASAL LIKE SUBTYPE OF BREAST CANCER

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Background & objectives: The aim of the study was to determine basal-like subtype of breast cancer (BC), its tumour expression of breast cancer 1 (BRCA1) protein, the predominant type of lymphocytes and the expression of programmed death ligand 1 (PD-L1) by immune cells.

Methods: We studied 100 patients with invasive BC, grouped into four surrogate molecular subtypes - Luminal A-like and Luminal B-like, HER2 positive non-luminal and triple negative (TN), determined by immunohistochemical (IHC) method.

IHC was performed to find basal-like subtype of BC, to distinguish PD-L1 and BRCA1 antigens and to detect subtypes lymphocytes, using CD20, CD3, CD4, CD8 and FoxP3 antibodies.

Results: In our cases, the basal-like BC were mainly TN ( $p < 0.05$ ), mostly with special histological subtypes ( $p = 0.036$ ). Their immune response was represented predominantly by high concentration of intratumoral cytotoxic CD8+ T-lymphocytes ( $p < 0.05$ ) and stromal PD-L1 positive immune cells ( $p = 0.008$ ). In these tumours, the BRCA1 expression was more often absent in the tumour cells ( $p < 0.001$ ).

The basal-like subtype of BC and IHC negative expression of BRCA1 were associated with <5-year survival ( $p = 0.001$  and  $p = 0.017$ , respectively).

Conclusion: The established dependencies can be incorporated in a prognostic algorithm and predictive morphological screening, allowing better selection of patients with BC for subsequent genetic analysis of BRCA1 gene and for application of appropriate therapy.

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Volume479IssueSUPPL 1PageS68-S68Supplement1Special IssueSIMeeting AbstractPS-02-009

### 2. A STUDY ON TUMOR INFILTRATING LYMPHOCYTES IN DIFFERENT SUBTYPES OF BREAST CANCER

Polina D. Dimitrova, Savelina L. Popovska, Ivan N. Ivanov

Department of Pathology, Medical University – Pleven

#### Summary

The study aimed to investigate immune cell infiltration in different subtypes of breast cancer (BC). Retrospectively were selected 100 patients with primary BC, grouped into four molecular surrogate subtypes (Luminal A and Luminal B-like, HER2-positive and triple-negative - TN), determined by immunohistochemistry (IHC). In each patient, a percentage of stromal tumor-infiltrating lymphocytes (TILs) was determined by hematoxylin-eosin staining. IHC was performed using primary antibodies CD3, CD4, CD8, CD20, and FOXP3. Immunophenotyped lymphocytes were counted (separately intratumoral and stromal) and semiquantitatively graded. In the studied tumors, 10% were defined as lymphocyte-predominant BC. A high count of intratumoral

and stromal TILs subsets was found mainly in TN and HER2-positive BC. The stroma is the preferred localization for immune cells in all four BC subtypes. CD3+ T predominates over CD20+ B lymphocytes, with CD8+ T cytotoxic and FoxP3+ T regulatory cells dominating T subtypes. HER2 and TN are more immunogenic than Luminal A and Luminal B – like subtypes of BC. The T-cells' immune response was predominant in the studied cases of BC, with a predominance of CD8+ Tc and Foxp3+ Treg cells located mainly in the stroma.

**Keywords:** breast cancer, tumor-infiltrating lymphocytes, immunohistochemistry

*J Biomed Clin Res Volume 14 Number 1, 2021*

### 3. THE TRANSITION FROM CONVENTIONAL TO DIGITAL SLIDES (VIRTUAL MICROSCOPY) IN PATHOLOGY LAB CLASSES IN THE CONTEXT OF COVID 19 PANDEMIC: THE STUDENTS' POINT OF VIEW.

Ivan N. Ivanov<sup>1</sup>, Savelina L. Popovska<sup>1</sup>, Krasimir T. Petrov<sup>1</sup>, Polina D. Dimitrova<sup>1</sup>, Stefan V. Trifonov<sup>2</sup>, Rosen N. Hristov<sup>1</sup>, Zornitsa P. Todorova

Although the application of digital pathology for teaching purposes is widely accepted, the abrupt change from conventional slides to digital slides and its implementation in practice from the students' point of view is not well studied. The aim of the following study was to evaluate the students' opinion on an abrupt transition from conventional slides to virtual microscopy in pathology lab classes in the context of COVID-19 pandemic. The slides for all lab classes in pathology were digitalized using the infrastructure of the "Center of competence", Medical University- Pleven. Digital slides were implemented in an on-line database and used parallel with routine slides for two classes and then only virtual microscopy (digital slides) were used for teaching in distance education classes. The opinion and experience of 52 students was assessed using short questionnaire, three weeks later. The median age of the questioned students was 20 years (19-28). Female were 33 and male were 19 of the enquired students. Digital slides are very good or excellent substitution of routine slides according to 38 (73,07%) students; 6 (11,54%) students consider them good enough; 6 (11,54%) consider them as suboptimal and 2 (3,85%) have no opinion. Virtual microscopy should be kept after **the end of COVID 19** crisis according to 49 (94,23%) students. Virtual microscopy is suitable for implementation and use for pathology classes with no significant need of "how to use" training.

**KEY WORDS:** conventional microscopy, virtual microscopy, lab classes, students' point of view. *J*

*Biomed Clin Res Volume 14, Number 1, Supplement 1, 2021*

### 4. GENETIC LANDSCAPE OF PRIMARY LUNG ADENOCARCINOMA SINGLE INSTITUTION EXPERIENCE

N. Chilingirova, S. Popovska, E. Betsheva, T. Dineva

Cancer is now known as a disease of genomic alterations. The role of genetics in lung cancer development, a leading cause of cancer death worldwide, is becoming even more important in the last decade. Mutational analysis and genomics profiling have advanced the field of lung cancer research, emphasizing the critical role of some driver mutations in disease occurrence,

progression and treatment response. Molecular testing has become an essential part of oncology, as the number of molecular biomarkers and viable therapeutic targets for the treatment of patients with non-small cell lung cancer (NSCLC) continues to expand. NSCLC (comprising 80% of all lung cancer cases) remains one of the major public health problems, with very poor prognosis, treatment response rate and a 5-year-survival rate of less than 15%. The discovery of numerous specific molecular alterations in the last decade has led to the tremendous changes in the treatment strategy, moving from standard therapies to novel personalized approaches including targeted therapies. The main goal and challenge of the personalized medicine is to improve the diagnosis and efficacy of therapy, thus promoting longer survival of patients and better quality of life. Critical point in achieving that aim is the establishment of a precise diagnostic tool which would enable more efficient and prompt identification of the genetic background of the tumor. The aims of our pilot study is to investigate the genetic profile of primary lung adenocarcinoma in the Bulgarian population and to compare the accuracy and practical value of two diagnostic approaches with clinical significance for the routine testing – PCR-based detection through rt-mPCR (real-time, multiplex polymerase chain reaction) and NGS (next generation sequencing). DNA-samples of 10 patients (3 male, 7 female) with stage IIIB-IV lung adenocarcinoma was extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue. Initial testing was performed in search of known EGFR-driver mutations by rt-mPCR. Subsequently, a NGS-analysis with TruSight Cancer Panel, Illumina® (94 genes and 284 SNPs) and/or ArcherDx (Archer® VariantPlex Solid Tumor panel) was performed on Illumina MiSeq device. Bioinformatical pipeline included BaseSpace (for alignment and variant calling) and VariantStudio analysis. The effect of rare (<3% global frequency) missense variants was predicted using RadialSVM and LR scores. Variants were classified into 3 groups – pathogenic mutations associated with cancer development (driver mutations), probably pathogenic variants that might contribute to disease progression and prognosis, and variants of unknown clinical significance. At least one clear-cut driver mutation was identified in each patient sample. As expected, the most prevalent genetic alteration in lung adenocarcinoma were those in EGFR, particularly c.2572T>C, (p.Leu858Arg) and EGFR (c.2369C>T, p.T790M) in patients with secondary TKI-inhibitor-resistance, as well as in KRAS (c.32G>T, p.G12C). A novel, undescribed variant in EGFR (c.2506\_2507insAA, p.Arg836GlnfsTer11), was identified in one sample. Given its biological effect – frame-shift with occurrence of preterminal stop-codon, we can hypothesize its etiological importance. However, further analysis is necessary, in order to understand the potential meaning in TKI-therapy response. Results from NGS confirmed data from initial PCR-based testing and revealed new variants with potential clinical significance. The great heterogeneity in all patients highlights the importance of the comprehensive, highthroughput approach in NSCLC genome testing for identifying targets with clinical significance and of the personalized approach. Given the small sample size and the abundance of biomarkers with clinical relevance in NSCLC, we believe that NGS must be routinely integrated into practice as a time- and tissue-sparing method compared to PCR. Furthermore, establishing a centralized database of driver and other genetic alterations in the Bulgarian population is essential for the future research, new target identification and treatment options development.

## 5. FAMILIAL LYNCH SYNDROME WITH EARLY AGE OF ONSET AND CONFIRMED SPLICE SITE MUTATION IN MSH2: A CASE REPORT

Zornitsa Bogomilova Kamburova Savelina Lubenova Popovska Katya Stefanova Kovacheva Krasimir Todorov Petrov Slavena Enkova Nikolova

### ABSTRACT:

Lynch syndrome (LS) is an autosomal dominant cancer syndrome. It can be caused by mutations of several genes, including MLH1, MSH2, MSH6, PMS2, MLH3 and MSH3, which are responsible for DNA mismatch repair, and LS affects 3-5% of patients with colorectal cancer (CRC). LS is associated with a high risk of cancer in several different locations, although the most commonly affected regions are the colon (20-70% risk), endometrium (15-70% risk), stomach (6-13% risk) and ovaries (4-12% risk). In the present report, the familial case of LS with a detected pathogenic variant in the MSH2 gene is described. The proband was a male who was diagnosed with CRC at the age of 25 years. Genealogy analysis revealed a total of seven affected relatives (including the proband), one of whom (I degree relative, mother) had synchronous cancers (endometrial and ovarian) and five others (of II and III degree relation) had ovarian cancer. Genetic analysis using next generation sequencing detected a heterozygous germline mutation in the MSH2 gene (c.1386 + 1G >A) in the proband and his mother, confirming the diagnosis of LS. The results of the recommended genetic test in an asymptomatic relative of the proband (II degree relative, uncle), found the same familial mutation. Subsequent prophylactic colonoscopy of this relative revealed early stage CRC. The presented case confirms the need for specific genetic analysis, alongside genetic counseling, in hereditary cancer syndromes. Active genetic prophylaxis in patients with LS allows early detection of primary cancers in other locations, and pre-symptomatic genetic analysis of relatives is an option for early diagnosis.

*Biomedical Reports*, March 14, 2022, <https://doi.org/10.3892/br.2022.1522>, Article Number: 39

## 6. LYNCH LIKE SYNDROME WITH GERMLINE WRN MUTATION IN BULGARIAN PATIENT WITH SYNCHRONOUS ENDOMETRIAL AND OVARIAN CANCER

Zornitsa Bogomilova Kamburova, Polina Damyanova Dimitrova, Diana Strateva Dimitrova, Katya Stefanova Kovacheva, Savelina Lubenova Popovska & Slavena Enkova Nikolova

### ABSTRACT:

#### Background

Synchronous endometrial and ovarian cancer (SEOC) accounts for 50–70% of all synchronous gynecology cancers in women. Approximately 14% of SEOC cases are caused by Lynch syndrome (LS). The widespread introduction of “universal screening” at LS (all cases with CRC and all EC cases diagnosed before age 60 should be tested for MMR deficiency) has led to an increasing number of suspected LS cases- MMR-deficient tumors without germline mutation in the MMR genes.

These cases are attributed to the so-called Lynch-like syndrome (LLS).

### Case presentation

We present a case of LLS with a detected germline, likely pathogenic variant in the WRN gene. The proband was a woman diagnosed with SEOC at the age of 51 years. Histology of both tumors (endometrium and ovary) was endometrioid and showed loss of MLH1 and PMS protein expression. Genetic testing by next generation sequencing (NGS) detected a germline mutation (in the heterozygous state) in the WRN gene - c.4109del, p.(Asn1370ThrfsTer23) in the proband.

### Conclusions

The presented case contributes to the etiology of LLS and confirms the need for specific genetic testing, together with genetic counseling, in hereditary cancer syndromes. The use of combined information from clinicians, pathologists, genetic counselors, and data from NGS testing for cancer predisposition, clinical surveillance, and follow-up management in women with gynecology cancers, especially SEOC, could be improved. Hereditary Cancer in Clinical Practice.

*Hereditary Cancer in Clinical Practice, vol. 21, Article number: 13 (2023), Published: 14 July 2023*

### 7. OUR EXPERIENCE ON THE APPLICATION OF TELEPATHOLOGY AND DIGITAL PATHOLOGY FOR INTRAOPERATIVE DIAGNOSTICS ON FROZEN SECTIONS

*Ivanov V., Nikolova Z., Biserova E., Lyubenova L., Jikurashvili M., Nedqlkov K., Ivanova V., Dikov T., Ananiev J., Trifonov S., Baitchev I., Staneva D., Popovska S., Zornica P., Petrov K., Ivanov Iv.*

#### INTRODUCTION

Telepathology and digital pathology in frozen section practice is discussed and investigated in contemporary studies. Here we present our experience on digitalized frozen section preparation and interpretation. AIMS/OBJECTIVES The aim of this study was the evaluation of the application of telepathology and digital pathology for intraoperative diagnostics on frozen section. MATERIALS AND METHODS Subject of prospective and retrospective study is the evaluation and analysis of 44 samples (17 frozen sections and 27 standard ffpe tissue samples) from 10 patients. The issue samples were scanned using the infrastructure of the Centre of competence "Leonardo Da Vinci" and uploaded for online evaluation in three distant centers by experienced pathologists. The results were compared and analyzed. RESULTS The results demonstrated the lack of significant diagnostic discrepancy between the frozen section materials and the FFPE tissue materials between all four centers. Quality issues were reported in more than half of the frozen section images, as well as in about 1/3 of the FFPE scans. Different aspects of quality issues regarding tissue slides were found (including staining intensity and contrast, presence of artefacts like wrinkles and folds, precipitates of different origin, lack of parts that fell off during processing). Interpretability rate was over 80% of the subscribed slides. 149 poster SECTION CONCLUSION The application of telepathology and digital pathology for diagnostics on frozen section demonstrated promising results. Further investigation and additional specialized training of laboratory technicians is needed

*XX INTERNATIONAL MEDICAL SCIENTIFIC CONFERENCE FOR STUDENTS & YOUNG DOCTORS in Pleven – Abstract book 2023, P.6*

### 8. OPTIMIZING TISSUE SLIDES FOR RAPID DIGITALIZATION. A STEP TOWARDS INTRAOPERATIVE FROZEN SECTION ROUTINE TELECONSULTATIONS PROTOCOL.

*Nikolova Z., Ivanov V., Biserova E., Lyubenova L., Nedqlkov K., Jikurashvili M., Ananiev J., Trifonov S., Ivanova V., Dikov T., Baitchev I., Staneva D., Popovska S., Petrova Z., Petrov K., Ivanov Iv.*

#### INTRODUCTION

According to literature median specimen handling time of about 11min is required for whole slide imaging teleconsultation on frozen section (1). AIMS Our aim is to optimize tissue samples parameters (size and quality) for the need of intraoperative frozen section teleconsultations. MATERIALS AND METHODS Seventy one routinely prepared tissue samples approved and used for educational purposes (part of the educational slide collection of the department of general and clinical pathology) were digitalized on Olympus system. The studies were conducted within the framework of a project at the Center of competence "Leonardo Da Vinci". Slides were scanned routinely in one plane and if required (due to artifacts, a 7mm z-stack was performed). The scanned area, the time for scanning and uploading, the use of z-stack were recorded and analyzed. Parameters were statistically analyzed, using appropriate statistical tests (one way ANOVA and Kruskal-Wallis test). Results of  $p < 0,05$  were considered statistically significant. RESULTS The average time for scanning processing and uploading an image was 21min. (ranging from 10 min to 35min). From the scanned 71 slides, 5(7.04%) required rescanning due to lack of focus in substantial fields, that made interpretation difficult and uninterruptable. Due to the nature of the samples, z-stack scanning was used to achieve acceptable results in 4 of the cases. One case needed preparation of new slide due to tissue and staining artifacts (although was somewhat usable). Slide size was significantly related with scanning time  $f=18.17$ ,  $p=0.0001$ . Another factor  $Xx$  international Medical Scientific Conference, 16-20 oct 2023 172 significantly increasing the time for scanning is the use of z-stack  $K-W=6.5511$ ,  $p=0.0105$ . CONCLUSION Slides with scan area of 2mm<sup>2</sup> or less, scanned in one plane were ideal for tele consultation purposes as the required extra time was less than 20min.

*XX INTERNATIONAL MEDICAL SCIENTIFIC CONFERENCE FOR STUDENTS & YOUNG DOCTORS in Pleven – Abstract book 2023, P.24*

### 9. INFILTRATION BY INTRATUMOR AND STROMAL CD8 AND CD68 IN CERVICAL CANCER

*Polina Dimitrova, Mariela Vasileva-Slaveva, Velizar Shivarov, Ihsan Hasan and Angel Yordanov 5*

#### ABSTRACT:

Background and Objectives: The tumor microenvironment (TME) plays a major role in neoplastic development. Various types of cells can be found in the TME. These cells can be classified into two groups, immunosuppressive and immunostimulatory types, depending on the function they perform in the antitumor immune response (IR). By interacting both with each other and with tumor cells, different immune mechanisms are activated or inhibited, which can suppress or promote the development and progression of cervical cancer (CC). Our aim was to investigate some of the main components of the cellular immune response in TME—tumor-infiltrating



cytotoxic T cells (Tc, CD8+) and tumor-associated macrophages (TAMs, CD68+)—in patients with CC. **Materials and Methods:** We analyzed 72 paraffin-embedded tumor tissues of patients diagnosed and treated at Medical University Pleven, Bulgaria. Patients were classified according to the 2018 FIGO (International Federation of Gynaecology and Obstetrics) classification. From each patient, we selected one histological slide with hematoxylin eosin staining. In a microscopic evaluation, CD8+ T lymphocytes and CD68+ positive macrophages were counted in the tumor and stroma of five randomly selected fields at 40 magnification (HPF). We analyzed the relationship between intratumoral and stromal CD8 and CD68 expression and FIGO stage and N status. **Results:** There was no significant association between the expression levels of intratumoral and stromal CD68+ cells in the different FIGO stages and according to the lymph nodes' involvement. For CD8+ cells, the association of stromal infiltration was also not found, but T intratumor infiltration was associated with a higher FIGO stage, despite the fact that the results did not reach significance ( $p = 0.063$ , Fisher test). Intratumoral CD8+ cells were significantly associated with positive N status, ( $p = 0.035$ ). **Discussion:** The separation of tumor-infiltrating cytotoxic T cells and tumor-associated macrophages into intratumoral and stromal is inconsequential. In our study, the level of infiltration of CD68+ cells in tumors and stromata was not significantly associated with tumor progression or lymph node involvement. The results were different for CD8+ cells, in which levels of infiltration were associated with lymph nodes' statuses.

#### **Conclusions:**

The separate evaluation of CD68+ immune cells in the TME as intratumoral and stromal is not beneficial for defining prognoses, since the presence of these cells is not associated with the patient's stage. In our study, the presence of CD8+ cells was significantly associated with lymph node metastases. The prognostic value of the obtained results can be enriched with an additional study of the lymphocyte phenotype, including B and other subtypes of T lymphocytes, NK cells, as well as molecules involved in the immune response, such as HLA subtypes.

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P2

### **1. MESENCHYMAL STEM CELL REMODELING OF ADSORBED TYPE I COLLAGEN—THE EFFECT OF COLLAGEN OXIDATION**

by Regina Komsa-Penkova 1, Galya Stavreva 2, Kalina Belemezova 3, Stanimir Kyurkchiev 3, Svetla Todinova 4 ORCID and George Altankov

#### **ABSTRACT:**

This study describes the effect of collagen type I (Col I) oxidation on its physiological remodeling by adipose tissue-derived mesenchymal stem cells (ADMSCs), both mechanical and proteolytic, as an in vitro model for the acute oxidative stress that may occur in vivo upon distinct environmental changes. Morphologically, remodeling was interpreted as the mechanical rearrangement of adsorbed FITC-labelled Col I into a fibril-like pattern. This process was strongly abrogated in cells cultured on oxidized Col I albeit without visible changes in cell morphology. Proteolytic activity was quantified utilizing fluorescence de-quenching (FRET effect). The presence

of ADMSCs caused a significant increase in native FITC-Col I fluorescence, which was almost absent in the oxidized samples. Parallel studies in a cell-free system confirmed the enzymatic de-quenching of native FITC-Col I by Clostridial collagenase with statistically significant inhibition occurring in the oxidized samples. Structural changes to the oxidized Col I were further studied by differential scanning calorimetry. In the oxidized samples, an additional endotherm with sustained enthalpy ( $\Delta H$ ) was observed at 33.6 °C along with Col I's typical one at 40.5 °C. Collectively, these data support that the remodeling of Col I by ADMSCs is altered upon oxidation due to intrinsic changes to the protein's structure, which represents a novel mechanism for the control of stem cell behavior.

**Keywords:** *adipose tissue-derived mesenchymal stem cell; collagen type I; remodeling; oxidation*

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### **2. ALTERED THERMAL BEHAVIOR OF BLOOD PLASMA PROTEOME RELATED TO INFLAMMATORY CYTOKINES IN EARLY PREGNANCY LOSS**

Regina Komsa-Penkova 1, Avgustina Danailova 2, Sashka Krumova 2, Galya Georgieva 1, Ina Giosheva 2 3, Lidia Gartcheva 4, Ivan Iliev 2 5, Emil Gartchev 3, Kameliya Kercheva 3, Alexey Savov 3, Svetla Todinova 2

#### **ABSTRACT:**

Early pregnancy loss (EPL) is a relatively common pathology of which almost 50% of cases remain idiopathic. In the search for novel biomarkers, differential scanning calorimetry (DSC) is intensively used to characterize the thermodynamic behavior of blood plasma/serum proteome in health and disease. Herein, for the first time, we investigate the DSC denaturation profiles of blood plasma derived from patients suffering EPL compared to healthy pregnant and non-pregnant women. Data analysis reveals that 58% of the EPL thermograms differ significantly from those of healthy pregnant women. Thermal stabilization of a fraction of albumin-assigned transition with concomitant suppression of the major and enhancement of the globulin-assigned transition are characteristic features of EPL calorimetric profiles that could be used as a new indicator of a risk pregnancy. The presented results suggest an altered composition or intermolecular interactions of the plasma proteome of women with EPL. In addition, the alterations of the EPL thermograms correlate with the increased blood levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) and a higher prevalence of the polymorphism in the plasminogen activator inhibitor type-1 (PAI-1) gene, suggesting an expression of an overall enhanced immune response. The concomitant changes in plasma thermograms confirm the potential of the DSC approach for distinguishing changes in the pathological state of the blood plasma proteome.

**Keywords:** *4G/5G polymorphism in PAI-1 gene; blood plasma proteome; differential scanning calorimetry; early pregnancy loss; interleukin-6; tumor necrosis factor  $\alpha$ .*

*Int J Mol Sci. 2022 Aug 6;23(15):8764. doi: 10.3390/ijms23158764.*

### 3. MORPHOLOGICAL AND QUANTITATIVE EVIDENCE FOR ALTERED MESENCHYMAL STEM CELL REMODELING OF COLLAGEN IN AN OXIDATIVE ENVIRONMENT—PECULIAR EFFECT OF EPIGALLOCATECHIN-3-GALLATE

Regina Komsa-Penkova 1, Avgustina Danailova 2, Sashka Krumova 2, Galya Georgieva 1, Ina Giosheva 2 3, Lidia Gartcheva 4, Ivan Iliev 2 5, Emil Gartchev 3, Kameliya Kercheva 3, Alexey Savov 3, Svetla Todinova 2

#### ABSTRACT:

Early pregnancy loss (EPL) is a relatively common pathology of which almost 50% of cases remain idiopathic. In the search for novel biomarkers, differential scanning calorimetry (DSC) is intensively used to characterize the thermodynamic behavior of blood plasma/serum proteome in health and disease. Herein, for the first time, we investigate the DSC denaturation profiles of blood plasma derived from patients suffering EPL compared to healthy pregnant and non-pregnant women. Data analysis reveals that 58% of the EPL thermograms differ significantly from those of healthy pregnant women. Thermal stabilization of a fraction of albumin-assigned transition with concomitant suppression of the major and enhancement of the globulin-assigned transition are characteristic features of EPL calorimetric profiles that could be used as a new indicator of a risk pregnancy. The presented results suggest an altered composition or intermolecular interactions of the plasma proteome of women with EPL. In addition, the alterations of the EPL thermograms correlate with the increased blood levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) and a higher prevalence of the polymorphism in the plasminogen activator inhibitor type-1 (PAI-1) gene, suggesting an expression of an overall enhanced immune response. The concomitant changes in plasma thermograms confirm the potential of the DSC approach for distinguishing changes in the pathological state of the blood plasma proteome.

**Keywords:** 4G/5G polymorphism in PAI-1 gene; blood plasma proteome; differential scanning calorimetry; early pregnancy loss; interleukin-6; tumor necrosis factor  $\alpha$ .  
*Int J Mol Sci.* 2022 Aug 6;23(15):8764. doi: 10.3390/ijms23158764.

### 4. MORPHOMETRIC AND NANOMECHANICAL FEATURES OF PLATELETS FROM WOMEN WITH EARLY PREGNANCY LOSS PROVIDE NEW EVIDENCE OF THE IMPACT OF INHERITED THROMBOPHILIA

by Tonya Andreeva 1, Regina Komsa-Penkova 2, Ariana Langari 1, Sashka Krumova 1 ORCID, Georgi Golemanov 2, Galya B. Georgieva 2 ORCID, Stefka G. Taneva 1, Ina Giosheva 1,3, Nikolina Mihaylova 4 ORCID, Andrey Tchorbanov 4 and Svetla Todinova 1,\*

#### ABSTRACT:

Pregnancy is associated with hypercoagulation states and increased thrombotic risk, especially in women with thrombophilia. We combine atomic force microscopy (AFM) and flow cytometry to examine the morphology and nanomechanics of platelets derived from women with early pregnancy loss (EPL) and control pregnant (CP) and non-pregnant (CNP) women. Both control

groups exhibit similar morphometric parameters (height and surface roughness) and membrane stiffness of platelets. EPL patients' platelets, on the other hand, are more activated than the control groups, with prominent cytoskeletal rearrangement. In particular, reduced membrane roughness ( $22.9 \pm 6$  nm vs.  $39.1 \pm 8$  nm) ( $p < 0.05$ ) and height ( $692 \pm 128$  nm vs.  $1090 \pm 131$  nm) ( $p < 0.05$ ), strong alteration in the membrane Young modulus, increased production of platelets' microparticles, and higher expression of procoagulant surface markers, as well as increased occurrence of thrombophilia (FVL, FII20210A, PLA1/A2, MTHFR C677T or 4G/5G PAI-1) polymorphisms were found. We suggest that the carriage of thrombophilic mutations triggers structural and nanomechanical abnormalities in platelets, resulting in their increased activation. The activation state of platelets can be well characterized by AFM, and the morphometric and nanomechanical characteristics might serve as a new criterion for evaluation of the cause of miscarriage and offer the prospect of an innovative approach serving for diagnostic purposes.

**Keywords:** platelets; early pregnancy loss; atomic force microscopy; polymorphisms in thrombophilia genes; flow cytometry

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### 5. ALTERED MESENCHYMAL STEM CELLS MECHANOTRANSDUCTION FROM OXIDIZED COLLAGEN: MORPHOLOGICAL AND BIOPHYSICAL OBSERVATIONS

Regina Komsa-Penkova 1, Adelina Yordanova 2, Pencho Tonchev 3, Stanimir Kyurkchiev 2, Svetla Todinova 4, Velichka Strijkova 4 5, Mario Iliev 6, Borislav Dimitrov 1, George Altankov 7

#### ABSTRACT:

Extracellular matrix (ECM) provides various mechanical cues that are able to affect the self-renewal and differentiation of mesenchymal stem cells (MSC). Little is known, however, how these cues work in a pathological environment, such as acute oxidative stress. To better understand the behavior of human adipose tissue-derived MSC (ADMSC) in such conditions, we provide morphological and quantitative evidence for significantly altered early steps of mechanotransduction when adhering to oxidized collagen (Col-Oxi). These affect both focal adhesion (FA) formation and YAP/TAZ signaling events. Representative morphological images show that ADMSCs spread better within 2 h of adhesion on native collagen (Col), while they tended to round up on Col-Oxi. It also correlates with the lesser development of the actin cytoskeleton and FA formation, confirmed quantitatively by morphometric analysis using ImageJ. As shown by immunofluorescence analysis, oxidation also affected the ratio of cytosolic-to-nuclear YAP/TAZ activity, concentrating in the nucleus for Col while remaining in the cytosol for Col-Oxi, suggesting abrogated signal transduction. Comparative Atomic Force Microscopy (AFM) studies show that native collagen forms relatively coarse aggregates, much thinner with Col-Oxi, possibly reflecting its altered ability to aggregate. On the other hand, the corresponding Young's moduli were only slightly changed, so viscoelastic properties cannot explain the observed biological differences. However, the roughness of the protein layer decreased dramatically, from RRMS equal to  $27.95 \pm 5.1$  nm for Col to  $5.51 \pm 0.8$  nm for Col-Oxi ( $p < 0.05$ ), which dictates our

conclusion that it is the most altered parameter in oxidation. Thus, it appears to be a predominantly topographic response that affects the mechanotransduction of ADMSCs by oxidized collagen.

**Keywords:** YAP/TAZ; collagen; focal adhesion; mechanotransduction; mesenchymal stem cells; oxidation.

*Int J Mol Sci*

. 2023 Feb 11;24(4):3635. doi: 10.3390/ijms24043635.

## 6. MEMBRANE LESIONS AND REDUCED LIFE SPAN OF RED BLOOD CELLS IN PREECLAMPSIA AS EVIDENCED BY ATOMIC FORCE MICROSCOPY

Ina Giosheva, Investigation, Resources,1,2 Velichka Strijkova, Methodology, Formal analysis, Investigation,1,3 Regina Komsa-Penkova,4 Sashka Krumova, Writing – review & editing,1 Ariana Langari, Methodology, Investigation,1 Avgustina Danailova, Investigation,1 Stefka G. Taneva, Writing – review & editing,1 Tanya Stoyanova, Investigation,1 Lora Topalova, Investigation,1 Emil Gartchev, Resources,2 Galya Georgieva, Investigation,4 and Svetla Todinova, Conceptualization, Validation, Formal analysis, Writing – original draft1,\*

### ABSTRACT:

Preeclampsia (PE) presents with maternal de novo hypertension and significant proteinuria and is one of the leading causes of maternal and perinatal morbidity and mortality with unknown etiology. The disease is associated with inflammatory vascular response and severe red blood cell (RBC) morphology changes. This study examined the nanoscopic morphological changes of RBCs from PE women versus normotensive healthy pregnant controls (PCs) and non-pregnant controls (NPCs) applying atomic force microscopy (AFM) imaging. The results revealed that the membrane of fresh PE RBCs differed significantly from healthy ones by the presence of invaginations and protrusions and an increased roughness value (Rrms) ( $4.7 \pm 0.8$  nm for PE vs.  $3.8 \pm 0.5$  nm and  $2.9 \pm 0.4$  nm for PCs and NPCs, respectively). PE-cells aging resulted in more pronounced protrusions and concavities, with exponentially increasing Rrms values, in contrast to the controls, where the Rrms parameter decreased linearly with time. The Rrms, evaluated on a  $2 \times 2 \mu\text{m}^2$  scanned area, for senescent PE cells ( $13 \pm 2.0$  nm) was significantly higher ( $p < 0.01$ ) than that of PCs ( $1.5 \pm 0.2$  nm) and NPCs ( $1.9 \pm 0.2$  nm). Furthermore, the RBCs from PE patients appeared fragile, and often only ghosts were observed instead of intact cells at 20–30 days of aging. Oxidative-stress simulation on healthy cells led to RBC membrane features similar to those observed for PE cells. The results demonstrate that the most pronounced effects on RBCs in PE patients are related to impaired membrane homogeneity and strongly altered roughness values, as well as to vesiculation and ghost formation in the course of cell aging.

**Keywords:** preeclampsia, red blood cells, atomic force microscopy, membrane roughness, membrane impairment, cell senescence

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Published online 2023 Apr 12. doi: 10.3390/ijms24087100

## 7. BLOOD PLASMA CALORIMETRIC PROFILES OF WOMEN WITH PREECLAMPSIA: EFFECT OF OXIDATIVE STRESS

by Regina Komsa-Penkova 1, †ORCID, Sashka Krumova 2, †ORCID, Ariana Langari 2, Ina Giosheva 2,3, Lidia Gartcheva 4, Avgustina Danailova 2, Lora Topalova 2, Tanya Stoyanova 2, Velichka Strijkova 2,5, Alexey Savov 3 and Svetla Todinova 2,\*

### ABSTRACT:

Preeclampsia is a pregnancy-related disease with poor placentation and presents itself through hypertension and proteinuria. The disease is also associated with the oxidative modification of proteins in maternal blood plasma. In this work, we combine differential scanning calorimetry (DSC), capillary electrophoresis, and atomic force microscopy (AFM) to evaluate the changes in the plasma denaturation profiles of patients with preeclampsia (PE) as compared with those of pregnant controls. Our results demonstrate that the last trimester of pregnancy substantially affects the main calorimetric characteristics of blood plasma from pregnant controls relative to nonpregnant women. These variations correlate well with the changes in protein levels determined by electrophoresis. DSC analysis revealed significant deviations in the plasma heat capacity profiles of preeclamptic patients from those of pregnant controls. These alterations are expressed mainly in a substantial reduction in albumin-assigned transitions and an upward shift in its denaturation temperature, lower calorimetric enthalpy changes, and a reduced ratio of heat capacity in the albumin/globulin-assigned thermal transitions, which are more pronounced in severe PE cases. The in vitro oxidation model shows that the alteration of PE thermograms is partly related to protein oxidation. AFM data detected numerous aggregate formations in the plasma of PE samples and fewer small ones in the pregnant controls, which are not found in healthy nonpregnant samples. These findings could serve as a basis for further investigations to reveal the possible relationship between albumin thermal stabilization, the increased inflammatory state and oxidative stress, and protein misfolding in preeclampsia.

**Keywords:** preeclampsia; blood plasma proteome; differential scanning calorimetry; oxidative stress; protein thermal stabilization; capillary electrophoresis; atomic force microscopy; protein aggregates

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## 8. PLATELET POLYMORPHISM RS5918T > C IN THE INTEGRIN B3 GENE MODULATES MORBIDITIES IN PATIENTS WITH PSORIASIS

Borislav Dimitrov a, Galya Georgieva a, Klementina Gospodinova b, Pencho Tonchev c, Dimitar Gospodinov b, Galya Stavrevad and Regina Komsa-Penkova

### ABSTRACT:

Psoriasis Vulgaris is a complex multifactorial dermatological disease, with various genetic and environmental factors implicated in the onset and progression of the disease and comorbidities. Cardiovascular disease (CVD) and metabolic syndrome are essential psoriasis

comorbidities that suggest a potential hypercoagulable background of the disease. To better understand the link between psoriasis, hypercoagulation and comorbidities, we investigated the prothrombotic polymorphism rs5918T > C in integrin B3 (ITGB3) in 102 patients diagnosed with psoriasis and 97 healthy controls, all Caucasian. The patients, carriers of rs5918T > C polymorphism, were compared with non-carriers for metabolic risk factors related to metabolic syndrome and CV disease. Our results revealed that the incidence of ITGB3rs5918(C) allele carriage was only slightly increased in psoriatic patients compared to healthy controls (20.6% vs 18.6%), and psoriatic patients with the polymorphism showed an increased incidence of metabolic risk factors. Dyslipidemia, high triglycerides (42.9% vs 27.5%), high cholesterol (66.7% vs 45.5%) and low High Density Lipoprotein (HDL) (47.6% vs 32.8%) were significantly more prevalent ( $p = .019$ ) among psoriatic carriers of the rs5918(C) polymorphism compared to psoriatic non-carriers. The incidence of metabolic syndrome was significantly higher among polymorphism carriers (52.4%) compared to non-carriers (20.5%) within the psoriatic patient group ( $p = .014$ ), whereas CVD incidence was higher but non-significantly. The carriage of ITGB3rs5918(C) polymorphism in patients with psoriasis was associated with a higher risk of metabolic syndrome and dyslipidaemias and a higher but non-significant prevalence of CVD compared to non-carriers. However, the frequency of this polymorphism was similar in psoriasis patients and healthy controls.

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<https://doi.org/10.1080/13102818.2023.2212083>

#### **9. MORPHOMETRIC AND NANOMECHANICAL FEATURES OF PLATELETS FROM WOMEN WITH EARLY PREGNANCY LOSS PROVIDE NEW EVIDENCE OF THE IMPACT OF INHERITED THROMBOPHILIA.**

Andreeva T., Komsa-Penkova R., Langari A., Krumova S., Golemanov, G., Georgieva, G., Taneva B., Giosheva S., Todinova S

##### **ABSTRACT:**

Pregnancy is associated with hypercoagulation states and increased thrombotic risk, especially in women with thrombophilia. We combine atomic force microscopy (AFM) and flow cytometry to examine the morphology and nanomechanics of platelets derived from women with early pregnancy loss (EPL) and control pregnant (CP) and non-pregnant (CNP) women. Both control groups exhibit similar morphometric parameters (height and surface roughness) and membrane stiffness of platelets. EPL patients' platelets, on the other hand, are more activated than the control groups, with prominent cytoskeletal rearrangement. In particular, reduced membrane roughness ( $22.9 \pm 6$  nm vs.  $39.1 \pm 8$  nm) ( $p < 0.05$ ) and height ( $692 \pm 128$  nm vs.  $1090 \pm 131$  nm) ( $p < 0.05$ ), strong alteration in the membrane Young modulus, increased production of platelets' microparticles, and higher expression of procoagulant surface markers, as well as increased occurrence of thrombophilia (FVL, FII20210A, PLA1/A2, MTHFR C677T or 4G/5G PAI-1) polymorphisms were found. We suggest that the carriage of thrombophilic mutations triggers

structural and nanomechanical abnormalities in platelets, resulting in their increased activation. The activation state of platelets can be well characterized by AFM, and the morphometric and nanomechanical characteristics might serve as a new criterion for evaluation of the cause of miscarriage and offer the prospect of an innovative approach serving for diagnostic purposes.

**Keywords:** *platelets; early pregnancy loss; atomic force microscopy; polymorphisms in thrombophilia genes; flow cytometry*

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#### **10. CARTILAGE TISSUE ENGINEERING**

A. Kukov1, I. Ivanova1, V. Raykov2, G. Altankov3, I. Altankova1

##### **ABSTRACT:**

Tissue engineering is a relatively new discipline that combines the principles of engineering and biological sciences to develop analogues that can significantly restore the functions of damaged tissues. In the current review, we focus on the main achievements of the leading authors in the field of cartilage tissue engineering and regeneration. This discipline is based on an association of biomaterials (scaffolds), cells and biological or environmental factors, also known as the "tissue engineering triad". Chondrocytes, fibroblasts, various types of stem cells, progenitor cells from cartilage tissues are described for their chondrogenic potential. The importance of different scaffolds to reproduce the characteristics of the cartilage extracellular matrix (ECM) is highlighted. These bioconstructs provide cells with an environment capable of supporting their viability, proliferation and secretory activities. In cartilage tissue engineering, many scaffolds are studied, classified into three major groups: natural, synthetic, and hybrid. The importance of growth factors along with other components of ECM such as hyaluronic acid and chondroitin sulfate for proper cell growth and development is also emphasized. Despite the difficulties in cartilage tissue engineering, at the present time new approaches to improve the stability and functionality of cartilage regeneration continue to be sought.

**Key words:** *cartilage, tissue engineering, 3D, scaffolds, stem cells, chondrocytes*  
*Bulgarian Medical Journal, 16, 2022, № 3, 9-19*

#### **12. 3D BIOPRINTING OF CARTILAGE TISSUE.**

A. Kukov1, I. Ivanova1, V. Raykov2, G. Altankov3, I. Altankova1

Tissue engineering and regenerative medicine aimed at creating functional constructs mimicking native tissue for repair and/or replacement of damaged tissues or organs have evolved rapidly in the last decades. However, traditional tissue engineering approaches comprising of 3D bioconstructs, growth factors and cells, scaffolds, showed a limited success in making of complex 3D shapes and in vivo tissue regeneration leading to the impossibility of clinical applications, yet. In this point of view, 3D bioprinting is now being explored for tissue engineering as it involves the building of complex tissue in a layer by layer fashion, this way manufacturing precise geometries

due to controlled nature of matter deposition, assisted by computer graphics. The aim of our review is to present the 3D bioprinting technology along with associated 3D bioprinting strategies including extrusion printing, ink-jet printing, stereolithography and laser assisted bioprinting techniques. We further attempt to highlight the steps involved in 3D bioprinting technology on construction of cartilage-like 3D models, based on the available reports from recent literature. Finally, we conclude with current challenges with 3D bioprinting technology along with potential solution for future technological advancement of efficient and cost-effective 3D bioprinting methods.

**Key words:** 3D bioprinting, cartilage, scaffold, stem cells, chondrocytes  
*Bulgarian Medical Journal, 2023, 17(1), 22-34.*

Keywords: breast cancer, tumor-infiltrating lymphocytes, immunohistochemistry

*J Biomed Clin Res Volume 14 Number 1, 2021*

*J Biomed Clin Res Volume 14, Number 1, Supplement 1, 2021*

P3 – YHF

### **1. FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS) WITH NAVIGATION SYSTEM IN CHILDHOOD – OUR EXPERIENCE. PRESENTATION OF CLINICAL CASES**

*B. Duhlenki, Al. Valkov, Tsv. Mladenov, M. Yulduz, G. Nikolov, Tsv. Stoyanov, Kr. Atanasova*

#### **Abstract**

Introduction: Functional endoscopic sinus surgery (FESS) is the gold minimally invasive standard in diagnosing and surgically treating many diseases of the nose and paranasal cavities. An advantage of FESS is the possibility of application in all age groups.

Materials and methods: We observed pediatric patients attended the Otorhinolaryngology Clinic in the University Hospital “Dr. Georgi Stranski” – Pleven in 2021. FESS surgery was performed in the “Integrated interdisciplinary operating unit with navigation and telesurgery systems” at the Center of competence on personalised medicine, 3D and telemedicine, robotic and minimally invasive surgery „Leonardo da Vinci” in Medical University – Pleven.

Clinical cases: Case 1: A 7-year-old male patient with orbital complication of rhinosinusitis, with left orbital preseptal cellulitis, without ophthalmoplegia or loss of vision, + ptosis of the eyelid and data on pansinusitis from CT images. Performed FESS found lysis of lamina papyracea with involvement of anterior and posterior ethmoidal cells. Postoperative treatment was done with Ceftriaxone 1g/12h i.v. for 7 days, nasal glucocorticoids and antihistamines.

Case 2: A 17-year-old female patient with suggested primary ciliary dyskinesia with a recurrent rhinosinusitis, persistent nasal obstruction, and thick viscous secretions that did not respond to conservative treatment. Sweat test for cystic fibrosis (-). FESS reshaping of the natural openings of the maxillary sinuses and anterior ethmoidectomy were performed bilaterally.

Conclusion: FESS is a minimally invasive method, which is suitable for application in pediatric patients. When applied by trained professionals, FESS with an integrated navigation system is optimal for the diagnosis and surgical treatment of chronic and acute rhinosinusitis in children.

**Keywords**

*FESS, endoscopic surgery of the nose and sinuses, chronic rhinosinusitis, acute rhinosinusitis, pediatric patients*

*Scientific Online Resource System*

*International Bulletin of Otorhinolaryngology*

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P3 – Хурьрзуря

### **1. REVIEW ON ANASTOMOTIC LEAK RATE AFTER ICG ANGIOGRAPHY DURING MINIMALLY INVASIVE COLORECTAL SURGERY**

*Tsanko I. Yotsov, Martin P. Karamanliev, Svilen I. Maslyankov, Dobromir D. Dimitrov*

#### **Summary**

Colorectal cancer is the 3rd most common type of cancer worldwide. The most devastating complication after colorectal surgery remains the anastomotic leak (AL). Many techniques have been developed to reduce its rate. One such new method is perfusion angiography using indocyanine green (ICG). A literary search in PUBMED on 1.03.2021 for full-text English articles published between 2014 and 2021 was performed. ICG, colorectal cancer, and angiography were the keywords we used. The review was performed following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The literature search yielded 27 results when searching the database of PUBMED with the above keywords. Twentyone out of 27 identified articles were included. Six were excluded from the analysis – four case reports, one review on the evolution of treating gastrointestinal cancers, and one containing no information on AL rate with ICG. One included article was RCT, sixteen were cohort studies, and four were meta-analyses or reviews. All articles reported a reduction in the anastomotic leak rate. However, the reduction was significant only in nine of them. Anastomotic leak is a severe complication and a subject of extensive research. Perfusion angiography with ICG is a step towards predicting and preventing AL, although it does not guarantee success in all cases.

**Keywords:** *anastomotic leak, ICG angiography, colorectal cancer, minimally invasive surgery*

*J Biomed Clin Res Volume 14 Number 2, 2021*

### **2. PURSE STRING FAILURE AT THE BEGINNING OF THE LEARNING CURVE IN TRANSANAL TOTAL MESORECTAL EXCISION**

*Martin Karamanliev, Tsvetomir Ivanov, Tsanko Yotsov, Emil Filipov, Tashko Deliyiski, Dobromir Dimitrov*

Background: Transanal total mesorectal excision (TaTME) is a novel technique developed to overcome the difficulties and improve the oncological results in patients with narrow pelvis and bulky mesorectum. Achieving an air-tight purse-string suture is a crucial step in an oncologically safe TaTME and could be challenging at the beginning of the learning curve. Purse-string failure could theoretically increase the risk of local recurrence by tumor cell spillage and aerosolization of these tumor cells by the transanal insufflation.

**Materials and Methods:** The first 10 TaTME cases performed by a single team at our institution

were included. The leading surgeon went through all steps of training. The incidence of purse-string failure was studied. This work was supported by the European Regional Development Fund through the Operational Programme "Science and Education for Smart Growth" under contract №BG05M20P001-1.002-0010-C01(2018-2023).

**Results:** Mean age of the patients was 72.2 years. Neoadjuvant radiotherapy was conducted in five patients (5/10), neoadjuvant chemoradiation – in three patients (3/10), and no neoadjuvant therapy – in two patients (2/10). Purse-string failure was reported in one patient (1/10) presented with stool spillage during rectotomy. A second prolene running suture was done to close the rectal stump over the previous suture and a meticulous wash-out was performed. The rest of the procedure was carried out without other complications. Protective ileostomy was done in all cases. Within 30 days postoperatively 2 patients were presented with anastomotic leakage. Nevertheless, patients recovered up to 12 days without surgical intervention required.

**Conclusions:** The learning curve should be taken into consideration when adopting a new surgical procedure. Therefore, specific training in TaTME is essential. Purse-string failure could increase the risk of local recurrence and may be solved by applying a second running suture. Additionally, primary purse-string reinforcement in TaTME was proposed.

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<https://doi.org/10.1016/j.ejso.2020.11.273>

### 3. TRANSANAL TOTAL MESORECTAL EXCISION (TaTME): A LITERATURE REVIEW

*Martin P. Karamanliev, Dobromir D. Dimitrov*

#### Summary

Total mesorectal excision (TME) has become the golden standard for treating rectal cancer since Heald introduced it [1]. Transanal total mesorectal excision (taTME) is an innovative surgical method for rectal cancer. A nonsystematic literature review on the articles on taTME in the PubMed and Scopus database was performed. 'TaTME' and 'transanal total mesorectal excision' keywords were used. The search was restricted to articles in English on more than 25 patients analyzed and followed-up. Fourteen articles were identified, most of them from Europe and China. Of these, eight were original studies, and six were systematic reviews and meta-analyses. TaTME is safe and efficient in experienced hands. It could be superior to laparoscopic total mesorectal excision (laTME) concerning perioperative complications. Its advantages in oncological outcomes over laTME are to be proven in structured randomized clinical trials (RCTs).

*Keywords: rectal cancer, laparoscopic surgery, literature review*

*J Biomed Clin Res Volume 13 Number 1, 2020*

### 4. QUALITY OF LIFE AFTER TRANSANAL TOTAL MESORECTAL EXCISION IN RECTAL CANCER PATIENTS – A SINGLE CENTER INITIAL EXPERIENCE

*M. Karamanliev; D. Dimitrov*

**Aim:** To study the quality of life in rectal cancer patients before and after transanal total mesorectal excision (TaTME). Sixteen consecutive TaTME rectal cancer patients after the introduction of TaTME at our institution were included.

**Method:** Patients completed EuroQol-5D, EORTC QLQ-C30, EORTC QLQ-CR29, International Prostate Symptom Score (IPSS) questionnaires, LARS, and Vaizey score preoperatively and every 3 months postoperatively. The data were assessed for normality. A K-related sample analysis was then used to compare the results from the questionnaires. This work was supported by the ERDF, through the OP SESG, with a leading organization MU-Pleven, grant no BG05M20P001-1.002-0010.

**Results:** Questionnaires were filled from 15 patients (93.75%), two patients were operated on in less than 3 months and did not fill the postoperative questionnaires. A total of 13 patients were included in the analysis. We analyzed the results from the preoperative questionnaire and the last available one. The longest period is 3 years after operation and the shortest is 3 months. All data were not normally distributed ( $p < 0.05$ ). Statistically significant improvement in the following indicators postoperatively occurs compared to preoperative levels: pain/discomfort in EuroQol-5D ( $p = 0.014$ ), physical functioning ( $p = 0.046$ ), financial problems ( $p = 0.025$ ) and global health in QLQ-C30 ( $p = 0.001$ ), degree of anxiety/depression in QLQ-CR29 ( $p = 0.020$ ) and specific quality of life in the IPSS questionnaire ( $p = 0.011$ ). No statistical differences were found in: visual analogue scale for self-assessment in EuroQol-5D ( $p = 0.114$ ), social functioning in QLQ-C30 ( $p = 0.705$ ), faecal incontinence for patients without stoma in QLQ-CR29 ( $p = 0.317$ ), LARS score ( $p = 0.763$ ) and Vaizey score ( $p = 0.782$ ).

**Conclusion:** Quality of life after transanal total mesorectal excision in rectal cancer patients seems promising. Larger international randomized studies are needed to prove if there is an advantage over other approaches.

**Colorectal Disease Special Issue: Abstracts of the ESCP 17th Scientific & Annual Meeting, 21 - 23 September 2022, Dublin, Ireland**

### 5. COMPLICATIONS IN TRANSANAL TOTAL MESORECTAL EXCISION (TaTME) – EARLY EXPERIENCE

*Martin P. Karamanliev, Tsanko I. Yotsov, Dobromir D. Dimitrov*

#### Summary:

Transanal total mesorectal excision (TaTME) is a trending and promising surgical procedure to treat rectal cancer with oncologically oriented precision. Complication rates are promising after the learning curve is passed. A prospective study on the first 12 consecutive TaTME patients was done. The primary aim was the intraoperative and the early and late postoperative complications rate. One persisting failure as an intraoperative complication was reported: two anastomotic leaks and a ventral hernia as postoperative complications. TaTME is safe in terms of intra- and postoperative complications.

**Keywords:** *rectal cancer, laparoscopic surgery, complications.*

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DOI: <https://doi.org/10.2478/jbcr-2022-0018>

## 6. MESENTERIC VASCULAR EVALUATION WITH PRE OPERATIVE MULTIDETECTOR COMPUTED TOMOGRAPHIC ANGIOGRAPHY AND INTRAOPERATIVE INDOCYANINE GREEN ANGIOGRAPHY TO REDUCE ANASTOMOTIC LEAKS AFTER MINIMALLY INVASIVE SURGERY FOR COLORECTAL CANCER

Tsanko Yotsov , Martin Karamanliev , Svilen Maslyankov , Sergey Iliev , Nikolai Ramadanov , Dobromir Dimitrov

### Abstract

**Background:** The aim of this prospective study was to determine the effect of mesenteric vascular evaluation using pre-operative multidetector computed tomography angiography (MDCTA) and intraoperative indocyanine green (ICG) angiography on reducing the anastomotic leak rate of colorectal cancer patients undergoing minimally invasive resection.

**Methods:** Twenty-seven consecutive patients with colorectal cancer were studied, 18 males and 9 females, average age  $69.1 \pm 3.9$  years. All patients underwent pre-operative mesenteric vascular evaluation using MDCTA with three-dimensional (3D) reconstruction and intraoperative evaluation of perfusion using ICG angiography. Twelve patients underwent laparoscopic resection (Olympus Visera Elite II OTV-S200) and 15 patients underwent robotic resection (DaVinci Si). Colorectal resection lines and anastomoses were guided by intraoperative ICG perfusion. Postoperative anastomotic leaks were assessed.

**Results:** Pre-operative MDCTA 3D reconstructions defined the left colic and sigmoid artery anatomy and guided operative planning. The intraoperative ICG angiography resulted in a change of the planned lines of resection in seven patients (26%). The rate of postoperative anastomotic leaks in this study was 0% (0/27), compared to a leak rate of 6.8% at our institution in the preceding two years.

**Conclusion:** Pre-operative evaluation of mesenteric vascular anatomy using MDCTA with 3D reconstruction and intraoperative evaluation of perfusion using ICG angiography were found to be technically feasible and safe. An appropriately designed study should be undertaken to prove whether it was truly effective at reducing the postoperative anastomotic leak rate in colorectal cancer patients undergoing minimally invasive resection at our institution.

**Keywords:** Anastomotic leak; Colorectal cancer; Colorectal surgery; Computed tomography angiography; Fluorescein angiography; Minimally invasive surgical procedures.

*JSLs. 2022 Jul-Sep; 26(3): e2022.00022.*

*DOI: 10.4293/JSLs.2022.00022*

## 7. LEARNING CURVE OF ROBOTIC TOTAL MESORECTAL EXCISION VERSUS TRANSANAL TOTAL MESORECTAL EXCISION A SINGLE CENTER STUDY

Martin Karamanliev, Tsanko Yotsov, Dobromir Dimitrov

**Introduction:** Rectal cancer treatment has changed over the last several decades. Total mesorectal excision (TME) has proven to be the gold standard in rectal cancer surgery. Transanal total mesorectal excision (TaTME) and robotic total mesorectal excision (RoTME) for low and mid rectal cancer are implemented to overcome some of the difficulties of the laparoscopic approach. The aim of this study is to show a single-center experience in the learning curves of both RoTME

and TaTME.

**Material and methods:** A single-center prospective study comparing the first 17 consecutive RoTME cases from January 2016 to May 2019 to the first 16 consecutive cases of TaTME from July 2019 to June 2021 was conducted. The difference in the time periods is due to the later implementation of TaTME in the center. All procedures were performed by a single team.

**Results:** A total of 33 patients were included in the study – 17 RoTME patients and 16 TaTME patients. The groups were homogeneously distributed in terms of patients' characteristics and stage. Comparing the two groups, no statistically significant differences between them were found in terms of complication rates ( $p=0.692$ ), positive circumferential resection margins rates ( $p=0.000$ ), frequency of anastomotic leak rates ( $p=0.596$ ), time from completion of radiotherapy to surgery ( $p=0.229$ ) and time from surgery to ileostomy closure ( $p=0.880$ ). A statistically significant shorter operative time was found in the TaTME group ( $p=0.008$ ).

**Conclusion:** The learning curve should be considered in all procedures. A structured training pathway for TaTME and RoTME is essential. No differences between RoTME and TaTME in the learning curve were observed in our center.

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## 9. SUCCESS RATE AND SAFETY OF TOTALLY IMPLANTABLE ACCESS PORTS PLACED BY THE CEPHALIC VEIN CUTDOWN TECHNIQUE IN ONCOLOGICAL PATIENTS A SINGLE CENTER STUDY

Martin Karamanliev, Tsanko Yotsov, Dobromir Dimitrov

### Abstract

Totally implantable access ports (TIAPs) are commonly used in oncologic patients undergoing ongoing chemotherapy. The methods of choice for implantation are the subclavian vein puncture approach and the cephalic vein cutdown technique, followed by internal jugular vein access and external jugular vein access.

**Keywords:** cancer chemotherapy port-a-cath.

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## 10. РОБОТ АСИСТИРАНА ПРЕДНА РЕЗЕКЦИЯ НА РЕКТУМА ПРИ ПАЦИЕНТИ С РЕКТАЛЕН КАРЦИНОМ – ЩЕ РЕШИ ЛИ ПРОБЛЕМИТЕ С ОБУЧИТЕЛНАТА КРИВА И ЧЕСТОТА НА КОНВЕРСИИТЕ?

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### Въведение:

Тоталната мезоректална ексцизия (ТМЕ) е златен стандарт при оперативното лечение на рака на ректума след Въвжгането и от Хийлг през 1981г. Лапароскопската ТМЕ

(ЛаТМЕ) доказа, че е равна на отворената ТМЕ с предимствата на по-бързо възстановяване, минимална травма и по-кратък болничен престой. Въпреки това дори в последните проучвания честотата на конверсии при е висока и варира 8-30% дори в high-volume центрове. Роботизираната ТМЕ (РоТМЕ) има потенциала чрез по-добра визуализация и маневреност на инструментите да доведе до по-ниска честота на конверсии при запазена онкологична сигурност. Освен това съществуват данни, че обучителната крива може да е по-кратка от тази на ЛаТМЕ и е по-ергономична и с по-малка степен на умора за хирурга.

#### **Материали и методи:**

Представени са първите 30 пациенти, на които е извършено РоТМЕ при пациенти с ректален карцином в периода в периода 2014 – 2021 в клиниката по онкологична хирургия към УМБАЛ “Георги Странски” – Плевен. Това проучване е финансирано по проект №BG05M2OP001-1.002-0010-C01.

#### **Резултати:**

Първото голямо рандомизирано проучване целящо да покаже намаление на честотата на конверсии при РоТМЕ сравнена с ЛаТМЕ е ROLARR проучването. Въпреки че се отчитат конверсии 8,1% в РоТМЕ групата и 12,2% в ЛаТМЕ групата, проучването не доказва сигнификантна разлика, вероятно поради твърде голямата разлика заложена в дизайн от 50% редукция. При анализа на обучителната крива на първите ни 30 случая се открива сигнификантна разлика в оперативното време на първите 5 случая (средно – 352,3 мин) сравнени с последните 5 случая (средно – 188,5 мин)( $p=0,038$ ). Забелязва се и тенденция за намаляване на усложненията – 3 пациенти с инсуфициенция на анастомозата при първите 15 случая срещу 1 пациент с инсуфициенция при последните 15 случая.

#### **Заклучение:**

Роботизираните платформи предоставят множество предимства при дисекцията в малък таз при оперативното лечение на ректален карцином. За преминаването на обучителната крива са необходими 30-50 случая. Предстои доказване на редукцията на конверсии на РоТМЕ спрямо ЛаТМЕ.

### **11. ТРАНСАНАЛНА ТОТАЛНА МЕЗОРЕКТАЛНА ЕКСЦИЗИЯ (ТАТМЕ) – ЩЕ СЕ ПРЕВЪРНЕ ЛИ В СТАНДАРТ ЗА ЛЕЧЕНИЕ НА НИСЪК И СРЕДЕН РЕКТАЛЕН КАРЦИНОМ?**

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#### **Въведение:**

Трансаналната тотална мезоректална ексцизия (ТаТМЕ) е иновативен метод за лечение на нисък и среден ректален карцином въведен през 2012г. В клиничната практика от екипа на проф. Лейси. Революционното в интервенцията е дисекцията на ректума отдолу-нагоре в дисталната (хоризонталната) му част, която е и най-

предизвикателната при отворена и минимално инвазивна ТМЕ. Налични са първоначални данни за намаляване на честотата на позитивните циркумференциални резекционни линии (ЦРЛ) при ТаТМЕ сравнени с отворена и лапароскопска ТМЕ. Негативната ЦРЛ е доказана като един от най-важните онкологични показатели свързани с понижаване на нивата на локални и системни рецидиви на ректалния карцином.

#### **Материали и методи:**

Извърши се литературен обзор по темата. Представени са първите 16 пациенти, на които е извършено ТаТМЕ при пациенти с нисък и среден ректален карцином в периода в периода юли 2019 – юни 2021 в клиниката по онкологична хирургия към УМБАЛ “Георги Странски” – Плевен. Това проучване е финансирано по проект №BG05M2OP001-1.002-0010-C01.

#### **Резултати:**

Лапароскопската ТМЕ премина тестване за non-inferiority спрямо отворена ТМЕ в COLOR II и последващите метаанализи. В проучванията публикувани през последните години с пациенти подложени на ТаТМЕ включващи над 25 пациенти в сериите, позитивните ЦРЛ варират 0-13% със медианна честота 5-6%. Първото мултицентрово рандомизирано проучване, което цели да покаже редукция на позитивни ЦРЛ при ТаТМЕ сравнено с лапароскопска ТМЕ е COLOR III. Дизайнът включва 1098 последователни пациенти със среден или нисък рак на ректума. Включени са пациенти с нисък и среден ректум (0-5см и 5-10см от АКЛ оценени с ЯМР) в I-III стадии на заболяването. Данните за всички пациенти се разглеждат на централно ниво за намаляване на грешките в определяне на стадии, операбилност, разстояние от АКЛ и др. Пациентите се рандомизират в съотношение 2:1 в полза на ТаТМЕ. Данните ще бъдат анализирани въз основа на „намерение за лечение“ (intention to treat). Първичната крайна цел е процент позитивни ЦРЛ. Проучването има за цел да демонстрира намаляване с 4 % на позитивни ЦРЛ след ТаТМЕ в сравнение с лапароскопска ТМЕ. Изчислената честота на позитивни ЦРЛ при ЛаТМЕ е около 7%. Проучването е структурирано да докаже редукция до 3% при ТаТМЕ. Към януари 2022 са рандомизирани 705 случая.

Първоначалните ни резултати от първите 16 случая на ТаТМЕ показват средно оперативно време 263,75 мин, конверсия при двама пациенти, кръвозагуба при всички пациенти от 0 до 50мл, отлично качество на резектата определено като “complete” при 14 пациенти (87,5%) и „near-complete“ при 2 пациенти (12,5%) и един пациент с инсуфициенция на анастомозата, установена като малкотазов абсцес дрениран трансанално.

#### **Заклучение:**

За момента златния стандарт за лечение на ректален карцином е тотална мезоректална ексцизия, като лапароскопската ТМЕ премина тестване за non-inferiority спрямо отворена ТМЕ. Останалите минимално инвазивни методи (роботизирана ТМЕ и ТаТМЕ) Все още са в процес на доказване на предимствата си. Очакват се резултати от рандомизирани клинични проучвания и метаанализи. Първоначалните резултати на ТаТМЕ са обещаващи.



## 12. СЕНТИНЕЛНА АКСИЛАРНА ЛИМФНА ДИСЕКЦИЯ С ИНДОЦИАНИН ГРИЙН – ВИДЕО ПРЕЗЕНТАЦИЯ

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### Въведение:

Сентинелната аксиларна лимфна дисекция е златен стандарт при лечението на селектирани пациенти с рак на гърдата и малигнен меланом на кожата. След въвеждането на сентинелната лимфна биопсия се наблюдава еволюция на агентите използвани за детекция: багрила, технециева сцинтиграфия, магнитни частици, метални частици (семена), carbon dye и ICG. Индоцианин грийн е иновативен и обещаващ агент за детекция на сентинелни лимфни възли, който показва, че е сигурен, надежден и с висока степен на детекция (успеваемост). Изпълнението на метода налага наличие на флуоресциращия агент индоцианин грийн и камера с възможност за излъчване на близки до инфрачервени вълни (near-infrared) и улавяне на флуоресценция. Метаанализи в областта показват, че индоцианин грийн е по-добър индикатор от багрилен метод (Изосулфан, Патент Блу) или радиоизотоп самостоятелно и не е по-лош индикатор от багрилен метод комбиниран с радиоизотоп (dual техника).

### Видео презентация:

Представяме видео случай на сентинелна аксиларна лимфна дисекция с индоцианин грийн в клиниката по онкологична хирургия към УМБАЛ „Георги Странски“ – Плевен. Представени са основните стъпки, начини на откриване на сентинелни лимфни възли, разлики с останалите методи, предимства и недостатъци. Смятаме, че основни предимства на метода са лесна изпълнимост и видимост на флуоресценцията през надлежащи тъкани (до 1 см). Това проучване е финансирано по проект №BG05M20P001-1.002-0010-C01.

### Заключение:

Сентинелната аксиларна лимфна дисекция с индоцианин грийн е сигурен и изпълним метод в световен мащаб и на национално ниво.

## 13. INTRODUCTION OF STEREOTACTIC VACUUM ASSISTED BREAST BIOPSY IN BULGARIA

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### Summary:

Breast cancer is the most common cancer in women worldwide. The gold standard for biopsy is core needle biopsy. However, in certain cases, core needle biopsy cannot be applied, and the method of choice is vacuum-assisted biopsy. It is a minimally traumatic and precise method for diagnosing microcalcifications and small breast lesions. We aimed to present the initial experience with stereotactic vacuum-assisted biopsy in breast diseases at the Department of Surgical Oncology. We show indications and contraindications for this kind of biopsy and present our initial experience. From February 2020 to December 2022, 29 stereotactic vacuum-assisted biopsies were performed. Benign histology was found in 9 cases, malignant – in 15, and 5 cases were

precancerous. Therefore, being an innovative, minimally invasive, and highly accurate method for diagnosing breast lesions with a good cosmetic effect, it allows early diagnosis of breast cancer, and, last but not least, the procedure can be curative for benign lesions.

**Keywords:** stereotactic vacuum-assisted breast biopsy, microcalcifications, breast cancer

## 14. ПРИЛОЖЕНИЕ НА ICG ПРИ СЕНТИНЕЛНА ЛИМФНА БИОПСИЯ НА МАЛИГНЕН МЕЛАНОМ

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### Въведение:

Малигненият меланом е най-злокачествения и агресивен тумор в човешката патология, който има висок метастатичен потенциал.

Ключова роля при диагностично-терапевтичния процес има биопсията на сентинелни лимфни възли.

Целта на нашето проучване е да представим първоначалния ни опит с биопсия на сентинелни лимфни възли при малигнен меланом по метода с ICG.

Материали и методи: От м. януари 2022г. до м. януари 2023г. В Клиниката по онкологична хирургия към УМБАЛ „Д-р Георги Странски“ сме направили 26 сентинелни лимфни биопсии на пациенти с малигнен меланом по метода с ICG.

### Резултати:

Пациентите са на възраст от 31 до 85 години. При 18 от тях са уточнени между 1 и 5 сентинелни лимфни възли, които са верифицирани хистологично. В два от случаите е направена билатерална сентинелна лимфна биопсия.

### Заключение:

Сентинелната лимфна биопсия има значителна информативна стойност за състоянието на регионалните лимфни възли, позволява откриването на микрометастази и е най-важният прогностичен фактор. Осъществяването на сентинелната лимфна биопсия по метода с ICG е надежден метод за диагностика и преценка последващо поведение.

## 1. ANALYSIS OF ABDOMINAL VS. ROBOTIC RADICAL HYSTERECTOMIES FOR PATIENTS WITH CERVICAL CANCER: A BULGARIAN EXPERIENCE

Grigor A. Gorchev, Slavcho T. Tomov, Desislava K. Kiprova, Aleksandar D. Lyubenov, Nadezhda Hinkova, Vesela D. Tomova & Sarfraz Ahmad

### Abstract

To assess and compare the peri-operative, oncologic, and survival outcomes for women with cervical cancer (CC) treated with abdominal radical hysterectomy (ARH) versus robotic radical hysterectomy (RRH) approaches in Bulgaria. We retrospectively analyzed patients with histologically diagnosed CC operated via ARH or RRH methods during January-2008 to April-2019. The data analyzed include patients and tumor characteristics, peri-operative outcomes, and disease status. Kaplan–Meier method and Cox regression analysis were performed to determine

disease-free survival (DFS) and overall survival (OS). There were consecutive 1347 patients (ARH = 1006, RRH = 341), which formed the basis of study analyses. Women in the RRH group had significantly shorter median hospital length-of-stay than ARH cases (7 vs. 11 days,  $p < 0.001$ ), higher post-operative hemoglobin (116 vs. 108 g/L,  $p < 0.001$ ), and fewer blood transfusions (7.3% vs. 21.5%,  $p < 0.001$ ), respectively. The overall incidence of post-operative complications was also lower in the RRH vs. ARH group (2.1% vs. 9.4%,  $p < 0.001$ ). Median follow-up time for ARH vs. RRH groups was 4.32 vs. 5.24 years, respectively ( $p < 0.001$ ). Kaplan–Meier analysis demonstrated that the RRH cohort had a significantly higher survival rate compared to the ARH group (CC-specific death 8.5% vs. 16.5% respectively). Mean time to recurrence did not differ significantly in either surgical approach ( $p = 0.495$ ). Cox multivariate regression showed no significant impact of surgical approach on DFS or OS. No significant difference in DFS or OS between ARH vs. RRH for CC was observed. RRH approach does not lead to inferior oncologic outcomes and is associated with better peri-operative outcomes. In regard to “all stages” of CC, we found robotic surgery safer compared to laparotomy, and thus consider RRH a better surgical treatment option for patients with CC.

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## 2. PERI OPERATIVE AND SURVIVAL OUTCOMES ANALYSIS OF PATIENTS WITH ENDOMETRIAL CANCER MANAGED BY THREE SURGICAL APPROACHES:

### A LONG TERM BULGARIAN EXPERIENCE

*Slavcho T. Tomov, Grigor A. Gorchev, Desislava K. Kiprova, Aleksandar D. Lyubenov, Nadezhda H. Hinkova, Vesela D. Tomova, Zornitsa V. Gorcheva & Sarfraz Ahmad*

#### Abstract

The study aim was to assess the peri-operative, oncologic, and survival outcomes for patients with endometrial cancer (EC) managed by abdominal hysterectomy (AH), laparoscopic hysterectomy (LH), or robotic hysterectomy (RH) approaches at premier centers in Bulgaria. We analyzed histologically diagnosed EC cases operated via any of the three surgical methods during 2008–2019. Data analyses included patients and tumor characteristics, peri-operative outcomes, and disease status. We grouped FIGO stages I and II to represent early-stage EC and to investigate their survival. Kaplan–Meier and Cox regression analyses were performed to determine disease-free survival (DFS) and overall survival (OS). Consecutive 917 patients (AH = 466; LH = 60, RH = 391) formed the basis of study analyses. Most of demographics and tumor characteristics of the patients were comparable across the groups except few minor variations (e.g., LH/RH cases were younger, heavier, more stage IA, endometrioid, G1, low-risk group). LH and RH group cases had significantly lower operative time than AH ( $p < 0.001$ ), shorter hospital length-of-stay ( $p < 0.001$ ), higher post-operative Hgb ( $p < 0.001$ ). RH cases had fewer blood transfusions than AH or LH ( $p < 0.001$ ). Cox multivariate analyses indicate that OS was not influenced by the type of surgical approach. Despite the fact that the DFS in “early-stage” EC is significantly better in AH group than RH, the type of surgery (i.e., AH, LH, or RH) for “all stages” is insignificant factor for DFS. With our long-term experience, minimally invasive surgical approach resulted in superior peri-operative, oncologic, and survival outcomes. Specifically, RH is not only safe in terms of post-

operative results, but also for mortality and oncologic rates.

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## 3. EXTRUSION BIOPRINTING OF HYDROXYETHYLCELLULOSE BASED BIOINK FOR CERVICAL TUMOR MODEL

*Antonina Gospodinova, Vladislav Nankov, Slavcho Tomov, Murad Redzheb, Petar D. Petrov*

#### Abstract

The present study demonstrates the extrusion printing of highly viscous and thixotropic hydroxyethylcellulose-based bioinks blended with various concentrations of sodium alginate (SA) and embedded with HeLa cells. The cell viability is shown to be inversely proportional to the relative SA content and can be as high as 81.5 % following one day of incubation. Furthermore, the biocompatibility of the hydrogel matrix supports cell proliferation resulting in an order of magnitude larger number of cells after a 7-day incubation. The cell viability is negatively affected mostly by the extrusion printing itself with some cell death occurring during their embedding in the hydrogels. After embedding the HeLa cells in the blends containing 1 and 2.5 % SA, the cell viability is not significantly affected by the residence time of up to 90 min before the bioink extrusion. The printed constructs can be utilized as a cervical tumor model.

**Keywords:** Hydroxyethylcellulose (HEC) Alginate Rheology Extrusion Bioprinting HeLa Carbohydrate Polymers

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<https://doi.org/10.1016/j.carbpol.2021.117793>

P4 – Роботизирана урология

## 1. ИНТРАОПЕРАТИВНИ И РАННИ УСЛОЖНЕНИЯ СЛЕД РАДИКАЛНА ПРОСТАТЕКТОМИЯ

*Boyan Atanasov, Nikolay Kolev, Alexandar Vanov, Jitian Atanasov, Nikolay Nikolov, Rumyana Lyoskova, Pencho Genov, Anton Partenov, Angel Anatoliev, Simona Minkova, Vladislav Dunev*

#### РЕЗЮМЕ

Простатният карцином е един от най-значимите здравни проблеми на нашето съвремие. Той заема второ място като причина за смърт от онкологично заболяване в Европа и САЩ. Златен стандарт в лечението на локално ограничена простатен карцином е радикалната простатектомия. Тя може да бъде извършена чрез ретроперитонеален достъп, перинеален достъп, лапароскопски достъп или чрез робот-асистирана операция. Въпреки напредъка в оперативната техника, често се срещат усложнения и нежелани събития, свързани с хирургичната процедура, които влияят на качеството на живот на пациентите.

**КЛЮЧОВИ ДУМИ:** карцином на простатната жлеза, радикална простатектомия

*Клинична урология том 1, брой 3/2021 с.3-7*

[https://clinical-](https://clinical-urology.com/index.php/%D1%81%D0%BF%D0%B8%D1%81%D0%B0%D0%BD%D0%B8%D0%B5)

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## 2. УСЛОЖНЕНИЯ СВЪРЗАНИ С ИНСУФЛИРАНЕТО НА CO<sub>2</sub>, ПРИ ЛАПАРОСКОПСКА РАДИКАЛНА ПРОСТАТЕКТОМИЯ

Боян Атанасов, Николай Колев, МУ – Плевен

### ВЪВЕДЕНИЕ

Пневмоперитонеумът е най-често използваният метод, за създаване на достъп до перитонеалната кухина за лапароскопия. Разширяването на коремната кухина, чрез инсуфлиране на газ осигурява адекватна хирургична експозиция и позволява безопасно извършване на оперативните интервенции. Механичните ефекти от повишеното налягане върху сърдечно съдовата система биват – повишено следнатоварване, повишено венозно съпротивление, повишено средно системно налягане.

Трансперитонеалната абсорбция на въглеродния диоксид е причината за хиперкапния, която представлява проблем за анестезията. В сравнение с отворената операция, следоперативната белодробна функция е по-добра след лапароскопия.

Възможни усложнения: пневмоперикард, пневмоперитонеум, пневмоторакс, тензионен пневмоторакс, подкожен емфизем, сърдечна аритмия, газова емболия с въглероден диоксид, болка в рамото.

**ЦЕЛ:** Да извършим литературен обзор и да анализираме наличната информация с цел повишаване на информираността по темата.

**ЗАКЛЮЧЕНИЕ:** Нужни са обширни и задълбочени познания на възможните усложнения свързани с инсуфлирането на въглеродния диоксид при лапароскопска радикална простатектомия, за да можем ефективно да се справяме с тях.

**КЛЮЧОВИ ДУМИ:** Пневмоперитонеум, лапароскопска радикална простатектомия.

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<https://clinical-urology.com/index.php/%D1%81%D0%BF%D0%B8%D1%81%D0%B0%D0%BD%D0%B8%D0%B5>

## 3. ЧЕСТОТА, ПРЕВЕНЦИЯ И ЛЕЧЕНИЕ НА УСЛОЖНЕНИЯТА СЛЕД РАДИКАЛНА ПРОСТАТЕКТОМИЯ

Боян Атанасов, Николай Колев, МУ - Плевен

### ВЪВЕДЕНИЕ

I. Интраоперативни усложнения. Интраоперативни са тези усложнения, които настъпват от момента на позициониране на пациента върху хирургичната маса до края на оперативната интервенция. Видове: усложнения свързани с позиционирането на пациента, усложнения свързани с поставянето на троакарите, усложнения свързани с инсуфлирането на CO<sub>2</sub>, сърдечна аритмия, съдови усложнения, чревни наранявания (с изключение на ректума), лезии на ректума, увреждане на уретера, наранявания на пикочния мехур, неврологични усложнения Ранни усложнения: По дефиниция ранни са тези следоперативни усложнения, които настъпват от извеждането на пациента от операционната до края на първият месец след операцията. Към тях спадат: 1. Тромбоемболични усложнения: миокардни инфаркти, белодробната емболия и дълбоката венозна тромбоза. Въпреки малката им честота те водят до сериозни, животозастрашаващи състояния. 2. Усложнения на оперативната рана- серома,

подкожен хематом, инфекция на раната, дехисценция на раната. 3. Лимфоцеле. 4. Изтичане на урина от анастомозата. 5. Ретенция на урината. 6. Късно кървене 7. Постоперативни инфекции на уринарния тракт.

III. Късни усложнения 1. Склероза на мехурната шийка. 2. Ингвинална херния .3. Еректилна дисфункция

**ЦЕЛ:** Да извършим литературен обзор на възможните усложнения и поведение в случаите на настъпване на същите по време на и след извършване на радикална простатектомия.

**ЗАКЛЮЧЕНИЕ:** Усложненията при извършване на радикална простатектомия, изискват от операторите да бъдат добре запознати с тях, с цел тяхното предвиждане и адекватно поведение при възникване на някои от същите.

**Ключови думи:** радикална простатектомия, интраоперативни, ранни и късни усложнения

Списание: "Клинична Урология", Том 2, брой 2/ 2022; страници 5 до 21

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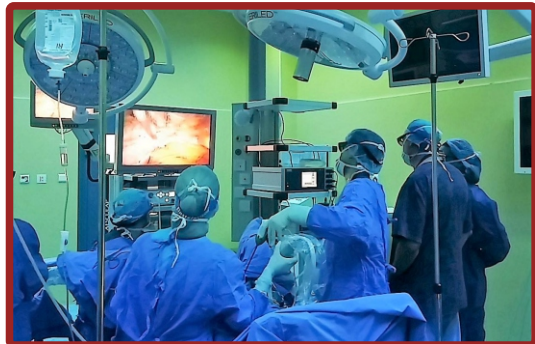
## 1. ROBOTIC ASSISTED LAPAROSCOPIC SURGERY FOR RECTAL CANCER (RALS): A REVIEW OF THE LITERATURE

Emil T. Filipov, Tsvetomir M. Ivanov

### Summary

Surgical treatment of rectal cancer is still difficult even in big centers. The limited pelvic space, problematic operative exposure, complex surgeries with more common anastomotic complications make the results unsatisfying. After the concept of total mesorectal excision (TME) was introduced by Heald, the results have improved dramatically. Advances in technology added further excitement about awaited promising results. Surgeons tried to apply all new methods to search for the best treatment: – atraumatic, painless, safe, with low recurrence rates, fast recovery, with an acceptable price, and easy to learn or teach. Robotic-assisted laparoscopic surgery (RALS) was introduced to overcome the limitations of conventional laparoscopic and open surgery and improve on their main advantages. A non-systematic literature review on the articles on RALS in the PubMed and Scopus database was performed. RALS, robotic-assisted laparoscopic surgery, and rectal cancer keywords were used. The search was restricted to articles in English, with main endpoints of interest on short-term and long-term surgical results and oncological outcomes. Fifty-seven articles from Europe, the USA, and Asia were identified. RALS was tried in large series in patients with different pathology and showed its values. However, there are still many controversies on its superiority, cost, and advantages. RALS is safe and efficient in experienced hands. It could be superior to conventional laparoscopic surgery (CLS). Its advantages in oncological outcomes over CLS are to be proven in structured randomized clinical trials (RCTs).

**Keywords:** rectal cancer, robotic-assisted laparoscopic surgery, RALS, literature review  
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