O P I N I O N

by Prof. Dr. Maya Georgieva Argirova, PhD
Head of Burns and Plastic Surgery Department,
UMHATEM "N. I. Pirogov" - Sofia,
member of the scientific jury

of Assoc. Dr. Nikolay Svetoslavov Yanev, PhD

for a dissertation thesis on the topic of "Algorithm for clinical application of virtual planning, modeling and 3D printing in local, regional and micro-vascular reconstructions of complex maxillofacial defects"

to acquire the scientific degree "Doctor of Sciences"
District 7. Health care and sports, Professional direction
7.1. Medicine, Scientific specialty "Neurosurgery"

The opinion was prepared on the basis of Order No. RD-26-1325/30.05.2022 of the Executive Director of UMHATEM "N. I. Pirogov", on the basis of Art. 32, par. 2 and 3 of the Regulations for the development of the academic staff at UMHATEM "N.I. Pirogov", Sofia, according to the decision of the Scientific Council, Protocol No. ND-01-2/18.05.2022.

Associate Professor Yanev presents a dissertation, an abstract and the other necessary documents in accordance with the Regulations for the Development of the Academic Staff at N.I. Pirogov UMBALSM - Sofia.

Biographical data

Associate Professor Nikolay Svetoslavov Yanev, PhD, was born on July 5, 1976 in the city of Ruse.

In 1994, he completed secondary education at 31 Secondary School for Foreign Languages and Management "Ivan Vazov" - Sofia

In 2002, he received a master's degree in dentistry at the Faculty of Dental Medicine in Sofia with excellent results.

In 2010, he received a second master's degree in medicine, Faculty of Medicine, MU - Sofia, also with excellent success.

In 2011, a specialty in maxillofacial surgery was recognized at MU - Sofia and a doctorate in medicine again at MU, Sofia, for the successful defense of a dissertation on the topic: "Mechanism directed treatment of pain - experimental models and pharmacological effects", developed in the Department in pharmacology and toxicology at the Sofia University

In 2013, a recognized specialty in oral and maxillofacial surgery in Great Britain (UK GMC Specialty registration – Oral and Maxillofacial Surgery)

In the period 2012 - 2018 he worked in Great Britain as:

07. 2012–04. 2013 – Clinical Fellow, Head and Neck Department, University College London Hospital NHS Foundation Trust, UK

04. 2013–07. 2015 – Clinical Fellow and Honorary Clinical Fellow Maxillofacial Surgery, Head and Neck Department, Royal Derby Hospital, UK

08. 2015–09. 2019 - specialist maxillofacial surgeon, Specialized Hospital for Maxillofacial Surgery - Sofia (SBAL for LCH)

02. 2016–03. 2017– Locum Consultant Maxillofacial Surgeon, Head and Neck Department, Royal Derby Hospital, UK

12. 2016–03. 2018 – associate professor at the Department of Pharmacology and Toxicology of the MU – Pleven

12. 2016 – associate professor, Medical University – Pleven

04. 2017–04. 2018 – Consultant Maxillofacial Surgeon, Head and Neck Department, Royal Derby Hospital, UK

In 2018 – pan-European certification of the acquired specialty in oral and maxillofacial surgery according to the requirements of the Board of Oral and Maxillofacial Surgery of the European Council of Medical Specialties (UEMS) and acquisition of the title – Fellow of the European Board of Oral and Maxillofacial Surgery (FEBOMFS)

04. 2018–12. 2019 – associate professor at the Research Institute of the MU – Pleven

09. 2019 – associate professor, UMBALSM "N. I. Pirogov" - Sofia

09. 2019–05.2022 – head of the Department of ENT, UMBALSM "N. I. Pirogov"

Membership in professional organizations

2010 – 2016 – representative of Bulgaria in the European Association for Craniomaxillofacial Surgery (European Association for Craniomaxillofacial Surgery – EACMFS) and full member (Active Member)

2010 - 2016 - representative of Bulgaria in the International Association for Oral and Maxillofacial Surgery (International Association for Oral and Maxillofacial Surgery - IAOMS) and its full member (Fellow)

He is currently a member of: British Association of Oral and Maxillofacial Surgery (BAOMS); The Society of Oral and Maxillofacial Surgeons in Bulgaria; The Bulgarian Medical Union; The Bulgarian Dental Union; General Medical Council (UK), with a specialty in oral and maxillofacial surgery recognized in Great Britain; Fellow of the European Board of Oral and Maxillofacial Surgery (FEBOMS); SORG Associate Member.

Characterization and evaluation of the dissertation work

Dr. Yanev's dissertation examines and analyzes the most modern methods of reconstructive treatment of large defects in the maxillofacial area. The latter lead to functional and aesthetic impairments, aspiration, speech difficulties and reduced quality of life for patients. Reconstruction of such defects is considered one of the most challenging procedures in head and neck surgery. Maxillofacial tumor resection begins with CT-based segmentation to delineate the neoplasmic lesion and undamaged healthy tissues. The relevant anatomy is translated into DICOM format, allowing the surgeon to create virtual 3D models of the target regions and simulate the surgical field and donor sites if necessary. A patient-specific treatment plan is created following a specific diagnostic and technological process finalized by implant design and 3D printing. 3D printing has evolved over the past three decades and has the potential to revolutionize the field of reconstructive medicine as a whole. Three-dimensional (3D) printing technology is an innovative technique that enables the production of customized

implants that conform to the exact anatomy of an individual defect and has therefore attracted considerable attention over the past few decades, particularly among head and neck surgeons. This technique uses metals, ceramics and plastics to produce three-dimensional (3D) objects for medical use. The 3D model is constructed layer by layer according to specific and precisely programmed parameters. The built object is removed and followed by post-processing procedures to obtain a functional part. The advantages of 3D-based technology in maxillofacial surgery are obvious and established: efficiency, accuracy and achieving an optimal clinical result. While their main disadvantages are the high price and the need for additional training.

The presented thesis consists of 246 standard pages and is illustrated with 12 tables and 147 figures. It is structured correctly. Contains: used abbreviations, introduction, literature review, aim and objectives, own research, material and methods, results and discussion, conclusion, implications, bibliography. The bibliography includes 253 literary sources, of which 15 are in Cyrillic.

The scientific work is structured according to the classic structure for these theses. Introduction - 1 page, literature review 77 pages, goal - and tasks - 1 page, material and methodology - 25 pages, own research - 90 pages, discussion - 26 pages, conclusion - 1 page, implications - 3 pp., contributions – 2 pp. and bibliography 18 pp. A list of scientific publications and participation in scientific forums related to the topic of the dissertation is presented.

The literature review covers 77 pages and is highly informative, showing the current state of microvascular surgery and defining it as the most complex level of the modern reconstructive ladder. The Bulgarian experience in microvascular and digital-assisted reconstructive facial surgery in Bulgaria was also shared retrospectively.

The aim of the dissertation work is specific and clearly formulated - the creation of an algorithm for clinical application of the methods of virtual 3D planning, modeling and printing in local, regional and microvascular reconstructions of extensive bone defects in the maxillofacial region, after the relevant surgical treatment and tracking its results.

The five tasks are specific, correctly defined and fully correspond to the set goal. Their implementation gives an exact answer to the specified goal.

1. Systematization of the necessary preparatory studies and the steps in the process of virtual planning, modeling and corresponding bony maxillofacial surgical intervention.

2. Production of individual 3D jaw models for patients with bone resections and reconstructions and individualization of standard reconstructive implants based on them, as an initial stage of application of digital methods in surgical practice.

3. Complete process of digital planning, modeling, operative simulation, production of surgical transfer guides and 3D patient-specific implants.

4. Intraoperative application of the individualized standard implants according to the produced 3D jaw models, as well as the 3D printed patient-specific implants and surgical guides.

5. Summarizing an algorithm for applying the methods of virtual 3D planning, modeling and printing in local, regional and microvascular reconstructions of extensive bone defects in the maxillofacial area.

Task 5 overlaps with the set goal.

The clinical **material** covers a period of 4 years (from May 2016 to April 2020) and presents a descriptive and clinical-analytical study with the follow-up of 22 patients with diseases in the maxillofacial area requiring surgical intervention to remove extensive areas of various bone and soft tissue structures of the face and one-time reconstruction using the methods of 3D virtual planning, modeling and printing. Patients were included according to clearly defined criteria. The last criterion of the three mentioned explains the low number of patients in the clinical contingent, namely opportunities for independent or assisted financing of the creation of the 3D printed model or implants in the conditions of the health system in Bulgaria. Patients were divided into two groups of 12 and 10 patients.

The working methods used are classical - clinical, diagnostic (laboratory, instrumental, informational, technological and medical-engineering), surgical, statistical and post-operative monitoring. They are completely sufficient and reliable for giving a correct answer to the set tasks.

Results:

The results of the scientific development demonstrate the specific approaches for virtual 3D planning, modeling and printing, as well as their clinical application in complex cases of resections and reconstructions in the maxillofacial area. The data for the included patients, divided into two groups, are presented in graphical and tabular form with detailed explanatory text and good visualization. The first group (12) includes the patients in whom 3D models of the maxillofacial skeleton were produced by the described methods with a view to physical preoperative orientation and shaping of the standard titanium plates in an individualized implant relative to the model. The second group (10) included patients in whom complete virtual planning of the complete skeletal surgical intervention was carried out, including with simulation of bone microvascular reconstruction and surgical guides were produced, with a view to exact transfer of the virtual plan in the real operation, as well as production of a three-dimensional patient-specific implant to support the reconstructive bone segments and restore the correct and harmonious facial contour. For the first time in our country, a protocol has been created for a computed tomography examination of patients undergoing microvascular reconstructive surgery in the head and neck area, with a donor area in a remote part of the body. This protocol allows the generated image information to be directly exported to the planning server and simultaneously used for the purposes of digital planning methods. In the two groups of patients presented, CT scanning of the donor area was applied to the lower half of the body (pelvis and lower limbs), but this protocol can be applied to other donor areas of the body. The systematization and precise interpretation of thin-section computer-tomographic imaging methods, as well as their examination in the direction of virtual planning and modeling, are in the essence of the creation of national and international interdisciplinary medical-engineering cooperation.

The ability to depict the normal anatomy or the corresponding pathological change of the bone structures in the face, in the form of a patient-specific 3D model, applied by the author and his team to the patients of the first group is a significant achievement of the application of digital methods in the field of clinical surgical practice. The benefits of the individual models are summarized and presented in a table. In the first group of patients, 12 individual models were three-dimensionally printed, of which: 5 – depicting the real bone anatomy, with the available bone pathology; 3 – the real bone anatomy, with no pathology present in it and 4 –

with a reconstructed image of the bone, due to the presence of an extensive destructive process using mirror image technology. These models were used in 5 microvascular reconstructions and 8 regional axial reconstructions.

In the second group of patients, for each individual case, a complete process of generating digital models of the maxillofacial pathology as well as the donor site for microvascular skeletal reconstruction was carried out; virtual planning and simulation of the resection and reconstructive phases of the operative intervention; production of sets of surgical guides to transfer the virtual plan to the real operation (without two patients), as well as production of 3D patient-specific implants, accompanied by 3D models of the reconstructed facial structures and of the donor bone areas, for perioperative verification. For all patients of the II group, this process was carried out together with the medical engineering team of the company KLS Martin (Tutlingen, Germany), by means of periodic online conference meetings for each clinical case. This state-of-the-art clinical approach has been used in 9 microvascular and 4 regional axial reconstructions.

Based on the presented resection and reconstructive defects in the II group of patients involving the lower jaw, laser-sintered patient-specific implants were virtually constructed. Following the general design approved by the KLS Martin Group (Tutlingen, Germany), all resection guides are planned without any distance from the corresponding bony structures in the facial area. Reconstructive guides, on the other hand, are planned with different bone-to-guide distance, in order to study the adaptation, interaction, accuracy and comfort of work with different volume of bony structures and periosseous soft tissues.

The individualized standard titanium implants according to the produced 3D jaw models in the patients of the I group are associated with the application of 5 microvascular and 8 regional axial reconstructions. The 3D printed surgical guides and patient-specific implants in the patients of the II group were respectively applied in 9 microvascular and 4 regional axial reconstructions

Bone-based microvascular reconstructions are fibular and iliac microvascular bone reconstructions. The regional reconstructions in both groups of patients are represented by the pectoral, latissimus dorsi and the temporal flap, and by the cervical flaps - the region of the sternocleidomastoid and platysma muscles.

Microvascular reconstructions in both groups of patients were performed in a single-stage, multi-team manner, with the participation in various cases of 2 to 3 three-member surgical teams, 2 to 3 two-member anesthetic teams, 3 to 4 operating nurses and 2 to 4 operating nurses. In all applied and described 10 laser-sintered patient-specific implants, the following were established: absolutely exact adaptation to the recipient bed and bone graft (in the case of microvascular reconstructions), as well as complete comparability in length, volume and three-dimensional orientation with respect to the virtual plan.

Based on the clinical experience acquired and described in the presented work, an algorithm was created for the application of digital-assisted methods in cases of local, regional and microvascular reconstructions of complex and extensive defects in the maxillofacial area. With its help, the approaches to digitally-assisted surgery are systematized in cases of complex maxillofacial bone pathology with an impending or existing extensive defect, in which the possibilities for operative intervention are integrated only with the help of an orienting individual patient-specific 3D model - facial- jaw and/or donor (first line of the algorithm) and

for a fully developed concept of virtual planning, modeling, resection and reconstructive simulation and 3D printing of surgical guides and patient-specific implants, combined with microvascular bone reconstruction (second line of the algorithm). The two columns of the algorithm lead to the final phase – implementation of a corresponding comprehensive surgical treatment – digital-assisted maxillofacial resection and/or local, regional or microvascular reconstruction of the complex tissue defect.

In conclusion, the dissertation work of Dr. Nikolay Yanev, PhD presents the author's personal surgical experience of the clinical application of virtual planning, modeling and 3D printing in cases of local, regional and microvascular reconstructions of complex maxillofacial defects.

In recent years, the development of microvascular surgery has been greatly aided by the new digital technologies in medicine. Studying the European and world experience of leading maxillofacial institutions and actively participating in the work of various international scientific and clinical structures, the author and his team created the presented algorithm for the restoration of extensive maxillofacial defects. The dissertation work represents a contribution to the reconstruction of the serious functional and aesthetic postoperative consequences and offers modern and comprehensive treatment to the patients ensuring their good quality of life.

I accept the significance of the dissertation, the presented contributions and conclusions. Some of them could be merged, which does not detract from their value. The scientific research and its results are presented in a synthesized form of the dissertation work and are demonstratively illustrated. The dissertant has fulfilled the goal he set for himself. The submitted abstract meets the requirements of the LDASRB. 15 publications in scientific journals and 5 participations in scientific forums related to the development are presented. Of these, the dissertant is the lead author in 7 scientific publications and 4 scientific reports. A declaration of originality and authenticity is provided. The dissertation meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB) and the Regulations of UMHATEM "N. I. Pirogov", Sofia, for its application.

Due to the above, I confidently give my positive assessment regarding the dissertation work of Dr. Nikolay Yanev, PhD on the topic "Algorithm for clinical application of virtual planning, modeling and 3D printing in local, regional and microvascular reconstructions of complex maxillofacial defects" and offer to the scientific jury to award him the scientific degree "Doctor of Sciences" in District 7. Health care and sports, Professional direction 7.1. Medicine, Scientific specialty "Neurosurgery".

03.07. 2022 г. Prof.Dr.Maya Argirova, PhD