To the Chairman of the Scientific Jury,
appointed by order No. RD-26-1325/30.05.2022.
of the Executive Director of UMHATEM, N.I. Pirogov"

OPINION

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Regarding: Dissertation thesis for the award of the scientific degree "Doctor of Sciences" in the scientific specialty "Neurosurgery" in the field of higher education 7. Health care and sports by professional direction 7.1. Medicine, which is presented for defense according to the decision of the Scientific Council with protocol No. ND-01-2/18.05-2022

Topic: "Algorithm for clinical application of virtual planning, modeling and 3D printing in local, regional and microvascular reconstructions of complex maxillofacial defects"

Author: Associate Professor Nikolay Svetoslavov Yanev, PhD

I. Biographical data and career development of Assoc. Dr. Nikolay Yanev, MD

Assoc.Prof. Dr. Yanev was born in Ruse in 1976. Graduated in 1994. the 31 High School "Ivan Vazov" - Sofia. From 1994 to 1996 serves his compulsory military service. In 2002 obtained a master's degree in Stomatology (Dental Medicine) in Stom. University of Sofia - Sofia. Since 2003 was appointed as a resident doctor at the Maxillofacial Surgery (MFS) Department of the Military Medical Academy - Sofia, and from 2005 to 2012. worked and specialized at SHAT for MFS - Sofia. In 2010 obtained a master's degree in Medicine at the Sofia University, and in 2011 a specialty in MFS. In the same year, he successfully defended his dissertation on the topic of: "Mechanism of targeted treatment of pain - experimental models and pharmacological effects", developed at the Department of Pharmacology and Toxicology of the Sofia University and obtained the educational and scientific degree "Doctor". From 2012 to 2017 specialized and worked in Great Britain (University College London Hospital NHS Foundation Trust, UK; Clinical Fellow Maxillofacial Surgery, Head and Neck Department, Royal Derby Hospital, UK). From 2016 to 2018 is an associate professor at the Department of Pharmacology and Toxicology of the MU - Pleven, in 2019. to the Research Institute of the MU - Pleven, and from 2019 to 05. 2022. heads the department of MFS of UMHATEM «NI.Pirogov».

Assoc. Dr. Yanev has completed numerous qualification courses on MFS in Austria, Bulgaria, Belgium, Great Britain, Germany, Spain, Poland, Slovenia - including microvascular reconstructions in the maxillofacial area. Between 2010 to 2016 he is a member and representative for Bulgaria of the European Association for Cranio-Maxillofacial Surgery and the International Association for Oral and Oral Surgery. He is also a member of other national and international unions, societies and associations.

Associate Professor Dr. Yanev is the author and co-author of 34 scientific publications, participates in 10 textbooks and monographs, and in 6 research projects.

II. Volume and structure of the presented dissertation work

The dissertation work of Assoc.Prof. Dr. Nikolay Yanev, PhD, is written on 246 pages, illustrated with 12 tables and 147 figures. The bibliography includes 253 literary sources, of which 15 are in Cyrillic

and the rest in Latin. It contains: introduction, literature review, aim and tasks, own research - material and methods, results, discussion, conclusion, implications, bibliography.

In the review, the author traces the historical development of methods and techniques for reconstruction of extensive defects in the maxillofacial region with tissues from neighboring and distant areas of the body. Describes arterialized axial flaps as well as tissue transfer via microvascular anastomoses. tissues close to the operative area and distant areas of the body. Describes arterialized axial flaps as well as free tissue transfer feasible through microvascular anastomoses. It examines three-dimensional virtual surgical planning, through CT images in DICOM format, their segmentation, STL file generation, modeling through CAD design, as well as new techniques and materials for 3D printing. The development of these modern digital technologies in medicine clearly arouses a deep interest in Assoc. Prof. Dr. Yanev, and he formulates the goal of his dissertation work: 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 area, after the relevant surgical treatment and follow-up of its results. For its implementation, the author sets 5 tasks.

III. Relevance of the topic

The reconstructions of complex defects in the maxillofacial region are a serious challenge. They go through various stages to reach acceptable healing results. After World War II, free bone grafts were established, the success rate of which with secure fixation reaches 70%, but their resorption is unpredictable. In 1979 a myocutaneous vascularized graft from m. pectoralis major to repair defects in the head and neck area was described. Other pedicled flaps are also developed, which feeding vessels are in the transfer peduncle. For their maintenance, "reconstructive plates" are used, but failures exceed 45%. Microsurgery, which also began at the end of the 1970s (in 1978, a vascularized iliac graft was used for mandibular reconstruction, and in 1989 - a fibular one), has been affirmed in recent decades. The possibilities for the transfer of viable bone and soft tissue have increased, and the act of tumor ablation and restoration is performed in one operative time. Microsurgery was used in patients aged 1 to 86 years. and transplant survival is over 90%. According to Wolff's principle, they are in an optimal situation for bone regeneration and remodeling when they are anatomically formed and placed in a functional "working" position. This is already achieved through virtual CT images and 3D models are realized with CAD/CAM technologies. They ensure accurate preoperative planning of resections, formation of transplants and reconstructive plates. Operative time (from 0.42h to 1.4h), blood loss, infection conditions and costs (estimated at €16 per minute) are reduced, which offset the cost of the models. Thanks to microsurgical vascular and nerve anastomoses, and with progress in understanding human immunology, complex facial allotransplantations are now a fact. Therefore, the aspiration of Assoc. Dr. Yanev to develop an algorithm for clinical application of virtual planning, modeling and printing of surgical guides and 3D patient-specific implants in reconstructions of maxillofacial defects is fully justified. The topic of his dissertation is in in unison with modern interdisciplinary medical-engineering achievements.

IV. Materials and methods

For a period of 4 years (May 2016 - April 2020), Assoc. Prof. Dr. Yanev treated and monitored 22 patients with primary or secondary extensive bone defects of the face, causing significant functional and aesthetic disorders. He divides them into two groups. In the 1st one 12 patients were included, in which, after processing the CT data of the facial skeleton, 3D models were produced, presenting a real image of the bone pathology, and in more severe cases, they ware reconstructed using the "mirror image" technique. In the 2nd group of 10 patients, complete 3D virtual planning of the complete operative intervention with simulation of bone reconstruction was carried out, surgical guides were also applied, as well as three-dimensional patient-specific implants to support the reconstructive segments.

The dissertant presents the criteria for the inclusion of patients, the clinical, laboratory and standard methods for their examination. I attribute a significant role to the protocol developed under the guidance of Assoc.Prof. Dr. Maria Nedevska, PhD, (Head of the Imaging Department of St. Ekaterina Hospital, Sofia) for native and two-phase contrast CT of the maxillofacial region and angiography of pelvis and

lower limbs with an average slice thickness of 0.5 mm and a rotation time of 0.5 sec. It is fundamental for the implementation of precise digital planning.

In the 1st group of 12 patients, the medical-engineering collaboration for the digitally assisted surgical approach with the laboratory of CAD/CAM/CAE technologies of TU Sofia (led by Prof. G. Todorov, d.s.. and by the team of chief assistant proffesor eng.Sofronov) and Mimics Software (Materialise, Leuven, Belgium). In the II group of 10 patients, a complete process of generating digital models of the maxillofacial pathology and donor areas was carried out together with the medical engineering team of the KLS Martin company (Tutlingen, Germany) through the KLS IPS Gate® platform and periodic online conferences. It is combined with virtual planning and simulation of the resection and reconstructive phases of the operation, creation of surgical guides to transfer the virtual plan into real microvascular interventions, production of 3D patient-specific implants accompanied by 3D models of the restored structures and of the donor bone areas. These successfully implemented collaborations between Associate Professor Dr. Yanev and other medical and engineering specialists prove his enviable collaborative abilities.

The dissertation describes the approach of maxillofacial resections and microvascular reconstructions in one operative time, with the participation of a resection (led by Dr. Slavkov) and a reconstructive surgical team (led by Assoc.Prof.Dr. Yanev). I consider the role of each of them significant without ranking it. The radicality and ablastic nature of the operation predetermines the healing success, and the well-secured autograft and the performed microvascular anastomoses - the recovery. Associate Professor Dr. Yanev describes the preparation of the operating room, the positioning of the patient, the team, the operating diploscope, as well as some technical stages of the interventions. He also presents the cases of resections with regional arterialized flaps performed by one surgical team (led by Assoc. Dr. Yanev), for the support of which reconstructive plates formed according to 3D models are often used. It examines the immediate and early period of observation of patients, which, in addition to general somatic indicators, includes visual, palpatory and ultrasound assessment of the blood supply to the flap. Unfortunately, I did not find information about postoperative antiplatelet, anticoagulant, etc. drug therapy. The statistical methods are also listed (data were processed with the help of chief assistant professor Dr. Eng. Krastin Yordanov from TU - Varna).

V. Results

Only in this chapter do we get to know in more detail the distribution of patients by pathology and the performed resections and reconstructions. They are presented in table 6 and table 7. In the 1st group of 12 patients, Assoc.Prof. Dr. Yanev includes: 1 with ossifying fibroma, 1 with amelablastoma, 2 with medically induced osteonecrosis of the jaw and 8 with carcinomas. In them, 12 individual models were 3D printed, of which 5 depict the existing bone pathology, 3 - the real bone anatomy, without any pathology present in it, and in 4, the "mirror image" technique of the healthy side was applied, due to the presence of an extensive destructive process in the affected side. The models were used in 5 microvascular and 8 regional axial reconstructions. 9 reconstructive plates (1 for the upper and 8 for the lower jaw), 5 miniplates (3 for the area of the mandibular mentum and 2 for the zygomaticomaxillary and nasomaxillary complexes) and 2 orbital titanium implants were preoperatively bent and adapted to them. Assoc.Prof. Dr. Yanev describes each of the patients under number - in detail at each stage of the planned, carried out treatment and conducted monitoring.

In the II group, the dissertant includes 10 patients: 3 with sarcomas, 5 with ameloblastomas, 1 with adenocarcinoma and 1 with osteonecrosis. And here each one of them is described as a separate case study. In all cases, a complete process of generating digital models of the maxillofacial pathology, as well as the donor area, was carried out; virtual planning and simulation of operations; production of surgical guides and 3D patient-specific implants and 3D models for preoperative verification. This approach was used in 9 microvascular and 4 regional axial reconstructions.

In total, 14 microvascular and 12 regional axial reconstructions were performed in both groups of patients. There are 8 fibular bone reconstructions (3 one-segment, 4 two-segment and 1 four-segment, and some of them had a modeled articular process, which is not clear how it was achieved, and according

to the type of the flap - 4 are osseous, 2 - myoosseous and 2 - osteocutaneous. Microvascular iliac reconstructions are 2 - two-segment and myoosseous.

VI. Discussion of the results

According to task 1. The precise and systematized approach of contrast thin-section CT is closely related to the quality of the overall image that the digital platform generates and presents. Information can be directly exported to the server and used for the purposes of digital planning methods. With them, surgeons and medical engineers work in the process of planning, processing and printing. The studies carried out according to this protocol create high-quality images and detailed visualization not only of the bone components, but also of the blood supply of the examined areas. They are the essence of interdisciplinary cooperation in the process of preparation and realization of the clinical material in the dissertation work. The same protocol could be used in other donor areas of the body.

According to task 2. The benefits of the application of individual 3D models are: detailed diagnosis and treatment planning; direct visualization of anatomical structures; creation of surgical guides/templates; precise planning of incisions and resections; objective evaluation of bone defects for grafting; precise bending and adaptation of standard titanium reconstructive implants; possibility of manufacturing individual prosthetic elements, fixation and distraction devices; reduced surgical and anesthetic time; predictable results; improved communication with colleagues; explanatory information for patients.

According to task 3. In the 2nd group of patients (without the 2nd), a complete process of generating digital models of the maxillofacial pathology, as well as the donor areas for microvascular skeletal reconstructions, was carried out; the resection and reconstructive phases of the surgical interventions were virtually planned and simulated with surgical guides (without 2 patients). On this basis, laser-sintered and patient-specific mandibular implants are also virtually constructed. The process was carried out together with a team from the KLS Martin company

According to task 4. In group I patients, in relation to the applied individualized standard reconstructive titanium implants according to the produced 3D jaw models, a relatively good degree of adaptation to the recipient bone structures is reported, but often after additional intraoperative correction. They were applied in 5 microvascular and 8 regional axial reconstructions. The latter in both groups of patients were performed with pectoral and latissimus dorsi flaps, temporal and cervical from the sternocleidomastoid and platysma muscles. In group II patients, the analysis of the work with the surgical guides shows that they adapt exactly to the planned contour and the resection lines are easy to shape. When using them, a very good precision of adaptation to the donor bone structures (fibular and iliac), absolute matching of the planned angulation of the holes for fixing the bone graft to the patient-specific implant and in its relationship with the recipient skeletal structure is reported. In all 10 laser-sintered patient-specific implants, very precise adaptations to the recipient sockets and bone grafts, as well as complete comparability in lengths, volumes and three-dimensional orientation to the virtual plan, were found.

According to task 5. Based on the acquired clinical experience, the dissertant creates an algorithm for the application of digital-assisted methods in cases of local, regional and microvascular reconstructions of complex and extensive defects in the maxillofacial region. Through it, it systematizes the approaches to operative intervention only with the help of an orienting individual patient-specific 3D model (maxillofacial and/or donor) - the first line of the algorithm, as well as 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 - a second line of the algorithm. Both lines are based on information from thin-slice CT of the facial skeleton with or without recipient and donor angiography (in the case of microvascular reconstructive intervention)

VII. Conclusions

Based on the achieved results and their discussion, Associate Professor Dr. Yanev formulated 16 conclusions for each of the five tasks.

VIII. Contributions

Based on the research conducted and the conclusions drawn, the dissertant presents 8 contributions. He does not divide them into theoretical, original, scientifically applied and confirmatory. I consider the following to be the most important of them:

A specialized protocol has been created for CT examination of patients undergoing microvascular reconstructive surgery in the head and neck area, with a donor area in a remote part of the body. It allows the generated image information to be directly exported to the planning server and simultaneously used for the purposes of digital planning methods.

The first series of fully virtual planned and 3D modeled microvascular reconstructions of extensive maxillofacial defects stabilized by laser-sintered patient-specific implants was performed. This clinical project is based on international technological cooperation and Bulgaria's own surgical experience.

A series of virtually planned resection and reconstructive surgical guides were applied for the first time in clinical practice in our country for the exact transfer of the virtual plan in each of the performed real operative interventions.

An algorithm for the clinical application of the methods of virtual 3D planning, modeling and printing in maxillofacial reconstructions was created, which could be used on an interdisciplinary basis by all specialists working in this complex area of the human body.

IX. Characterization and evaluation of the dissertation work

The dissertation work of Associate Professor Dr. Yanev is written in a good literary style and excellently illustrated. Its non-standard structuring makes its overall understanding not an easy task. This is confirmed by the repetitions and numerous references which the author makes to different parts of it. The number of operated patients is small, but due to the specific pathology, the small population and the insufficient financing of the procedures in our country, it can be considered sufficient for the set goal. The results presented through each of the 22 clinical cases sound casuistic and mixed with the research methodology. The observation period is only up to 4 years, and the success of the operative methods is proven over time. I believe that the independent use of titanium reconstructin plates in 8 mandibular reconstructions to support vascularized axial lamps is not fully justified. Although 3D-formed cranial models are known to be a temporary solution due to prerequisites for soft tissue breakthrough, infections, metallosis, mechanical failure with loosening of screws and plate fractures. Today, they are used in a limited way when the removal of a malignant blastoma process cannot be done radically or the patient's deteriorated general condition does not allow autogenous bone grafting. It does the author credit to share the intraoperative failures and postoperative complications that occurred. I consider the conducted research to be the personal work of Prof. Dr. Yanev in good collaboration with home or foreign medical and engineering specialists. The discussion of the results is comprehensive in terms of the tasks set, and the conclusions logically follow from it. The abstract contains and illustrates all parts of the dissertation work. Associate Professor Dr. Yanev presents 15 scientific publications, of which only 4 are related to the topic - #1, #6, #7, #12. The research was carried out with international technological cooperation and the author's own surgical experience. This approach, presented for the first time in our country, meets the modern standards of interdisciplinary and high-tech medical work. The dissertation work is mainly confirmatory and scientifically applied in nature. I believe that the advanced technologies presented in it will improve clinical practice in Bulgaria in reconstructive surgery of various specialties (neurosurgery, maxillofacial, oral and plastic reconstructive surgery).

X. Conclusion

The topic "Algorithm for clinical application of virtual planning, modeling and 3D printing in local, regional and microvascular reconstructions of complex maxillofacial defects" developed by Assoc.Prof. Dr. Nikolay Yanev, PhD, is current, scientifically and clinically significant. The purpose of the study is

clearly defined, the set tasks are performed and analyzed in depth. The results contribute to the implementation of new technologies in the operative treatment of significant and complex maxillofacial defects. This shows that the author has deep theoretical knowledge and professional qualities. The above gives me the reason, regardless of the critical remarks, to positively evaluate the dissertation work and to vote "YES" for awarding Assoc. Prof. Dr. Nikolay Yanev, PhD, the scientific degree "Doctor of Sciences" in the scientific specialty "Neurosurgery" in the field of higher education and professional direction Medicine.

Sofia, **Author of the Opinion:**

30.06.2022г. **Prof.Dr. Anton Yordanov Djorov PhD, DMS**