

REVIEW

of the official opponent professor Andrii Netliukh

to the dissertation of

Dipak Chaulagain "PROGNOSTIC FACTORS INFLUENCING CLINICAL
OUTCOME IN SURGICALLY TREATED GLIOBLASTOMA",

for the scientific degree of Doctor of Philosophy in the field of knowledge

22 Health care in the specialty 222 Medicine

Relevance of the topic. Dipak Chaulagain has elected the topic that is important for modern neurosurgery. The relevance of the conducted research does not raise questions, first of all, it is due to the high prevalence of glioblastomas (GBM), high recurrence and early mortality rates of patients after removal of the malignant gliomas, which, according to various data, ranges from 3.7% to 18.5%, despite the introduction of the latest microneurosurgical technologies. As a result, surgical removal of GBMs is quite often resultant in intraoperative damage of eloquent brain areas and cortical veins, extensive blood loss, which negatively affects the radicality and outcomes of operations.

Prognosis is also defined by histological subtype of the tumors. The directions that can solve these questions are: studying the sources of blood supply depending on the location of the tumors; development of a scheme of diagnostic and therapeutic measures in patients with signs of malignant GBM; assessment of the impact of surgery on early and long-term results of GBM treatment, taking into account the extent of tumor resection, the quality of patients life, and the rate of tumor recurrence; development of criteria for the differentiated treatment of the tumors of different histochemistry types.

The research of Dipak Chaulagain is devoted to the solution of these questions. Thus, the topic of the dissertation consists an actual medical and social problem.

Connection of work with scientific programs, plans, topics. Reviewed scientific study was performed within the framework of planned complex works State Higher Educational Institution "Uzhhorod National University" according to the number of state registration No 0121U112168 'Scientific rational of monitoring of

the factors influencing the health of Zakarpattia oblast population and forming the modern management in health care system' (2010-2020 pp).

The Validity of Scientific Statements, Conclusions, and Recommendations

The conclusions are based on data from respectable group of 120 glioblastoma patients treated at a single center over a 10-year period. The data set is robust, and the statistical analysis is comprehensive, utilizing multiple methods, including Cox regression models, Kaplan-Meier survival analyses, and Chi-square tests to evaluate the relationships between extent of resection and various clinical outcomes. The classification of extent of resection was improved based on precise methodology of MRI volumetric analysis before and after surgery what consists a special scientific interest. The results of this research are implemented to the educational plans of the Department of Neurology, Neurosurgery and Psychiatry of Uzhhorod National University.

Practical Application of the Results

The practical implications of the study are clear and could have a significant impact on clinical practice. The recommendation to prioritize gross total resection in GBM surgeries whenever feasible is grounded in solid evidence, with the study showing that patients who achieve gross total resection have a two-fold higher likelihood of surviving beyond one year compared to those who undergo subtotal resection, and more than eight times the survival rate compared to partial.

The study also highlights the importance of advanced intraoperative technologies, such as 5-ALA fluorescence-guided surgery, intraoperative ultrasound, and neuronavigation, to maximize resection while preserving brain function. These technologies are increasingly being used in high-income countries but are less commonly available in regions with limited healthcare resources. Dr. Chaulagain's work could serve as a strong argument for investing in these technologies in Ukraine and other countries with similar healthcare challenges.

Moreover, the findings underscore the importance of patient selection and surgical planning. For example, the strong correlation between preoperative Karnofsky Performance Status (KPS) and extent of resection suggests that patients with higher preoperative KPS scores are more likely to benefit from aggressive

resection. This finding can help guide decisions about whether to pursue gross total resection in patients with poor baseline functional status.

The results of this research are implemented to the practical work of Uzhhorod Regional Clinical Center of Neurosurgery and Neurology.

Characteristics of the Study. Evaluation of Content, Design, and Completion. The dissertation is written in English language on 170 pages, 111 pages of the main text and consists of an introduction, literature review, material and research methods, results, summary of the obtained results and discussion, conclusions and practical recommendations. The results of the research are illustrated in the text of dissertation with 40 tables and 54 figures. The structure of the dissertation is logical, beginning with a thorough literature review that sets the stage for the research questions and hypotheses.

The list of conventional abbreviations contains 45 abbreviations. Of them, TRT (Telomerase Reverse Transcriptase) is not used in the text; O6-MeG (O6-methylguanine), PTEN (Phosphotyrosin Kinase Phosphatase 1), ATRX (α -Thalassemia mental Retardation X-Linked Protein), BBB (Blood Brain Barrier) and some other occur once in the text of the work; QOL (Quality-of-Life) occurs twice in the text of the work, so abbreviations' list could be improved and shortened. And finally we found abbreviations as PT, PC, INR (page 59), that are not listed or at least explained for reader.

Object of the research is defined very shortly as "glioblastoma". We would recommend extending it in a sense of either location or treatment strategy.

Introduction takes 5 pages, the author emphasizes here relevance, defines the purpose and tasks of the work. The purpose of the work corresponds to the chosen topic, formulated sufficiently concisely and at the same time meaningfully, the five tasks of the work are defined in accordance with the set goal and aimed at its achievement. The purpose is to evaluate the effect of extent of tumor resection on survival outcomes in glioblastoma and the factors that influence the extent of resection in glioblastoma patients. It should be noted that in the clinical process, appropriate surgical treatment is a cornerstone of achieving the best treatment result;

therefore the goal is to improve the results of treatment of GBMs, which is extremely important in modern conditions.

In the Chapter 1. LITERATURE REVIEW on 29 pages we see as author analyzes modern literature, dedicated to classification of the central nervous system tumors, pathology of glioblastoma, pays attention to the clinical symptoms and diagnosis, management of glioblastomas. Special attention is paid to the influence of surgical resection on glioblastomas' treatment outcomes. The review of the literature is comprehensive, covering the most recent classifications of glioblastoma by the World Health Organization (WHO) and delving into both the biological properties of glioblastoma and the current challenges in surgical management.

It should be noted that drawings from other sources look inappropriate in this section.

In Chapter 2. PATIENTS AND METHODS on 11 printed pages author describes patients' profiles, define study procedures. The methodology section is detailed, providing a clear explanation of how patients were selected, how tumor volumes were measured, and how extent of resection was calculated. The statistical methods are appropriate for the data set and research questions, with clear justifications provided for the use of each analytical technique.

The attention is also paid to preoperative patient evaluation, operational definitions, treatment regimen and monitoring of patients, follow-up of patients during and after treatment. Here are discussed study variables, which could potentially influence the results, and are given issues of statistical procedures, ethical considerations.

We should note that statement of inclusion criteria is confusing, because here are noted adult patients "diagnosed with IDH1-wildtype glioblastoma and underwent tumor removal surgery" that means opposite order of events. In the subchapter "2.3.2. Examination" author states Group C – 0-40% of the Karnofsky performance score (KPS) that obviously is a wrongly printed because 0 % on KPS cannot be included to the clinical patients group. Some inaccuracy is noted on calculations below illustration 2-5 where the postoperative tumor volume was defined as $3.0 \times 3.0 \times 1.98 = 63/2 = 8.91 \text{ cm}^3$. Proposed on Table 2-1 age grouping in the study does

not correspond to WHO definition of human age. Proposed on Table 2-4 pre-and post-operative KPS score grouping as group A and B does not correspond to previously defined grouping on subchapter 2.3.2 where we find groups A, B and C.

Chapter 3. RESULTS consists the main dissertation's results on 37 pages. The author analyzes here the results of descriptive statistics, multivariate analysis, cox regression and hazard ratio et cetera to prove the statistical correlations between patient characteristics, treatment strategy, complications and adjuvant therapies, so it let author to finally resume the advantages of his complex treatment approach. The results section is presented clearly, with well-organized tables and figures that illustrate the key findings. The multivariate analysis provides an in-depth look at how various factors interact to influence surgical outcomes, and the survival curves effectively communicate the variations between the different extents of tumor resection groups.

The sample consisted of 120 cases and out of these, nearly 57% were 40-60 years of age and the older patient (>60 years) were just 20%. It is interesting finding, that the least common location of the tumor was occipital region — only 3% of the patients had GBM located there, that corresponds to the literature data - 3.6%. It explains a high risk of functional disability while majority of tumors were located in functional brain areas.

I would like to note that it does not make sense to use a colored background in the tables, as this is a blatant distraction and introduces some confusion (tables 3-3, 3-5, 3-6 and others). Figure 3-13 "Mean score for measurement variables" is presented in the form of a graph, but it reflects different characteristics of patients, which makes it difficult to perceive information, as it creates the illusion of some dynamics.

The section contains a lot of statistical tables and graphs, which should have been explained in the text of the work to facilitate understanding.

I would recommend giving the subsections names that reflect the characteristics of the patients, rather than the statistical methods used by the author.

The chapter, in our opinion, is overloaded with tables (35 tables) and figures (31 figures and diagrams), part of which would logically be given in chapters 3 reflecting patients grouping and characteristics.

Chapter 4. DISCUSSION & SUMMARIZING OF THE OBTAINED DATA takes 27 lists of paper and contains a summary of the dissertation research. The results obtained by the author, when compared with data from the literature, made it possible to identify criteria and factors that influence the choice of treatment method and, accordingly, the results of treatment of patients with glioblastomas. The chapter is well illustrated consisting 14 graphs that make a comprehensive summary for previously given data.

The chapter contains too many references. Here it was worth focusing the reader's attention on the discussion of the author's own results.

Seven conclusions, they logically flow from the author's scientific research and correspond to the set tasks and goals. The conclusions and results of the conducted research are sufficiently fully covered in 17 scientific works published by the author with 10 scientific publications directly stemming from his dissertation research. These include articles in reputable journals, one indexed by Scopus, as well as conference presentations at national and international neurosurgical meetings.

It should be noted that the conclusions should have been shortened, taking into account that the dissertation was set only 5 tasks. In particular, conclusions 2, 6, contain links on statistically unreliable data and formulations of an uncertain nature as "interestingly".

The practical recommendations reflect the experience gained by the author during the research. In our opinion, they should have been given a clear advisory character, as "we recommend" or "it is beneficial to", avoiding a theoretical presentation of information.

The practical recommendations to minimize postoperative complications and to integrate advanced neurophysiological monitoring during surgery are also well-founded. Given the study's finding that postoperative complications, although not directly correlated with overall survival, indirectly affect treatment options (such as eligibility for adjuvant chemotherapy), these recommendations are highly relevant to improving patient outcomes.

The list of used literary sources occupies 24 pages, contains 133 references, of which 23 are for the period 2020-2024, and reflects both fundamental works and the

current state of the problem. It was appropriate to pay more attention to the works of Ukrainian scientists.

The dissertation is written in a literary language, competently, contains a complete analysis of all clinical data and is excellently illustrated with tomograms and diagrams, which significantly facilitates the perception of the material.

It is remarkable that was revealed statistically significant relationship between the preoperative volume and the percentage of resection. In particular, in most cases that underwent total resection, the preoperative volume was within the range 20-50 cm³ (37.3%), subtotal resection - less than 20 cm³ (51.4%), and partial resection was most often performed in patients with larger tumors (50-100 cm³, 55.6%).

During the review of the work, the following remarks arose, which relate to the design of the results of the dissertation and are of a debatable nature:

1. The work contains a number of spelling and syntax errors
2. It would be worthwhile to draw conclusions for each section, which would facilitate the perception of the material and would allow the main conclusions to be unloaded.
3. It should be noted that the author uses different dimensions, it is worth unifying the number of decimal places in decimal fractions at least within one table (for example, tables 3-6) or paragraph.
4. One limitation of the study is its retrospective design, which inherently carries the risk of selection bias. While the sample size of 120 patients is respectable, it is limited to a single institution, which may reduce the generalizability of the findings.
5. Additionally, the study could have benefitted from a more detailed discussion of the limitations associated with MRI-based volumetric analysis, particularly regarding the accuracy of this method in differentiating between tumor tissue and postoperative changes such as edema or inflammation.
6. Another limitation is the lack of a more nuanced discussion of the balance between aggressive resection and functional outcomes. While the dissertation clearly shows that gross total resection improves survival, it would have been valuable to explore more deeply the potential trade-offs, especially in cases where aggressive resection risks significant neurological deficits.

A number of questions also arose:

1. What were the indications for the surgery in the case of a tumor volume of 0.6 cm³?
2. What is the origin of used classification of the extent of tumor resection? Was it elaborated by your team?
3. What additional diagnostic tools have you used for the patients with tumors that are localized in the proximity of critical areas (speech centers, motor cortex or visual cortex): fMRIs, tractography, EEG?
4. Total resection was performed just in 56% of all cases, while volumetric analysis of all observations before and after surgery demonstrated a median resection volume equal to 95.74%. How can you explain so high median volume of resection extent as you defined 95% and more as total one?

Conclusion

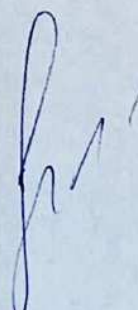
Dr. Chaulagain's dissertation makes a substantial contribution to the field of neuro-oncology, particularly in its focus on optimizing surgical outcomes for glioblastoma patients. By providing rigorous, statistically-backed evidence that gross total resection is a key factor in improving survival; the dissertation offers practical recommendations that can directly influence clinical practice. The use of MRI volumetric analysis for assessing extent of resection adds a level of precision and objectivity that is often missing from surgical studies, and the findings have broad implications for how glioblastoma is treated both in Ukraine and globally.

The research for this dissertation was conducted independently by the author, who conceptualized the idea and formulated the research plan. The author autonomously conducted information searches, performed an analytical review of contemporary literature on specific topics, and analyzed clinical and instrumental data. Consequently, the author was able to synthesize the gathered information, formulate a summary, and draw meaningful conclusions from the research findings. This underscores the author's individual contribution to the entire research process, demonstrating a comprehensive and self-driven approach to scholarly inquiry. Prospective studies that include functional outcomes alongside survival metrics would be a valuable next step.

All of the above allows us to conclude that the dissertation is an independent and completed scientific work that fully meets the requirements for a philosophy doctor degree dissertation, specified in the "Procedure for awarding the degree of doctor of philosophy and canceling the decision of a one-time specialized academic council of a higher education institution, scientific institution on the awarding of the degree of Doctor of Philosophy" approved by the Cabinet of Ministers of Ukraine (resolution No. 44, dated January 12th, 2022) and the requirements for the preparation of the dissertation in accordance with the order of the Ministry of Education and Science of Ukraine (No. 40, dated January 12th, 2017) "On the Approval of the Requirements for the Preparation of the Dissertation", and Dipak Chaulagain himself deserves for awarding the degree of Doctor of Philosophy in the field of knowledge 22 "Health Care" in the specialty 222 "Medicine".

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A.M. Netliukh,

I testify a Signature of Netliukh A.M.:

Scientific secretary
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S.P. Yahelo