BOHR International Journal of Neurology and Neuroscience
2024, Vol. 2, No. 2, pp. 42–44
DOI: 10.54646/bijnn.2024.20
www.bohrpub.com

RESEARCH

Early prediction of brain tumors postoperative progression of using the peripheral blood cells aggregation level indicators by surface Plasmon resonance method

N. Gridina[1*†], A. Guk[1†], A. Glavatsky[1], Ushenin Yu[2†], R. Khristosenko[2†], A. Khokhlov[1†], O. Velichko[1†], A. Samoilov[2] and E. Venger[2†]

[1]Romodanov Neurosurgery Institute, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine
[2]V. E. Lashkaryov Institute of Semiconductor Physics of NAS of Ukraine, Kyiv, Ukraine

***Correspondence:**
N. Gridina,
gridinanina@ukr.net

[†]**ORCID:**
N. Gridina
0000-0003-1137-8212
A. Guk
0000-0001-7721-729X
Ushenin Yu
0000-0002-5480-216X
R. Khristosenko
0000-0002-0440-2651
A. Khokhlov
0000-0002-6684-4199
O. Velichko
0000-0001-9202-8411
E. Venger
0000-0003-1508-1627

Received: 12 June 2024; **Accepted:** 23 August 2024; **Published:** 19 October 2024

The completeness of brain tumors removal, on which the continued growth depends, was determined using indicators of the peripheral blood cell aggregation level of using a SPR analyzer before and on the 7th day after surgery. An increase in the sensitivity of the method was achieved by adding a 0.25% solution of verapamil hydrochloride (Farmak) diluted 10,000 times to the blood under *in vitro* conditions. A decrease in SPR values on the 7th day after surgery compared to preoperative data may indicate total removal of the patient's tumor. If SPR indicators on the 7th day after surgical removal are increased compared to preoperative values, this indicates the presence of a tumor and tumor-associated inflammation and, therefore, subtotal removal of the tumor and the likelihood of relapse due to tumor progression.

Keywords: gliomas, tumor progression, SPR indicator, early diagnostics of relapses, radical tumor removal

Introduction

Effective treatment of brain tumors largely depends on the complete removal of the tumor during surgical removal, otherwise the tumor will continue to grow. For this purpose, surgical clinics are developing transcranial endoscopic approaches for the treatment of tumors of the third ventricle, determining the boundaries of the proliferation of malignant

tissues of gliomas using visualizing optical systems, etc., which will allow for more complete removal of these tumors.

In order to have an idea of the degree of completeness of tumor removal, it is necessary to develop a test that can be used to determine the degree of completeness of tumor removal by surgery.

The purpose of the work was to develop a test that determines the completeness of removal of tumor tissue in the brain using indicators of the level of aggregation of peripheral blood cells using a surface Plasmon resonance (SPR) analyzer.

Materials and methods

The study was performed on 34 patients with brain tumors before surgery and on the 7th day after surgery. A test by determining the level of SPR indices (1) before surgical removal of gliomas (varying degrees of malignancy) in comparison with similar indicators 5–7 days after surgery was developed.

Previous studies in malignant brain gliomas have found that blood cell aggregation levels are lower in gliomas II degree of malignancy (higher SPR indices) compared to an increased level of blood cell aggregation in gliomas IV degree of malignancy (lower SPR indices) (2–4).

For a more accurate differential analysis between brain gliomas of varying degrees of malignancy, 0.25% verapamil hydrochloride was used at a 10,000-fold dilution. This dilution of verapamil hydrochloride was chosen based on the residence time of glutamate in the synaptic cleft (5), since these processes are interrelated. Verapamil hydrochloride is a blocker of slow calcium channels on cell membranes and at the same time affects the level of blood cell aggregation through communication with NMDA receptors. Verapamil increases the level of blood cell aggregation in benign tumors, while SPR indicators decrease, and reduces the level of aggregation in malignant tumors, while SPR indicators increase. In healthy people, the level of blood cell aggregation is low, the SPR indicators are high, and with the addition of verapamil hydrochloride, the level of verapamil hydrochloride increases and the SPR indicators decrease. Therefore, the addition of verapamil hydrochloride to blood cells shows an opposite effect on the level of blood cell aggregation compared to that without the addition of verapamil hydrochloride. This methodological approach makes it possible to analyze the degree of malignancy of tumors based on the level of blood cell aggregation. It shows the completeness of the removal during surgery. The objectivity of the results based on SPR indices was compared with the data of imaging methods for determining the completeness of tumor removal after surgery MRI and CT with contrast. The agreement between the results was 100%.

Results

Blood cell aggregation level determining, expressed in terms of SPR, compared before and after surgery in patients with glioma of varying degrees of malignancy, indicates total or subtotal removal of the tumor during surgery (**Table 1**). As is known, it is often not possible to completely remove a tumor in the brain tissue due to the close adherence of the tumor tissue to vital structures of the brain.

Discussion

The use of imaging methods to determine the totality of tumor removal in the postoperative bed in the early postoperative period cannot always determine the complete absence of tumor cells in the brain tissue. When the close combination of a tumor and the inflammatory process resulting from necrosis of tumor cells became clear based on the experimental data obtained, it became possible to judge the growth or remission of the tumor process by the presence of tumor-associated inflammation (6, 7). Our previously obtained data and literature sources (8–12) may indicate a close interaction between inflammation and mesenchymal cells of the bone marrow, which in the postoperative period determines the rate of relapses and metastases in various types of oncological processes. The use of the SPR method makes it possible to evaluate stage II inflammation activated by tumor necrosis, which is not always determined

TABLE 1 | SPR indices for subtotal and total removal of gliomas (10,000-fold dilution of verapamil).

Glioma grade	SPR indices before surgery		SPR indices after surgery	
	SPR indices (total removal)	SPR indices (subtotal removal)	SPR indices (total removal)	SPR indices (subtotal removal)
Glioma (II degree) 12 patients	1.435 ± 0.36907	1.3524 ± 0.61757	1.2225 ± 0.20311	1.6553 ± 0.56026
Glioma (III degree) 10 patients	1.5362 ± 0.5049	1.08816 ± 0.23771	1.30366 ± 0.4326	1.4861 ± 0.54382
Glioma (IV degree) 12 patients	1.5863 ± 0.3340	1.2169 ± 0.3266	1.3524 ± 0.3548	1.5308 ± 0.5002

by generally accepted laboratory tests, because is a microinflammation.

Conclusion

Determining SPR indicators with a microsensor is a more subtle tool that determines microinflammation that accompanies the presence of tumor tissue. Microinflammation associated with the growth of remaining tumor tissue is not always recorded by generally accepted laboratory tests, which in some cases allows the tumor to be mistakenly considered to have been completely removed. The proposed method will allow, in case of objective determination by SPR indicators of the impossibility of total tumor removal, to carry out postoperative prevention of tumor progression in earlier stages of the postoperative period. This method also allows screening for the appearance of tumor growth at any time in the late postoperative period.

The method proposed by the authors for determining the completeness of removal of malignant brain tumors has no analogs. It differs from other methods in the availability and speed of determining indicators and does not require expensive reagents and radioactive labels. In addition, the proposed method may used for further development on other types of tumors, since it is universal, unlike tissue-specific tumor markers (13–15). Currently, several types of markers for tumors of neural origin have been developed. The problem is to distinguish markers of the inflammatory process from the tumor process. Our work addresses this issue by altering the transmembrane potential by adding varying concentrations of verapamil hydrochloride to blood cells *in vitro*. A comparison of the objectivity of the indicators of the proposed method and tumor markers of nervous origin will be planned in our subsequent works.

Author contributions

NG: author of idea of the work, development of a method for determining SPR indicators, writing an article and designing of article. AGu: consultation of patients with adenoma of pituitary gland for research. AGl: consultation of patients with gliomas for research. UY: development of the method of surface Plasmon resonance on devices of the "Plasmon" type. RK: installation of the working version of "Plasmon" device and its operation during research work. AK: search of blood samples for research. OV: dilutions of verapamil-hydrochlorid samples. AS: development of the method of surface Plasmon resonance on devices of the "Plasmon" type. EV: consultations on research of the SPR sensor. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the state funding.

References

1. Dorozhinsky G, Maslov V, Ushenin Y. Sensor devices based on surface Plasmon resonance. *Monograph.* (2016) 1:264.
2. Gridina N, Shvachko L, Draguntsova N. "Tumor-associated inflammation mechanisms correction by verapamil at brain gliomas progression. *Eur J Pharm Med Res.* (2016) 3:73–8.
3. Gridina N, Morozov A, Rozumenko V, Uschenin Y, Shvachko L, et al. Some aspects of the systemic mechanism of brain malignant gliomas progression and methodological approaches to its correction. *EC Neurol.* (2020) 12:80–90.
4. Gridina N, Morozov A, Rozumenko V, Ushenin Y, Shmeleva A, Draguntsova N, et al. New pathogenetic approaches to inhibit the growth of glioblastoma relapses. *EC Neurol.* (2020) 12:01–09.
5. Clements J, Lester R, Tong G, Jahr C, Westbrook G. The time course of glutamate in the synaptic cleft. *Science.* (1992) 258:1498–501.
6. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature.* (2008) 454:436–44.
7. Whiteside T. The tumor microenvironment and its role in promoting tumor growth. *Oncogene.* (2008) 27:5904–12.
8. Beachy P, Karhadkar S, Berman D. Tissue repair and stem cells renewal in carcinogenesis. *Nature.* (2004) 432:324–31.
9. Tanno T, Matsui W. Development and maintenance of cancer stem cells under chronic inflammation. *J Nippon Med Sch.* (2011) 78:138–45.
10. Feng Y, Wang J, Tan D. Relationship between circulating inflammatory factors and glioma risk and prognosis: A meta-analysis. *Cancer Med.* (2019) 8:7454–68.
11. Rodini C, Gonçalves P, Assoni A, Carvalho V, Oswaldo K. Mesenchymal stem cells enhance tumorigenic properties of human glioblastoma through independent cell-cell communication mechanisms. *Oncotarget.* (2018) 9:24766–77.
12. Pedachenko E, Morozov A, Gridina N, Glavatsky A, Kot L, Uschenin Y, et al. Correlations between indicators of blood cells aggregation level and the number of lymphoblasts and monocytes in patients with glioblastomas. *Online J Neurol Brain Disord.* (2021) 5:506–10.
13. Yang Y, Hu F, Wu S, Huang Z, Wei K, Ma Y, et al. Blood-based biomarkers: Diagnostic value in brain tumors (focus on gliomas). *Front Neurol.* (2023) 14:1297835. doi: 10.3389/fneur.2023.1297835
14. Jelski W, Mroczko B. Molecular and circulating biomarkers of brain tumors. *Int J Mol Sci.* (2021) 22:7039.
15. Kan L, Drummond K, Hunn M. Potential biomarkers and challenges in glioma diagnosis, therapy and prognosis. *BMJ Neurol Open.* (2020) 2:e000069.