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D. CHAULAGAIN, V.I. SMOLANKA,
A.V. SMOLANKA, T. HAVRYLIV

Uzhhorod Regional Clinical Center of Neurosurgery
and Neurology, Uzhhorod National University

Recurrence rate of glioblastoma and role of extent of resection: a retrospective study

Objective — to assess the recurrence rate of surgically treated glioblastoma (GBM) and its correlation with various factors, including the extent of resection (EOR), in a cohort of 120 patients. The role of EOR as a prognostic factor in recurrence will be investigated as part of this analysis.

Materials and methods. We conducted a retrospective analysis of 120 patients diagnosed with Wild-type Isocitrate Dehydronease (IDH) GBM multiforme, aged 18 years and above, who underwent surgical intervention at Uzhhorod Regional Neurosurgical Center between 2010 and 2020. These patients were subsequently treated with chemoradiotherapy. Our study aimed to investigate the recurrence rate and the impact of EOR on recurrence and overall survival in glioblastoma. The follow-up period for these patients ranged from 2 to 144 months, with a median follow-up duration of 36 months post-surgical resection. We employed the Chi-square test to assess the relationship and association between EOR and recurrence as well as overall survival variables, considering a statistically significant p-value of 0.05 or below.

Results. In our study comprising 120 cases, with 62 % being male (n = 74) and 38 % female (n = 46). On average, patients with glioblastoma survived for 14 months. The median survival time after partial and subtotal resection was 6 and 12 months, respectively, while patients who underwent gross total resection (GTR) had a median survival duration of 16 months. Regarding extent of resection (EOR), 56 % of patients had GTR (n = 67), 29 % had subtotal resection (STR) (n = 35), and 15 % had partial resection (PR) (n = 18). Throughout the follow-up period, approximately 86 % of patients had deceased since surgery (n = 103), while 14 % (n = 17) remained under follow-up. Notably, a significant association was observed between overall survival and EOR(%) (χ^2 (2) = 8.752, p < 0.05). The recurrence rate in our study, observed post-hospital discharge during a follow-up period ranging from 2 to 144 months (median 36 months), was approximately 39 % (n = 47) among patients who underwent surgical resection for glioblastoma. However, upon multivariate analysis, we found no association between resection type and EOR(%) (χ^2 (2) = 2.563, p = 0.278), with the majority of patients across all three EOR groups showing no recurrence.

Conclusions. Glioblastoma patients derive significant benefit from comprehensive treatment strategies, which typically involve maximal safe tumor resection followed by adjuvant therapy to improve overall survival outcomes. While maximal resection of the tumor is often pursued, our study did not find a significant association between the extent of resection and recurrence rates.

Keywords: glioblastoma, recurrence, extent of resection, overall survival.

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumour in adults [8]. At present, there is no widely agreed-upon treatment plan that includes medication, surgery, or radiation for the management of GBM [18].

Extensive studies conducted in the field of neuro-oncology have shown a clear link between a greater extent of resection (EOR) and better survival outcomes in patients newly diagnosed with GBM, research have shown that survival rates have increased gradually, ranging from 78 to 98 % [13, 17].

Only surgical resection has been linked to an increase in the median survival of GBM patients to 6 months. Combining surgical resection with radiation treatment significantly increases 12-month survival rates. Due to GBM's invasive characteristics,

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Dipak Chaulagain, MD, PhD, Department of Neurosurgery,
https://orcid.org/0000-0001-6428-8371
Kapushanska St, 24. 88018, Uzhhorod, Ukraine
E-mail: neurodipak@gmail.com

the combination of radiation treatment and chemotherapy has shown additional improvements in survival rates. An important development is the implementation of concurrent chemotherapy with temozolomide (TMZ) after surgical removal of the tumour and radiation therapy. This has resulted in a considerable improvement in survival rates, with patients living for an average of 14.6 months [7].

A study published in the Journal of Neuro-Oncology has found that patients with GBM who underwent gross total resection (GTR) had a median a median overall survival (OS) of 18.9 months. These results highlight the impact of various factors, such as the extent of resection, on the recurrence rates of GBM. Nevertheless, the rate of recurrence among patients who had GTR was seen to be 67.7 % [10].

Objective — to assess the recurrence rate of surgically treated glioblastoma (GBM) and its correlation with various factors, including the extent of resection (EOR), in a cohort of 120 patients. The role of EOR as a prognostic factor in recurrence will be investigated as part of this analysis.

Materials and methods

Patients and methods

At the Regional Center for Neurosurgery and Neurology in Uzhhorod, Ukraine, a retrospective analysis was conducted on 120 consecutive patients diagnosed with glioblastoma who underwent surgical intervention between January 1, 2010, and December 31, 2020. Follow-up data were collected until January 1, 2022. Patient inclusion criteria encompassed an age of at least 18 years, a radiological and histopathological diagnosis of glioblastoma, and being IDH wild type. Additionally, patients were required to undergo post-operative brain MRI within 72 hours after surgery. Volumetric analysis of gadolinium-enhanced T1 MRI scans was performed both pre- and post-operatively to ascertain the extent of EOR. EOR was categorized as Partial Resection (PR) if less than 70 % of the tumor volume was removed, sub-total resection (STR) if 70—95 % of the tumor volume was excised, and GTR if more than 95 % of the tumor volume was resected. The relationship and association between EOR and variables such as recurrence and OS were assessed using the Chi-square test, with a significance level set at a p value of 0.05 or below.

Results

In this study, data from 120 retrospective cases were meticulously evaluated, with thorough analysis, comparison, and assessment of the findings.

Descriptive statistics

Surgical Resection and Survival

Following the volumetric analysis of GBM tumor volume both pre-operatively and post-operatively, it was observed that approximately 56 % of patients achieved GTR (n = 67), while nearly 29 % underwent STR (n = 35), and the remaining 15 % underwent partial resection (PR) (n = 18) (Table 1 and Fig. 1).

Throughout the follow-up period, it was noted that approximately 86 % of patients had succumbed since undergoing surgery (n = 103), leaving 14 % (n = 17) of patients still under observation (Table 1 and Fig. 2).

Table 1

EOR(%) and survival

	f	%
EOR(%)		
GTR	67	55.8
STR	35	29.2
PR	18	15
Overall survival		
Dead	103	85.8
Alive	17	14.2

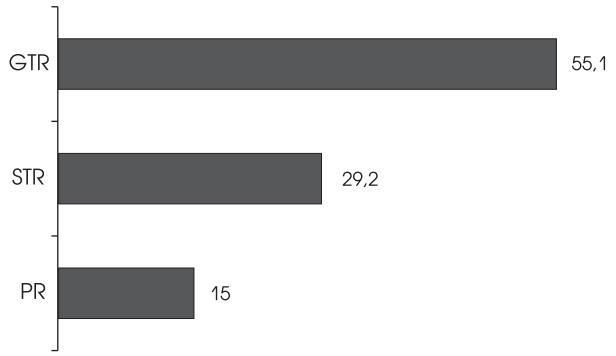

Fig. 1. *Levels of EOR(%)*

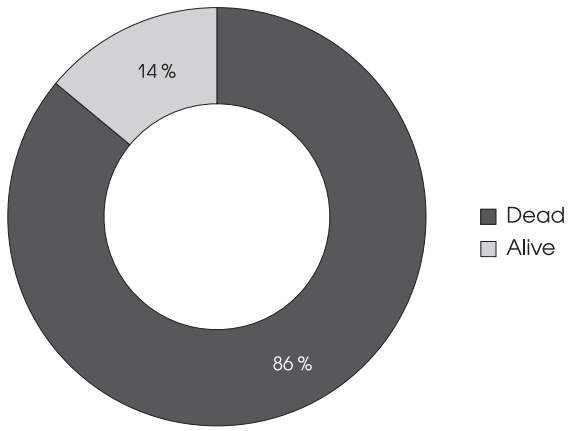

Fig. 2. *Levels of EOR(%)*

Recurrence

In this study, following discharge from the hospital, patients were monitored for a duration ranging from 2 to 144 months (with a median follow-up of 36 months). It was observed that approximately 39 % of patients

Table 2

Recurrence after surgical removal

	f	%
Recurrence — YES	47	39.2
Recurrence — NO	73	60.8

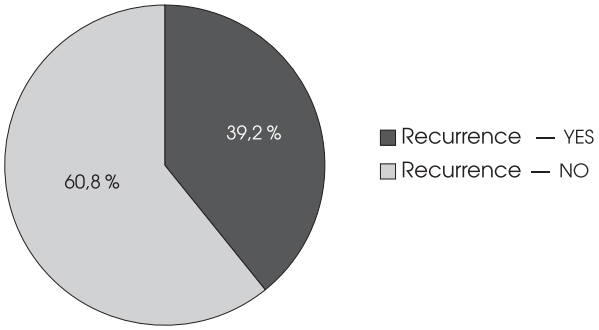

Fig. 3. *Recurrence after surgical removal*

(n = 47) who underwent surgical resection experienced recurrence in GBM patients (Table 2 and Fig. 3).

Multivariate Analysis

EOR Relationship with Overall Survival

A notable association was observed between OS and EOR (χ^2 (2) = 8.752, p < 0.05). Among patients who underwent GTR, approximately 22 % were found to be alive (n = 15). In contrast, only about 6 % of patients who underwent Subtotal Resection were alive (n = 2). Interestingly, all patients who underwent Partial Resection were deceased (100 %, n = 18). These findings underscore the significantly higher chances of survival associated with GTR compared to STR or PR (Table 3 and Fig. 4).

Table 3

Chi-Square Test between Overall Survival and EOR

			EOR			
			GTR	STR	PR	Total
Overall Survival	Dead	Count	52	33	18	103
		%	77.6	94.3	100.0	85.8
	Alive	Count	15	2	0	17
		%	22.4	5.7	0.0	14.2
Total		Count	67	35	18	120
		%	100.0	100.0	100.0	100.0

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	8.752	2	0.013

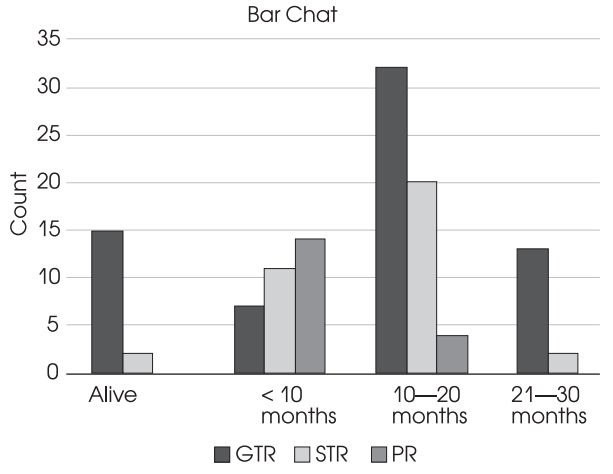

Fig. 4. *Overall survival with EOR(%)*

EOR Relationship with Recurrence

No significant association was identified between the type of resection and EOR (χ^2 (2) = 2.563, p = 0.278). It is noteworthy that the majority of patients across all three EOR groups did not experience recurrence (Table 4 and Fig. 5).

Discussion

In our investigation, we have delineated the median survival duration subsequent to GBM excision. Notably, our analysis underscores the impact of surgical resection extent on post-operative survival rates. Surprisingly, while recurrence rates did not demonstrate a direct correlation with median survival duration post-surgery, a significant association between the EOR and OS was observed.

Extensive studies have affirmed the substantial predictive value of EOR in determining survival outcomes. Notably, the rates of total tumor resection for GBM, characterized by its infiltrative nature, have been reported to range from 17.4 % to 40.0 %. Despite the recognition of multiple variables influencing EOR in clinical practice, empirical evidence supporting these factors remains elusive in the existing literature [8].

Through comprehensive analysis of pre-operative and post-operative volumetric data of GBM volume, we identified distinct categories of EOR in our patient cohort. Specifically, our findings revealed that 56 % of patients underwent GTR (n = 67), 29 % underwent STR (n = 35), and 15 % underwent PR (n = 18). The range of resection percentages spanned from 40.12 % to 99.87 %, with a median of 95.74 % (mean — 89.45 %, standard deviation — 13.39 %). These results underscore the efficacy of surgical interventions aimed at achieving complete excision of advancing IDH wild-type GBM. Notably, while debulking procedures appear safe for the management of rare IDH wild-type non-enhancing glioblastoma, their efficacy in improving survival outcomes remains unsubstantiated [4].

Optimal management of patients diagnosed with GBM necessitates a multidisciplinary approach

Table 4

Chi-Square Test Recurrence and EOR

			EOR			Total
			GTR	STR	PR	
Recurrence	Not recurrence	Count	39	20	14	73
		%	58.2	57.1	77.8	60.8
	Recurrence	Count	28	15	4	47
		%	41.8	42.9	22.2	39.2
Total		Count	67	35	18	120
		%	100.0	100.0	100.0	100.0

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	2.563	2	0.278

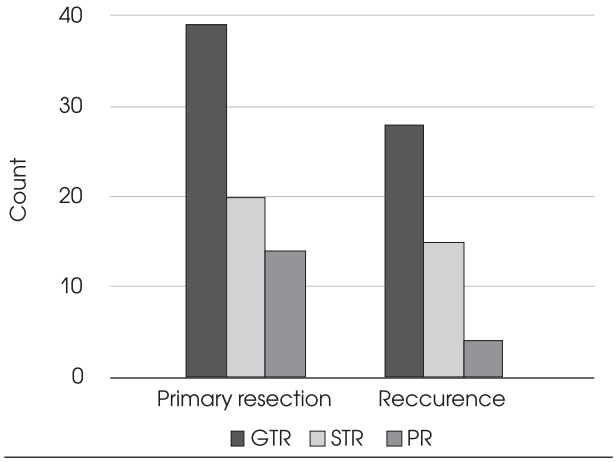

Fig. 5. *Recurrence with EOR(%)*

involving a team of specialized professionals. Extensive research underscores the significance of complete resection as an independent prognostic factor associated with favorable clinical outcomes. The concept of GTR continues to evolve within the medical community. Recent studies have proposed various enhancement cutoffs to define gross total resection, including thresholds such as 100 % [1, 11, 14, 16], 96 % [2], and 97 % [6, 15]. These advancements in defining resection criteria contribute to the ongoing refinement of surgical strategies aimed at enhancing patient prognosis and treatment efficacy.

N. Sanai et al. [18] demonstrated that patients with GBM who underwent complete removal of contrast-enhanced tumors exhibited superior outcomes compared to those with only 98 % reduction in tumor visibility enhancement. Additionally, their study revealed that resection rates exceeding 78 % were associated with a survival benefit among a cohort of 500 patients with GBM [18]. These findings underscore the importance of achieving high resection rates to improve clinical outcomes in GBM patients.

Advancements in the surgical management of GBM have led to a personalized and multimodal approach. Integration of advanced imaging techniques, refined surgical equipment, and meticulous intraoperative monitoring has significantly enhanced tumor resection while minimizing damage to surrounding brain tissue [5].

The consensus in current literature advocates for maximal safe surgical resection as the preferred approach [3, 19]. However, the debate surrounding the impact of PR on survival persists [9, 12]. Evidence suggests that significant resection is necessary to exert a substantial influence on survival outcomes.

From our study, it is evident that patients who underwent GTR had a significantly higher survival rate, with 22 % of them still alive (n = 15). Conversely, only 6 % of patients who underwent STR were still alive (n = 2), and all patients who underwent PR had deceased. The differences in median survival times were statistically significant between GTR (median survival time — 16 months) and STR (median survival time — 12 months) (χ^2 = 11.120, p < 0.01). Furthermore, GTR exhibited a significantly longer median survival time compared to PR (median survival time — 6 months; χ^2 = 47.929, p < 0.001), and STR also showed a significantly longer survival time compared to PR (χ^2 = 18.613, p < 0.001). These findings highlight the importance of achieving GTR for maximizing patient survival outcomes. Additionally, the statistically significant relationship between OS and EOR% further emphasizes the impact of surgical resection completeness on patient prognosis (χ^2 (2) = 8.752, p <0.05).

The recurrence rate of GBM varies considerably based on several factors, including the extent of surgical resection. Research published in the Journal of Neuro-Oncology indicates that patients who underwent GTR a median OS of 18.9 months. However, the recurrence incidence for these patients was reported to be 67.7 % [10]. Conversely, patients who underwent maximal safe resection exhibited a median OS of 15.2 months, as per findings published in the Journal of Neurosurgery. In this study, individuals who underwent gross complete resection experienced a recurrence incidence of 77.8 % [10]. These findings underscore the complexity of managing GBM and highlight the need for further research to optimize treatment strategies and improve patient outcomes.

The research indicates that patients with glioblastoma who underwent STR experienced a median OS of 11.2 months. Moreover, the recurrence incidence for patients who underwent STR was reported to be 90.9 % [13]. These findings emphasize the challenges associated with managing glioblastoma and highlight the importance of exploring strategies to improve treatment outcomes and reduce recurrence rates.

In our study, we observed a recurrence rate of 39 % (n = 47) among GBM patients who underwent surgical resection, with patients being followed for a median

of 36 months after hospital discharge. Interestingly, our analysis did not reveal a significant correlation between the type of resection and extent of resection percentage (EOR(%) (χ^2 (2) = 2.563, p = 0.278). Notably, there was a lack of recurrence observed across all three EOR groups (Fig. 5). These findings underscore the complex nature of GBM recurrence and highlight the need for further investigation into factors influencing tumor recurrence post-surgical resection.

Limitation

While our retrospective study provides valuable insights, it is important to acknowledge its limitations, including a small sample size and potential selection bias inherent in cohort studies. The requirement for pre- and post-operative tests for volumetric analysis may have led to the exclusion of certain glioblastoma patients from our study cohort. Additionally, the lack of routine measurement of EOR with postoperative MRI at our hospital may have impacted the accuracy of our findings. Moving forward, larger and more representative studies involving comparative imaging techniques are warranted to validate our findings and provide a more comprehensive understanding of the relationship between EOR and clinical outcomes in glioblastoma patients.

Conclusions

The treatment of glioblastoma necessitates comprehensive therapeutic strategies, including maximal safe resection coupled with adjuvant therapy, to enhance OS rates. Despite the maximal resection of tumors, our study revealed no significant association between the extent of resection and recurrence, with only 14 % of patients surviving. These findings underscore the complexity of managing GBM and highlight the need for further research to elucidate factors influencing recurrence and survival outcomes. Nonetheless, our study provides valuable insights that may guide treatment decisions regarding extent of resection and adjuvant therapy, aid in identifying patients at higher risk of recurrence, and inform postoperative surveillance imaging protocols for individuals with GBM.

Ethics approval and consent to participate. This study was approved by the Research Ethics Committee, Faculty of Medicine, Neurosurgery Department, Uzhhorod National University.

Availability of data and material. The datasets used during the current study are available from the corresponding author on reasonable request.

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No conflict of interests.

Authors' contributions: study supervision — V. S., A. S.; conception and design — D. C.; statistical analysis — D. C.; first draft of manuscript — D. C.; critical revision of the first draft — A. S., T. H.; revised submitted version — all authors; approval of submitted version — all authors.

References

1. Beiko J, Suki D, Hess KR, Fox BD, Cheung V, Cabral M, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro Oncol. 2014 Jan;16(1):81-91. doi: 10.1093/neuonc/not159.
2. Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg. 2012 Dec;117(6):1032-8. doi: 10.3171/2012.9.JNS12504.
3. Brem SS, Bierman PJ, Brem H, Butowski N, Chamberlain MC, Chiocca EA, et al. Central Nervous System Cancers. J Natl Compr Canc Netw. 2011 Apr;9(4):352-400. doi: 10.6004/jnccn.2011.0036.
4. Cahill DP. Extent of Resection of Glioblastoma. Neurosurg Clin N Am. 2021 Jan;32(1):23-29. doi: 10.1016/j.nec.2020.09.006.
5. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. Advancements in surgical management of glioblastoma: current trends and promising future directions. Int Neurolog J. 2023;19(5):155-159. doi: 10.22141/2224-0713.19.5.2023.1015.
6. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. Glioblastoma: a literature review. International Neurological Journal. 2023;18(8):32-37. doi: 10.22141/2224-0713.18.8.2022.987.
7. Chaulagain D, Smolanka V, Smolanka A, Munakomi S. The Impact of Extent of Resection on the Prognosis of Glioblastoma Multiforme: A Systematic Review and Meta-analysis. Open Access Maced J Med Sci. 2022 May 26;10(F):345-354. doi: 10.3889/oamjms.2022.8970.
8. Chaulagain D, Smolanka V, Smolanka, A, Havryliv, T. Role of extent of resection on the survival of glioblastoma multiforme: A monocentric retrospective study. Romanian Neurosurgery. 2023;37(2):190-197. https://doi.org/10.33962/roneuro-2023-034.
9. Hart MG, Metcalfe SE, Grant R, Grant GR, Solyom EF, Grosset DG. Biopsy versus resection for high grade glioma. Cochrane Database Syst Rev. 2019 Jun 6;6(6):CD002034. doi: 10.1002/14651858.CD002034.pub2.
10. Ius T, Isola M, Budai R, et al. Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients. J Neurosurg. 2012 Dec;117(6):1039-52. doi: 10.3171/2012.8.JNS12393.
11. Kreth FW, Thon N, Simon M, Westphal M, Schackert G, Nikkhah G, et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. Ann Oncol. 2013 Dec;24(12):3117-23. https://www.sciencedirect.com/science/article/pii/S0923753419367328.
12. Kreth FW, Warnke PC, Scheremet R, Ostertag CB. Surgical resection and radiation therapy versus biopsy and radiation therapy in the treatment of glioblastoma multiforme. J Neurosurg. 1993 May;78(5):762-6. doi: 10.3171/jns.1993.78.5.0762.
13. Lacroix M, Abi-Said, D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. 2001 Aug;95(2):190-8. doi: 10.3171/jns.2001.95.2.0190.
14. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: Neuro Oncol. 2004 Jul;6(3):227-35. doi: 10.1215/S1152851703000620.
15. Oppenlander ME, Wolf AB, Snyder LA, Bina R, Wilson JR, Coons SW, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg. 2014 Apr;120(4):846-53. doi: 10.3171/2013.12.JNS13184.
16. Pessina F, Navarria P, Cozzi L, Ascolese AM, Simonelli M, Santoro A, et al. Maximize surgical resection beyond contrast-enhancing boundaries in newly diagnosed glioblastoma multiforme: is it useful

and safe? A single institution retrospective experience. J Neurooncol. 2017 Oct;135(1):129-139. doi: 10.1007/s11060-017-2559-9.
17. Sanai N, Berger MS. Operative Techniques for Gliomas and the Value of Extent of Resection. Neurotherapeutics. 2009 Jul;6(3):478-86. PMID: 19560738. PMCID: PMC5084184.
18. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg. 2011 Jul;115(1):3-8. doi: 10.3171/2011.2.jns10998.
19. Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med. 2008 Jul 31;359(5):492-507. doi: 10.1056/NEJMra0708126.

Д. ЧАУЛАГАІН, В.І. СМОЛАНКА, А.В. СМОЛАНКА, Т. ГАВРИЛІВ
Обласний клінічний центр нейрохірургії та неврології
Ужгородського національного університету

Частота рецидивів гліобластоми та роль обсягу резекції: ретроспективне дослідження

Мета роботи — оцінити частоту рецидивів хірургічно вилікуваної гліобластоми (GBM) та її кореляції з різними факторами, включаючи ступінь резекції (EOR), у когорті зі 120 пацієнтів. У рамках цього аналізу досліджено роль ПНП як прогностичного фактора рецидиву.

Матеріали та методи. Проведено ретроспективний аналіз даних 120 пацієнтів із діагнозом мультиформна гліобластома (ГБМ) ізоцитратдегідрогенази дикого типу (ІЗД) віком понад 18 років, яким проведено оперативне втручання в Ужгородському обласному нейрохірургічному центрі в 2010—2020 рр. і хіміопроменеву терапію. Вивчали частоту рецидивів і вплив обсягу резекції (ОР) на рецидив та загальну виживаність. Період спостереження після хірургічної резекції становив від 2 до 144 міс (середня тривалість спостереження — 36 міс). Застосовували тест χ^2, щоб оцінити зв'язок між ОР і рецидивом та показниками виживаності. Статистично значущим вважали значення $p < 0,05$.

Результати. Серед пацієнтів було 74 (62 %) чоловіки та 46 (38 %) жінок. Розподіл за ОР був таким: 67 (56 %) пацієнтам проведено тотальну резекцію, 35 (29 %) — субтотальну резекцію, 18 (15 %) — часткову резекцію. Середня виживаність пацієнтів із ГБМ становила 14 міс, зокрема після часткової та субтотальної резекції — 6 і 12 міс відповідно, після тотальної резекції — 16 міс. Протягом усього періоду спостереження 103 (86 %) пацієнти померли після операції, а 17 (14 %) — залишалися під спостереженням. Установлено значний зв'язок між загальною виживаністю та ОР (χ^2 (2) = 8,752; $p < 0,05$). Частота рецидивів після виписки з лікарні впродовж періоду спостереження від 2 до 144 міс (медіана — 36 міс) становила 39 %. Однак за результатами багатофакторного аналізу не виявлено зв'язку між типом резекції та ОР (χ^2 (2) = 2,563; $p = 0,278$). У більшості пацієнтів у трьох групах, виділених за ОР, не було рецидивів.

Висновки. Пацієнти з ГБМ отримують значну користь від комплексних стратегій лікування, які зазвичай передбачають максимально безпечну резекцію пухлини й проведення ад'ювантної терапії для поліпшення загальних результатів виживання. Хоча часто намагаються досягти максимальної резекції пухлини, наше дослідження не виявило суттєвого зв'язку між ОР та частотою рецидивів.

Ключові слова: гліобластома, рецидив, обсяг резекції, загальна виживаність.

ДЛЯ ЦИТУВАННЯ

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Chaulagain D, Smolanka VI, Smolanka AV, Havryliv T. Recurrence rate of glioblastoma and role of extent of resection: a retrospective study. Ukrainian Neurological Journal. 2024;2-3:28-33. http://doi.org/10.30978/UNJ2024-2-3-28. Urkainian.