Article published online: 2023-09-27

Retrospective Evaluation of Cases Undergoing Stereotaxic Brain Biopsy

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Asian J Neurosurg 2023;18:602–608.

Abstract

Objective: The aim of this study is to evaluate the demographic, radiological and histopathological findings, tumoral biomarkers, and survival rates of patients who underwent a stereotactic brain biopsy and those diagnosed with glioblastoma, metastasis, and lymphoma, and the changes in the diagnosis distribution over the years.

Materials and Methods: The patients who underwent stereotactic biopsy in our clinic between 2012 and 2020 were evaluated retrospectively. Metastasis, glioblastoma, and lymphoma cases were evaluated as three main groups and the others were excluded. P53 gene expression, isocitrate dehydrogenase (IDH) mutation, and Ki-67 values in glioblastoma cases and Bcl-2, Bcl-6 proteins, and Ki-67 values in lymphomas and their relationship with survival were evaluated.

Results: High p53 expression was observed in 27.5% cases diagnosed with glioblastoma. IDH mutation was negative in all glioblastoma cases. Presence of Bcl-2 and Bcl-6 proteins was not associated with survival in lymphomas. Survival rate was significantly higher in cases diagnosed with lymphoma (26.9%) compared to those diagnosed with glioblastoma. A statistically significant increase was determined in patients diagnosed with lymphoma considering the distribution of diseases and incidence and in the distribution of other diagnoses over the years ($p < 0.05$).

Conclusion: As per the distribution of the disease in recent times, it has been observed that there is an increase in lymphoma cases. Histopathology and biomarkers have great importance in the diagnosis and treatment of cerebral lesions. We think that our findings will be supported by studies in which larger patient population and detailed biomarkers will be studied.

Keywords
- stereotactic brain biopsy
- primary central nervous system lymphomas
- glioblastoma
- cerebral metastasis

article published online
September 27, 2023

DOI https://doi.org/10.1055/s-0043-1774821.
ISSN 2248-9614.

Introduction

Although radiological imaging provides important data about the location, size, and neighborhood of pathological lesions, a biopsy is often the only way to reveal lesion morphology. Stereotactic brain biopsy comes to the fore for diagnosis and timely initiation of treatment in deep-seated lesions, multiple lesions, or lesions located in functionally critical areas in cases where microsurgery is not an option, such as in patients with severe comorbidities. Stereotactic brain biopsy is a minimally invasive method with low morbidity and mortality.[1,2] In recent years, less invasive brain biopsy methods come to the fore.

Among these methods, neuronavigation/ultrasonography/robotic arm-guided biopsy are the main ones. It is stated that these methods have advantages over the stereotactic biopsy method (effectiveness, frameless registration, and increasing safety and accuracy). However, since access to these methods is limited in many centers including our center, stereotaxic methods remain in place.

Updates in tumor grading systems have confirmed that the behavior of the tumor is determined by its genetic characteristics rather than its morphological appearance. There are many markers associated with diagnosis and prognosis for glioblastoma and primary cerebral lymphoma, the main tumor groups we examined in our study. Isocitrate dehydrogenase (IDH) mutation, which is one of the markers used for this purpose and used in glioblastomas, shows increased DNA methylation and is associated with increased survival.[2,3] Ki-67, which we examined in our study and examined in many tumors, shows tumoral proliferation, but its relationship with prognosis is uncertain.[4]

Bcl-2 protein is involved in apoptosis inhibition and is associated with poor prognosis in systemic B-cell lymphomas, but its prognostic role in primary central nervous system lymphomas is controversial. In fact, there are studies showing that Bcl-2 has no prognostic significance in systemic lymphomas or central nervous system lymphomas, and the prognosis depends on the age and general condition of the patient.[5,6] Bcl-6 protein is produced by germinal center B cells and plays a role in cell differentiation.[7,8] Although there are publications stating that high expression of Bcl-6 is a positive indicator on survival,[7] there are also results stating that Bcl-6 elevation is not associated with survival.[8]

Cerebral metastases are the other tumor group we evaluated in our study; they are the most common cranial tumors in adults.[9,10] Cerebral metastases can be seen in approximately 20% of patients with malignancy.[10] The increase in the incidence of cancer and the prolongation of the life span of patients with cancer increase the number of patients with cerebral metastases. Cerebral metastases are most commonly of lung origin. This is followed by breast cancer, skin tumors, and gastrointestinal system tumors.[9,10] In this research, cases who underwent stereotactic biopsy were analyzed retrospectively according to distribution of pathological diagnoses over the years, importance of immunohistochemical markers in diagnosis, and demographic characteristics.

Material and Methods

Our study was approved by the local ethics committee with the decision number HNEAH-KAEK 2021/228 dated 20.09.2021.

We retrospectively analyzed 110 patients undergoing stereotactic brain biopsy in our clinic between 2012 and 2020. Lymphoma, metastasis, and glioblastoma cases were evaluated comparatively, except for patients with abscesses, low-grade gliomas, and demyelinating diseases. Lymphoma and glioblastoma cases were evaluated with tumoral biomarkers. Metastasis cases were evaluated according to their primary focus.

Surgical Procedure

The CT-compatible Leksell Stereotaxy System (Elekta Instrument Aktiebolag, Sweden) was used in our study. Sedoanalgesia was administered after the patient was taken to the operating table. Surgical procedure and pathology samples were evaluated by a single neurosurgeon and pathologist.

Tumoral Biomarkers

P53 gene expression, IDH mutation, and Ki-67 values and their relationship with prognosis were evaluated in glioblastoma cases. Bcl-2, Bcl-6 proteins, Ki-67 values, and their relationship with survival were evaluated in lymphomas.

Radiological Findings

Radiologically, the lesions were grouped according to their localization and number of lesions. Basal ganglia, hippocampus, corpus callosum, thalamus, intraventricular, and periventricular lesions are defined as deep-seated lesions while frontal, occipital, parietal, and temporal lesions were defined as hemispheric lesions.

Statistical Analyses

Data analysis was performed using SPSS Statistics 22 (International Business Machines Statistical Package for the Social Sciences, Türkiye) statistical package software. The Kolmogorov–Smirnov test was used to test the conformity of data to normal distribution.

Data were expressed using descriptive statistics such as mean, standard deviation, median, and frequency. The Mann–Whitney U test was used to compare differences between the two groups for data that did not show normal distribution. The Kruskal-Wallis H test was used to measure the significance between two or more groups.

In addition, the chi-squared test was used to analyze categorical variables. In our study, a value of p-value less than 0.05 was considered significant.

Results

In this study, 36.4% ($n = 40$) cases were female and 63.6% ($n = 70$) were male.

The mean follow-up period was 34 ± 11 months. The age of the participants ranged from 5 to 83, with a mean of

Table 1 Distribution of cases according to gender, age, lesion area, and locality

		n (%)
Gender	**Female**	40 (36.4)
	Male	70 (63.6)
Age	Mean ± *(Standart deviation)*	57.4 ± 15.2
	Median *(Minimum–Maximum)*	59 (5–83)
Lesion area	Deep lesion	47 (42.7)
	Hemispheric	44 (40.0)
	Multiple	19 (17.3)
Location	Temporal Frontal Parietal	4 (3.6) 13 (11.8) 23 (20.9)
	Occipital	4 (3.6)
	Multiple	19 (17.3)
	Basal ganglia	14 (12.7)
	Corpus callosum	17 (15.5)
	Periventricular	2 (1.8)
	Thalamus	10 (9.1)
	Hippocampus Ventricular	1 (0.9) 3 (2.7)

57.4 ± 15.2 years (►**Table 1**). The mean age of the participants by groups was 62 ± 12 for glioblastomas, 62 ± 10 for primary cerebral lymphomas, and 59 ± 9 for metastases.

According to the pathological diagnosis of 83 patients, 36.4% ($n = 40$) cases were diagnosed with glioblastoma, 23.6% ($n = 26$) with lymphoma, and 15.5% ($n = 17$) with metastasis. The remaining 27 patients constituted 24.5% of low-grade gliomas and other non-neoplastic pathologies (infection, degenerative diseases, and abscess) were excluded (►**Table 2**).

The primary focus was present in 47.1% ($n = 8$) of 17 patients diagnosed with brain metastasis, while the initial diagnosis was a brain lesion in others. The primary focus was the lung in 58.8% ($n = 10$) of 17 patients with metastasis. 60% ($n = 6$) of 10 patients diagnosed with lung-derived metastases had lung adenocarcinomas. Other metastases are invasive ductal breast carcinoma, renal cell carcinoma, malignant melanoma, and bladder cancer, and there is no statistically significant difference between them ($p > 0.05$).

There was a statistically significant relationship between pathological findings and lesion locations ($p < 0.05$) (►**Table 1**). While glioblastomas were classified as hemispheric lesions at a higher rate (57.5%) than other groups, lymphomas were classified as deep-seated lesions more commonly (61.5%). Metastases were classified as multiple lesions (35.3%) at the highest rate. Frontal lesions were classified as glioblastoma at a significantly higher rate than lymphoma and metastasis (►**Table 3**).

Table 2 Distribution of glioblastoma and nonlymphoma diagnoses

	Pathology	*n*	%	*N*
Metastasıs	Lung adenocarcinoma metastasis	6	35.29	17
	Lung squamous cell cancer metastasis	2	11.76	
	Large cell lung cancer metastasis	2	11.76	
	Invasive ductal breast cancer metastasis	2	11.76	
	Malignant melanoma metastasis	1	5.88	
	Renal cell carcinoma metastasis	2	11.76	
	Transitional cell bladder cancer metastasis	2	11.76	
	Abscess	5	18.51	
	Anaplastic astrocytoma	4	14.81	
	Diffuse astrocytoma	4	14.81	
	Anaplastic oligodendroglioma	1	3.70	
	Xanthogranuloma of the choroid plexus	1	3.70	
	Demyelinating disease	3	11.11	
	No tumor, gliotic tissue	4	14.81	
Others	Cavernous hemangioma	3	11.11	
	Granulomatous inflammation (tuberculosis)	1	3.70	27
	Granulomatous inflammation (sarcoidosis)	1	3.70	

Table 3 Locations of glioblastoma, lymphoma, and metastases

			Locations			Total
			Deep locations	Hemispheric	Multiple	
Pathology	Glioblastoma	*n*	**15**	**23**	**2**	**40**
		%	37.5	57.5	5.0	100.0
	Lymphoma	*n*	16	4	6	26
		%	61.5	15.4	23.1	100.0
	Metastasis	*n*	4	7	6	17
		%	23.5	41.2	35.3	100.0
Total		*n*	35	34	14	83
		%	42.2	41.0	16.9	100.0

Ki-square= 18,100; $p = 0.001$.

Table 4 Distribution of glioblastoma, metastases, and lymphomas by years

			Date			Total
			2012–2014	2015–2017	2018–2020	
Pathology	Glioblastoma	*n*	7	14	19	40
		%	17.5	35.0	47.5	100.0
	Lymphoma	*n*	2	8	16	26
		%	7.7	30.8	61.5	100.0
	Metastasis	*n*	9	6	2	17
		%	52.9	35.3	11.8	100.0
Total		*n*	18	28	37	83
		%	21.7	33.7	44.6	100.0

Ki-square= 16,288; $p = 0.003$.

Evaluation of the distribution of diseases by years revealed a statistically significant difference ($p = 0.003$). An increasing trend was observed in lymphoma group over the years (►**Table 4**). The mean survival time of diagnosed with glioblastoma, lymphoma, and metastasis patients was 8.1 ± 6.6 months, 6.1 ± 6.7 months, and 10.6 ± 9.8 months, respectively. There was no statistically significant difference between survival times in the groups (►**Table 5**). It was observed that being under or over the age of 62 affected survival in glioblastoma. Survival time was significantly higher in those whose age was below average. However, no relationship was found between survival time and age in metastases and lymphomas.

High p53 expression was observed in 27.5% ($n = 11$) cases diagnosed with glioblastoma. IDH mutation was negative in all glioblastoma cases ($n = 40$). High p53 expression was detected in 11 (27.5%) of 40 patients with glioblastoma. No statistically significant difference was observed between high p53 expression and mean survival time ($p > 0.05$; ►**Table 6**).

All cases with lymphoma were diffuse large B-cell lymphoma. Bcl-2 was positive in 46.2% ($n = 12$) and Bcl-6 was positive in 65.4% ($n = 17$) in lymphomas cases (►**Table 6**). Negative or positive Bcl-2 and Bcl-6 were not associated with survival in lymphomas ($p > 0.05$). While the mean Ki-67 was 30.4 ± 19.4 in patients with glioblastoma, it was 77.3 ± 13.4 in patients with lymphoma. Survival was significantly higher in cases with lymphoma (26.9%) compared to those diagnosed with glioblastoma (2.5%) (►**Table 7**).

Discussion

Histopathological and tumoral biomarkers are important in oncological procedures such as targeted therapies and radiotherapy planning. Stereotactic biopsy enables safe biopsy with a low morbidity rate and treatment planning. Intraoperative use of frozen sections increases diagnostic accuracy in stereotactic biopsy.[1]

The mean age of patients ranges from 41 to 56.8 years in studies on stereotactic brain biopsy.[1,2] The mean age was 57.4 years in our study.

Studies investigating the pathological diagnosis of patients undergoing stereotactic brain biopsy revealed glioblastomas (23.3–52.3%), metastases (1.7–16.2%), and lymphomas (0.5–7%), respectively.[3–5] In our study, 36.4% were diagnosed with glioblastoma, 15.5% with metastasis, and 23.6% with lymphoma. Glial malignancies are often at the forefront of the literature. It is noteworthy that the rate of

Table 5 Comparison of mean survival times with pathological diagnoses

Pathology	Mean	*n*	Standard deviation	Median	Mean rank	Kruskal–Wallis H	*p*-Value
Glioblastoma	8,1026	39	6,67200	5,0000	44,42	5,061	0,167
Lymphoma	6,1579	19	6,75165	3,0000	37,11		
Metastasis	10,6471	17	9,89912	8,0000	50,09		
Others	12,7500	16	10,19477	11,5000	56,06		
Total	8,9890	91	8,22934	5,0000			

Table 6 Immunohistochemical distribution according to pathology results

Pathology		*n* (%)
Glioblastoma ($n = 40$)		
P53 high expression	No	29 (72.5)
IDH mutation	Yes	11 (27.5)
	No	40 (100)
	Yes	0 (0)
Diffuse large B-cell lymphoma ($n = 26$)		
Bcl-2	Negative	14 (53.8)
	Positive	12 (46.2)
Bcl-6	Negative	9 (34.6)
	Positive	17 (65.4)

Abbreviation: IDH, isocitrate dehydrogenase.

lymphoma is significantly higher in our study than in available studies. Another significant point is the increasing incidence of lymphoma over the years. This increasing incidence of primary central nervous system lymphomas may be associated with the organ transplantation and the increasing number of immunosuppressed patients due to viral or iatrogenic causes.[11,12]

Studies investigating lesion locations in which stereotactic biopsy was performed report the rate of hemispheric lesions as 38 to 47.9%, deep-seated lesions as 26.9 to 33%, and multiple lesions as 2.5 to 29%.[1,3] In our study, the rates of hemispheric, deep-seated, and multiple lesions were determined as 40, 42.7, and 17.3%, respectively. These rates show that deep-seated lesions were detected by biopsy in the majority of our patients, the rates of which are higher compared to available studies in the literature. This is attributed to the fact that lymphomas, which are deep-seated lesions, were more common in our study than in the literature. As it is known, radiological features of cerebral lesions provide significant information for follow-up and treatment. Lesion location is of significant value for structuring surgical procedures and predicting neurological postoperative complications that may occur in the patient.[13]

In recent years, histopathological diagnosis has been replaced by classifications based on the genetic characteristics of the tumor. Several parameters were examined with the aim to diagnose tumors and to guide the treatment. In our consideration, no IDH mutation was detected in any of the glioblastomas, which exhibits a rate of 90% in the literature. Our relatively high values may be associated with the fact that the patients who underwent biopsy generally included elderly patients with deep-seated infiltrative tumors who cannot surgical treated.[14,15]

The rate of Ki-67 in glioblastomas varies between 19.2 and 27% in the literature.[16,17] Moskowitz et al[18] found a mean survival of 9 months in 116 patients with a diagnosis of glioblastoma, reporting that the Ki-67 ratio was not a survival indicator. In this study, the mean Ki-67 rate was 30.4% in 40 patients diagnosed with glioblastoma. The mean survival of our patients is 8 months.[17,18] The Ki-67 rate was not found to exert a significant effect on survival.[12,15] P53 proteins produced by the tumor protein 53 gene are involved in apoptosis. Previous studies report high p53 expression levels in glioblastoma with rates of 25.4 to 54%.[19–21] This rate was 27.5% in this study. Newcomb et al[20] analyzed the

Table 7 Survival rates in glioblastoma and lymphomas

			Survival		Total
			Ex	Alive	
Pathlogy	Glioblastoma	*n*	39	1	40
		%	97.5	2.5	100.0
	Lymphoma	*n*	19	7	26
		%	73.1	26.9	100.0
Total		*n*	58	8	66
		%	87.9	12.1	100.0

Ki-square= 8,824; $p = 0.005$.

immunohistochemical data of 80 patients diagnosed with glioblastoma by age category. Among patients with and without high p53 expression, the mean survival was 27.1 to 20.1 months, 13.9 to 29.7 months, and 12.2 to 13 months in the age categories of 22 to 40 years, 41 to 60 years, and 61 to 80 years, respectively. However, high p53 expression was not found to play a role in mean survival. Among our patients, the mean survival is 11.3 months in those with high p53 expression, while the mean survival is 6.8 months in those not showing high p53 expression. Similarly, no statistically significant difference was found between high p53 expression and mean survival. In a study conducted with 46 patients diagnosed with glioblastoma, Malkoun et al[22] reported that high p53 expression and Ki-67 rate had no effect on the mean survival and response to temozolomide therapy. Tumor protein 53 mutations are higher in secondary glioblastoma cases with low-grade progression at younger ages. Our patients mostly consisted of elderly patients diagnosed with primary glioblastoma who had comorbidities and deep-seated lesions. Accordingly, the general clinical condition was thought to affect survival, except for immunohistochemical parameters.

More than 95% of primary central nervous system lymphomas belong to the diffuse large B-cell type. Burkitt lymphoma, T-cell lymphoma, lymphoblastic lymphoma, and marginal zone lymphoma can be rarely encountered in the central nervous system.[23,24] Diffuse large B-cell lymphoma was defined in all of our 26 cases diagnosed with primary central nervous system lymphoma. This was attributed to the absence of secondary central nervous system lymphoma in our study. In a 1997 study, Corn et al[11] predicted a significant increase in central nervous system lymphomas in the 2000s along with the increase in the number of immunocompromised patients, which has been confirmed due to factors such as organ transplant, viral infections, and widespread use of immunosuppressive treatments, resulting in an increase in central nervous system lymphomas over time. Accordingly, the rate of lymphomas was significantly higher in our series contrary to the literature data. In addition, the distribution of our lymphoma patients by years has revealed a statistically significant increase in a similar way.

Bcl-2 and Bcl-6 overexpression is assessed in the follow-up and treatment of non-Hodgkin lymphomas. Bcl-2 protein is involved in the inhibition of apoptosis and its positivity is seen in primary central nervous system lymphomas at a rate of 19 to 93%.[20,25,26] Publications reporting no correlation between high expression of Bcl-2 protein and mean survival in primary central nervous system lymphomas emphasize that the main factors affecting survival and prognosis include patient age, general performance status, presence of multiple lesions, and compliance with treatment.[20,26] Although Bcl-2 positivity is generally associated with poor prognosis in systemic diffuse large B-cell lymphomas, it has not yet been confirmed in primary central system lymphomas. Some studies report that Bcl-2 positivity is mostly seen in elderly patients and negatively affects the response to oncological treatment.[20,22] In our study, Bcl-2 positivity was found 46.2% among 26 lymphoma patients, exhibiting no statistically significant effect on survival. Bcl-6 protein is involved in cell differentiation and Bcl-6 protein positivity varies between 22 and 79% in primary central nervous system lymphomas.[25,26] The relationship between Bcl-6 positivity and mean survival remains controversial. Studies, where no significant relationship was observed between Bcl-6 expression and survival, report patient age as the main prognostic factor.[26,27] In the present study, age was not found to exert an effect on prognosis. Studies associating Bcl-6 expression with good prognosis report that patients with high Bcl-6 expression exhibited a positive response to chemotherapy.[26] In our study, Bcl-6 positivity was found at a rate of 65.4% among 26 lymphoma patients, and no statistically significant relationship was observed between Bcl-2 positivity and survival.

Brain metastases arise from lung (19.9–53%), breast (5.1–15%), malignant melanoma (6.9–9%), renal (2–6.5%), and colorectal cancer (1.8–5%) in the literature.[13,28,29] The primary focus was lung in 58.8% ($n = 10$) of 17 patients with metastasis in our patients group. About 11.7% of the metastases were derived from the breast, 11.7% from the kidney, 11.7% from the bladder, and 5.8% from malignant melanomas. Although our rates are similar to those in the literature, lung-derived metastases have been determined to be somewhat higher. The mean survival is reported to vary between 2.5 months and 1 year in brain metastases, depending on parameters such as patient age, control of primary malignancy, prevalence of metastasis, and performance status[29]. In their study of 1,200 patients, Gaspar et al[30] classified cerebral metastasis patients who received whole-brain irradiation according to general performance status, age, and presence of extracranial metastases. The mean survival was 7.7, 4.5, and 2.3 months in patients with good, moderate, and poor clinical status, respectively in this study.[30] In our study, the mean survival was 10.6 months in patients diagnosed with metastasis. High survival time is attributed to the compliance of our patients with treatment and the rapid application of adjuvant therapy, and maybe relatively small patient group.

Conclusion

In neurosurgery practice, histopathological diagnosis of a lesion detected via radiological imaging plays a significant role in treatment planning. Microsurgical resection may not always be possible in patients with deep-seated lesions, small lesions, multiple lesions, and lesions located in functionally critical areas or in patients with severe comorbidities. In such cases, stereotactic biopsy remains valuable as a minimally invasive approach. Patients who underwent stereotactic biopsy in our clinic were mainly diagnosed with glioblastoma, primary cerebral lymphoma, and metastases, respectively. It is noteworthy that the rate of lymphoma in our study is higher than in the literature. Another significant point is the increasing incidence of lymphoma over the years.

Statement of Ethics

Study approval statement:

Our study was approved by the local ethics committee with the decision number HNEAH-KAEK 2021/228 dated 20.09.2021.

Authors' Contributions

Abdullah Yolcu was involved in the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

Ezgi Akar drafted the work. Fügen Vardar Aker agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Selin Tural Emon provided final approval.

Funding

None.

Conflict of Interest

None declared.

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