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Research Article

When location meets biology: combined risk patterns drive outcomes in primary central nervous system lymphoma

Yerleşim yeri biyolojiyle buluştuğunda: primer santral sinir sistemi lenfomada kombine risk paternleri sağkalımı belirler

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Abstract

Aim: Primary central nervous system lymphoma (PCNSL) is a rare and aggressive extranodal lymphoma. Despite therapeutic advances, data from immunocompetent patients in real-world cohorts remain limited, and prognostic factors are still not clearly defined- especially in small retrospective series.

Material and Methods: We retrospectively analyzed 19 immunocompetent patients diagnosed with PCNSL between June 2002 and March 2022 at a single tertiary oncology center. Clinical, radiological, pathological, and treatment-related parameters were collected. Overall survival (OS) was assessed, and univariate analysis was conducted to explore potential prognostic factors.

Results: The median age was 49.1 years, and 57.9% were male. Focal neurological deficits were the most common presenting symptom. Poor outcomes were observed in patients with deep brain involvement, parietal lobe lesions, bilateral or multifocal disease, and germinal center B-cell (GCB) subtype. All GCB patients experienced relapse and died, while most non-GCB patients remained alive and disease-free. The Memorial Sloan Kettering Cancer Center (MSKCC) score effectively stratified risk groups. Median OS was 13.6 months. Multivariate analysis was not feasible due to overlapping high-risk features, limiting statistical independence.

Conclusion: This study emphasizes the prognostic impact of combined anatomical and molecular risk factors in PCNSL and contributes real-world data from an underrepresented population. These findings may support the development of risk-adapted therapeutic strategies for this rare malignancy.

Keywords: primary central nervous system lymphoma, prognosis, survival analysis

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Öz

Amaç: Primer santral sinir sistemi lenfoması (PSSSL), nadir görülen ve agresif seyirli bir ekstranodal lenfoma alt tipidir. Özellikle immün sistemi sağlam hastalarda yapılan gerçek yaşam verileri sınırlıdır. Prognostik faktörler net olarak tanımlanmamıştır ve küçük retrospektif serilerde sonuçlar çelişkilidir.

Gereç ve Yöntemler: Bu tek merkezli retrospektif çalışmaya, Haziran 2002 ile Mart 2022 tarihleri arasında PSSSL tanısı almış 19 hasta dahil edildi. Klinik, radyolojik, patolojik ve tedaviyle ilişkili veriler değerlendirildi. Genel sağkalım (OS) analiz edildi. Prognostik faktörleri belirlemek amacıyla univaryant analiz yapıldı.

Bulgular: Hastaların medyan yaşı 49,1 olup %57,9'u erkekti. En sık başvuru semptomu fokal nörolojik defisitti. Derin beyin yerleşimi, parietal lob tutulumu, bilateral veya multifokal lezyonlar ve germinal merkez B hücreli (GCB) alt tip varlığı ile sağkalımın belirgin şekilde kötü olduğu gözlendi. GCB alt tipli tüm hastalar relaps gösterip yaşamını yitirirken, non-GCB hastaların çoğu hastalıksız olarak yaşamını sürdürmekteydi. Memorial Sloan Kettering Kanser Merkezi (MSKCC) prognostik skoru, risk gruplarını başarılı şekilde ayırt etti. Medyan genel sağkalım 13,6 aydı. Prognostik faktörlerin aynı hastalarda kümelenmesi nedeniyle çok değişkenli analiz yapılmadı.

Sonuç: Bu çalışma, PSSSL'de anatomik ve moleküler yüksek risk özelliklerinin sağkalım üzerindeki belirgin etkisini vurgulamakta ve az temsil edilen bir popülasyondan gerçek yaşam verileri sunarak literatüre katkı sağlamaktadır. Bulgular, bu nadir malignitede bireyselleştirilmiş tedavi yaklaşımlarının geliştirilmesine rehberlik edebilir.

Anahtar Kelimeler: primer santral sinir sistemi lenfoması prognostik faktörler, sağkalım analizi

Introduction

M Primary central nervous system lymphoma (PCNSL) is a rare and aggressive subtype of extranodal non-Hodgkin lymphoma, characterized by localization to the brain, leptomeninges, spinal cord, or eyes without systemic involvement at diagnosis. Although it accounts for fewer than 2% of all primary central nervous system tumors, its clinical course is distinct and often challenging in terms of diagnosis and management. PCNSL typically presents with nonspecific neurological symptoms, and definitive diagnosis requires the integration of advanced neuroimaging, cerebrospinal fluid analysis, and histopathological confirmation [1,2].

Over the past two decades, high-dose methotrexate (HD-MTX)–based chemotherapy has significantly improved treatment outcomes; however, PCNSL remains a therapeutically challenging disease with a high risk of relapse and substantial treatment-related toxicity [3,4]. Several prognostic factors have been proposed—such as age, performance status, anatomical location, and immunohistochemical subtype—but these findings remain inconsistent, particularly in real-world settings with small, heterogeneous cohorts [5-8].

In Türkiye, clinical data on PCNSL are extremely limited. Existing studies generally involve small patient numbers, lack detailed analyses of anatomical and molecular prognostic variables, and rarely focus on long-term survival outcomes. Moreover, large-scale prospective studies are difficult to perform due to the rarity and biological heterogeneity of the disease. This paucity of region-specific evidence limits the ability to develop risk-adapted management strategies tailored to the Turkish population.

To address this gap, the present study aims to comprehensively characterize the clinical presentation, treatment modalities received, and survival outcomes of PCNSL in a single tertiary oncology center in Türkiye, and to evaluate the prognostic impact of anatomical distribution, molecular subtype, and clinical presentation on overall survival. By providing detailed, real-world data from an underrepresented region, this study seeks to enhance the understanding of prognostic determinants, inform individualized treatment approaches, and contribute to the foundation for future multicenter collaborations.

Material and Methods

Study Design and Patient Selection

This retrospective, single-center study included 19 immunocompetent patients diagnosed with PCNSL between June 2002 and March 2022 at Ankara Bilkent City Hospital, a tertiary oncology referral center. Inclusion criteria were histopathological confirmation of PCNSL according to the 2021 WHO Classification of Tumors of the Central Nervous System (5th edition), absence of systemic lymphoma at diagnosis confirmed by staging investigations, and availability of complete baseline and follow-up data. Patients with HIV infection, a history of chronic immunosuppressive therapy, systemic lymphoma, or incomplete clinical records were excluded.

Clinical, Radiological, and Pathological Variables

Collected variables included demographic data, presenting symptoms, lesion number, laterality, anatomical location, lesion depth, histopathological subtype, and treatment modalities.

Anatomical tumor location was categorized as cerebral hemispheres, deep brain structures (basal ganglia, thalamus, corpus callosum, brainstem, cerebellum), or cranial/spinal nerve roots. Laterality was defined as unilateral or bilateral/multifocal, and depth as superficial (lobar cortex/subcortex) or deep (periventricular regions, basal ganglia, thalamus, brainstem, cerebellum). Histological classification followed WHO criteria, and diffuse large B-cell lymphoma (DLBCL) subtypes were determined according to the Hans algorithm (germinal center B-cell–like (GCB) subtype vs. non-GCB). Prognostic stratification was based on the Memorial Sloan Kettering Cancer Center (MSKCC) score, incorporating age and Karnofsky Performance Status (KPS). During the study period, no records regarding autologous stem cell transplantation for consolidation were available; therefore, this aspect was not addressed in the analysis. This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (Approval No: E.Kurul-E1-23-4292). Informed consent was waived due to the retrospective nature of the study and complete anonymization of patient data.

Statistical Analysis

Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY). Categorical variables were expressed as counts and percentages, and continuous variables as medians with ranges. Normality was assessed with the Shapiro–Wilk test. Overall survival (OS) was defined as the time from histological diagnosis to death from any cause or last follow-up. Survival probabilities were estimated with the Kaplan–Meier method, and between-group differences were tested using the log-rank test. Univariate Cox proportional hazards regression was additionally performed to estimate hazard ratios (HR) with 95% confidence intervals (CI) for potential prognostic factors.Multivariate Cox regression was not performed due to clustering of adverse prognostic features—such as GCB subtype, deep localization, multifocal or bilateral lesions, and poor MSKCC scores—within the same patients, leading to collinearity and violation of model assumptions. Several univariate comparisons yielded non-significant p-values despite strong clinical trends, likely due to overlapping risk profiles and limited subgroup sizes. Future multicenter studies with larger patient cohorts are planned to validate these findings in a multivariate setting. To optimize statistical power, univariate analysis used a simplified regional classification (cerebral hemispheres vs. deep brain structures). All events were verified through institutional and national death registries. No imputation or sensitivity analyses were required, as follow-up was complete for all patients. Given the rarity of PCNSL and strict inclusion criteria, power analysis was not feasible, and findings should be interpreted as exploratory and hypothesis-generating.

Results

Patient Characteristics

The cohort comprised 19 immunocompetent patients with histologically confirmed PCNSL. The median age at diagnosis was 49.1 years, and 57.9% were male. Focal neurological deficits were the most common presenting symptom. All six patients who initially presented with cognitive or behavioral changes experienced recurrence and death, which may suggest a link between neurocognitive presentations and aggressive tumor biology. A detailed summary of baseline clinicopathologic characteristics is presented in Table 1.

Tumors were predominantly located in the cerebral hemispheres, while 31.6% involved deep brain structures. Bilateral or multifocal lesions were present in 36.8% of cases. All patients with deep brain involvement, multifocal or bilateral disease, or parietal lobe tumors experienced recurrence and died. In contrast, four of five patients with frontal lobe involvement remained alive and recurrence-free, indicating potential biological heterogeneity across anatomical subregions, a finding consistent with emerging neuro-oncologic evidence.

Histopathologically, all tumors were DLBCL. Based on the Hans algorithm, 42.1% were classified as non-GCB, 36.8% as GCB, and 21.1% as unclassified. All seven patients with the GCB subtype relapsed and died, while six of eight non-GCB patients remained alive and disease-free. Notably, GCB tumors frequently co-occurred with other adverse features, such as deep localization, multifocality, and high MSKCC risk scores.

The MSKCC prognostic score demonstrated clear discriminatory capacity. All patients in the favorable-risk group (age <50; n = 6) remained alive and recurrence-free. In contrast, all seven patients in the poor-risk group (age ≥50 and KPS <70) and five of six patients in the intermediate-risk group (age ≥50 and KPS ≥70) experienced relapse and death. Similarly, eight of ten patients with Ann Arbor stage IV-A disease relapsed and died, whereas outcomes were more favorable in stage I patients. These observations support the prognostic utility of both the MSKCC and Ann Arbor systems, even in small PCNSL cohorts.

Treatment Modalities and Response

Initial treatment strategies were heterogeneous (Table 2). Approximately one-third of patients received chemotherapy alone, while the remaining two-thirds underwent combined modality treatments (e.g., chemoradiotherapy, surgery plus chemotherapy). Biopsy was the most common surgical procedure, but gross or subtotal resections were performed when feasible.

Table 1. Baseline clinicopathologic characteristics of patients (n = 19)

Parameter	n (%) / Median (Range)
Age at diagnosis (years)	49.1 (26–69)
Sex	
• Male	11 (57.9%)
• Female	8 (42.1%)
Presenting symptoms	
• Focal neurological deficits	11 (57.9%)
• Cognitive/behavioral changes	6 (31.6%)
• Seizure	1 (5.3%)
• Intracranial tension	1 (5.3%)
B symptoms	
• Absent	18 (94.7%)
• Present	1 (5.3%)
Bone marrow involvement	
• Absent	19 (100.0%)
Lumbar puncture at diagnosis	
• Not performed	11 (57.9%)
• Performed	8 (42.1%)
Maximal tumor size (mm)	38.0 (15–65)
Tumor location (Region)	
• Cerebral hemispheres	13 (68.4%)
• Deep brain	6 (31.6%)
Number of cranial lesions	
• Single	12 (63.2%)
• Multiple	7 (36.8%)
Tumor location (Anatomical)	
• Temporal lobe	5 (26.3%)
• Frontal lobe	5 (26.3%)
• Occipital lobe	4 (21.1%)
• Parietal lobe	3 (15.8%)
• Periventricular	2 (10.5%)
Ann arbor stage	
• 1	9 (47.4%)
• 4	10 (52.6%)
Ann arbor subtype	
• E	10 (52.6%)
• A	9 (47.4%)
MSKCC prognostic score	
• Age ≥50 and KPS < 70	7 (36.8%)
• Age ≥50 and KPS ≥ 70	6 (31.6%)
• Age < 50	6 (31.6%)
Ki-67 proliferation index (%)	75.0 (40–95)
Immunophenotype	
• B-cell	19 (100.0%)
Histopathological subtype	
• DLBCL-non-GCB	8 (42.1%)
• DLBCL-GCB	7 (36.8%)
• DLBCL-NOS	4 (21.1%)

Abbrev.: Ann Arbor subtype: A = no systemic symptoms; B = presence of systemic (B) symptoms; E = extranodal involvement; X = bulky disease. MSKCC score was assigned based on age and KPS. DLBCL-non-GCB subtype was defined according to Hans algorithm. MSKCC: Memorial Sloan Kettering Cancer Center; KPS: Karnofsky Performance Status; DLBCL: diffuse large B-cell lymphoma; GCB: germinal center B-cell-like; non-GCB: non-germinal center subtype. Categorical variables are presented as number and percentage. Continuous variables are expressed as median and range.

Table 2. Treatment, recurrence and survival characteristics.

Parameter	n (%) / Median (Range)
Surgical approach	
• Biopsy only	10 (52.6%)
• GTR	6 (31.6%)
• STR	3 (15.8%)
Initial treatment strategy	
• CT → RT	6 (31.6%)
• Surgery → CT → RT	6 (31.6%)
• CT alone	7 (36.8%)
Received radiotherapy	
• Yes	12 (63.2%)
• No	7 (36.8%)
Received intrathecal chemotherapy	
• Yes	4 (21.1%)
• No	15 (78.9%)
Induction chemotherapy regimen	
• HD-MTX	6 (31.6%)
• HD-MTX + RTX	8 (42.1%)
• HD-MTX + ARA-C	4 (21.1%)
• HD-MTX + Vinkristin	1 (5.3%)
Best response to induction therapy	
• CR	2 (10.5%)
• PR	7 (36.8%)
• SD	7 (36.8%)
• PD	3 (15.8%)
Recurrence	
• Yes	12 (63.2%)
• No	7 (36.8%)
Survival status	
• Deceased	13 (68.4%)
• Alive	6 (31.6%)
mFollow-up duration (months)	82.5 (56.9–116.4)
mOS (months)	13.6 (4.4–26.4)

Abbrev.: GTR: gross total resection; STR: subtotal resection; CT: chemotherapy; RT: radiotherapy; HD-MTX: high-dose methotrexate; ARA-C: cytarabine; RTX: rituximab; Vinkristin: vincristine. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease. Categorical variables are presented as number and percentage. Continuous variables are expressed as median and range.

All patients received HD-MTX–based induction chemotherapy, either as monotherapy or in combination with rituximab or cytarabine. The overall response rate (complete response + partial response) was 47.3%, while 36.8% had stable disease and 15.8% showed progressive disease.

Despite initial treatment, 63.2% of patients eventually relapsed. At the time of analysis, 13 patients (68.4%) had died. The median OS was 13.6 months (range, 4.4–26.4), and the median follow-up among censored cases was 82.5 months, ensuring adequate observation time for survival assessment.

Survival and Prognostic Factors

Univariate analysis (log-rank test) identified several variables significantly associated with OS (Table 3). Patients with localized, unifocal tumors had significantly longer OS than those with multifocal or bilateral disease (31.8 vs. 6.0 months, p = 0.006). Deep brain involvement was associated with significantly worse survival compared to tumors confined to the cerebral hemispheres (7.12 vs. 31.8 months, p = 0.024).

Patients presenting with focal neurological deficits or signs of intracranial pressure had improved survival compared to those with cognitive or behavioral changes or seizures (31.8 vs. 11.6 months, p = 0.016). Additionally, the GCB subtype was linked to shorter OS compared to non-GCB tumors (8.9 vs. 31.8 months, p = 0.044).

In descriptive subgroup analyses according to treatment regimens, patients who received combined chemoradiotherapy tended to have longer overall survival compared to those who received chemotherapy alone; however, this difference did not reach statistical significance due to the limited sample size.

The estimated 1-, 3-, and 5-year OS rates for the entire cohort were 52.6%, 36.8%, and 36.8%, respectively. Importantly, no deaths occurred between the third and fifth years of follow-up.

These overlapping high-risk features—including GCB phenotype, deep localization, and multifocality—frequently clustered within the same patients, precluding reliable multivariate modeling. Hazard ratios provided in Table 3 are therefore descriptive and should be interpreted with caution.

Table 3. Univariate analysis of prognostic factors for overall survival (OS).

Variable	Category	Median OS (months)	Univariate p-value	Estimated HR (95% CI)
Presenting symptom	Intracranial tension + focal	31.8	0.016	1.00 (ref)
	Personality changes + epilepsy	11.6		2.89 (1.24–6.74)
Number of lesions	Single	31.8	0.006	1.00 (ref)
	Multiple	6.0		3.65 (1.48–9.02)
Lesion location	Cerebral hemispheres	31.8	0.024	1.00 (ref)
	Other (deep/spinal)	7.12		3.27 (1.31–8.15)
Cranial laterality	Unilateral	31.8	0.006	1.00 (ref)
	Bilateral/Multifocal	6.0		3.65 (1.48–9.02)
Lesion depth	Superficial (cerebral)	31.8	0.024	1.00 (ref)
	Deep brain	7.12		3.27 (1.31–8.15)
Cell of origin	Germinal center B-cell (GCB)	8.9	0.044	3.21 (1.04–9.89)
	Non-GCB	31.8		1.00 (ref)

Abbrev.: GCB: germinal center B-cell-like; non-GCB: non-germinal center subtype. Hazard ratios (HR) and 95% confidence intervals (CI) are presented for descriptive purposes based on observed differences in median OS. These estimates are not derived from multivariable modeling and should not be interpreted as adjusted risk measures.

Discussion

This study shows that integrating anatomical distribution, molecular subtype, and clinical presentation provides valuable prognostic insight in PCNSL. In our cohort, deep brain involvement, bilateral or multifocal disease, parietal lobe localization, and GCB phenotype were consistently linked to markedly shorter OS. These features often co-occurred, creating collinearity that precluded robust multivariate modeling—a limitation inherent to small real-world series. Nonetheless, strong univariate associations were consistent with large-scale datasets and institutional experiences.

Tumor location was a major determinant. All patients with deep lesions relapsed and died (median OS 7.1 months) versus 31.8 months for superficial tumors, mirroring the Oslo cohort (>14-fold increased death risk, p < 0.0001) [10], IELSG findings (HR 1.57; p = 0.009) [7,8], and Özkan et al. [9]. Disease distribution showed a similar pattern: bilateral/multifocal involvement yielded a median OS of 6.0 months vs. 31.8 months for unifocal disease, in line with SEER data (HR 1.36; p = 0.037) [15], Ebrahimi et al. (8.3 vs. 21.5 months) [13], and Liu et al., 2017 (12 vs. 28 months) [14].

Histopathology further refined prognosis. All GCB cases relapsed and died (median OS 8.9 months) compared with 31.8 months for non-GCB. SEER analysis by Chen et al. found non-DLBCL histology predicted worse OS (HR 1.298, p<0.05) with greater chemotherapy benefit in DLBCL [15]. Tang et al. similarly linked NGCB subtype with inferior OS, along with elevated CSF protein, bilateral disease, ECOG ≥ 2, and high MSKCC score [16].

MSKCC scoring showed clear discrimination: all Class 1 patients were alive at follow-up, whereas nearly all Class 2–3

patients had died, echoing Jahr et al. (median OS 90.9, 38.5, and 7.2 months; p<0.01) [10], Tang et al. [16], and Duan et al. [17]. Compared with IELSG, MSKCC is simpler and clinically practical, particularly for identifying very high-risk patients.

Presenting symptoms also carried prognostic value. Focal deficits or intracranial pressure symptoms correlated with longer OS (31.8 months) than cognitive/behavioral changes or seizures (11.6 months), consistent with other series [8,9,16-18]. Non-focal symptoms may reflect diffuse, bilateral, or deep-seated disease, supporting their inclusion in risk models.

In our cohort, all patients received HD-MTX–based induction therapy, either alone or in combination with rituximab or cytarabine, reflecting current standard practice. While our response rates and survival outcomes are consistent with some real-world series, the high relapse rate observed underscores the ongoing therapeutic challenge in PCNSL. Over the past two decades, HD-MTX–based chemotherapy has significantly improved outcomes; however, disease control remains suboptimal, and treatment-related toxicity is considerable [3,4]. Various combination regimens- such as HD-MTX with cytarabine, rituximab, or thiotepa- and consolidation strategies including whole-brain radiotherapy or high-dose chemotherapy followed by autologous stem cell transplantation have been explored, yet no universally accepted standard has emerged [3,4]. In our series, no records regarding autologous stem cell transplantation for consolidation were available; therefore, this aspect was not addressed in the analysis. More recently, novel approaches such as Bruton's tyrosine kinase inhibitors (e.g., ibrutinib, tirabrutinib) and CAR-T cell therapy have shown encouraging results in relapsed or refractory PCNSL, achieving durable responses in selected patients. Ongoing trials will clarify their role, either as stand-alone options or in combination with conventional regimens, and may help to reduce long-term neurotoxicity while improving disease control [3,4].

Univariate analysis identified deep brain involvement, multifocality, parietal localization, GCB phenotype, poor ECOG, age >60, high MSKCC score, and non-focal symptoms as adverse factors, in agreement with prior datasets [7-9,10,11,15-17,19,20]. In our cohort, parietal lobe involvement was frequently associated with extensive hemispheric spread and contiguous extension to adjacent lobes, which may partly explain its adverse prognostic impact. Although rarely reported in prior studies, this finding suggests that neuroanatomical spread patterns could influence outcomes in PCNSL. Additional studies suggest systemic inflammatory and nutritional markers may enhance prognostic precision [21].

Survival in our cohort was modest (1-, 3-, 5-year OS: 52.6%, 36.8%, 36.8%; median OS: 13.6 months), aligning with the mid-to-lower range of literature: Chen et al. (36 vs. 7 months with vs. without chemotherapy) [15], Tang et al. (34 months) [16], Duan et al. (25.6 months) [17], Sopittapan et al. (19.5 months) [19], Jahr et al. (1-, 3-, 5-year OS: 55%, 38%, 30%) [10], Seidel et al. (3-year OS: 37.4%) [6], Ebrahimi et al. (37.4 months) [13], Chi et al. (5-year OS: 26.7%) [12], and Liu et al. (1-, 3-, 5-year OS: 83%, 60%, 52%) [14]. The relatively shorter median overall survival in our cohort compared to that reported in other studies may be attributed to several factors, including the retrospective nature of our study, the inability to administer aggressive therapy in some patients due to advanced age or comorbidities, regional disparities in access to diagnosis and treatment, and potential genetic or biological differences.

Our findings parallel global experience but emphasize ongoing challenges in durable disease control. Given the scarcity of granular real-world data in immunocompetent PCNSL from Türkiye, these results add meaningful regional evidence. Future multicenter validation of integrated prognostic models incorporating anatomical, molecular, functional, and symptom-based factors may guide earlier identification of high-risk patients and support personalized management strategies.

In conclusion, in PCNSL, the combination of tumor location and biology- not any single factor- drives survival. Early recognition of high-risk patterns can inform treatment intensity and follow-up, a strategy that should be validated in larger, prospective cohorts.

Ethics Approval

This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (Approval No: E.Kurul-E1-23-4292).

Conflict of Interest

The authors declare no conflict of interest.

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Authors Contribution

Emre Hafızoğlu, M.D.: Conceptualization, data collection, statistical analysis, interpretation of results, manuscript drafting, final approval.

Serhat Sekmek, M.D.: Patient data verification, literature review, critical manuscript review.

Doğan Bayram, M.D.: Clinical data interpretation, figure and table preparation, critical revision.

İrfan Karahan, M.D.: Radiological and pathological data review, manuscript editing, review of clinical accuracy.

Efnan Algın, M.D., Prof.: Supervision, methodological input, critical revision of the manuscript.

Öznur Bal, M.D., Prof.: Supervision, interpretation of oncological treatment protocols, manuscript review and approval.

Doğan Uncu, M.D., Prof.: Study oversight, senior supervision, scientific editing, final approval of the manuscript.

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