Retrospective Evaluation of Childhood Central Nervous System Tumors Followed in a Pediatric Hematology Oncology Center: A Single Center Experience

Asli GENC[1], Arzu YAZAL ERDEM[2], Suna EMIR[3], Derya OZYORUK[2]

[1] University of Health Sciences, Ankara Bilkent City Hospital, Department of Pediatrics
[2] University of Health Sciences, Ankara Bilkent City Hospital, Department of Pediatric Hematology and Oncology
[3] Atilim University, Faculty of Medicine, Department of Pediatric Oncology

ABSTRACT

Central nervous system (CNS) tumors are one of the main causes of cancer-related deaths in childhood. Although approximately 60% of all patients are alive 5 years after diagnosis, a sequela due to the disease and treatments are common. In this study, we aimed to evaluate the demographic, clinical characteristics, and outcomes of the childhood CNS tumors in our center. A total of 141 patients between 0-18 years who were followed up and completed their treatment in our pediatric oncology center were included. The files were reviewed retrospectively. The median age of patients was 7 years (range 1 month-17.6 years). The male/female ratio was 1.1: 1. The most common presenting symptom was headache. The median time from the first symptom to diagnosis was 1.4 months. Medulloblastoma was the most common diagnosis (n= 28, 19.9%), followed by pilocytic astrocytoma (18.4%, n= 26) respectively. Out of 141 patients, a sequela was seen in 55 (39%) patients. The relationship between high-dose radiotherapy and the development of short stature was statistically significant (p= 0.009). The patients with metastatic disease were likely to have lower survival rates than nonmetastatic disease (p= 0.001). The presence of metastasis increased the death status 6.482 times (OR: 6,482, p= 0.001). The overall 5-year survival rate of all patients was found 80%. There was an association between the histopathological subtypes and overall survival rates (p= 0.001). In the multivariate analysis, metastasis was the most important factor in survival. According to Cox regression analysis, the two most important factors affecting overall survival were the histopathological subtype and the presence of metastasis.

Keywords: Central nervous system tumors, Childhood brain tumors, Survival

INTRODUCTION

Central nervous system (CNS) tumors include both malignant and benign tumors of the brain and spinal cord. Primary malign CNS tumors are the second most common childhood malignancy after leukemia in developed countries and the most common solid organ tumor of childhood. Even though significant progress has been made in the treatment of childhood tumors, CNS tumors are still an important cause of mortality and morbidity.[1,2] The clinical findings of intracranial tumors vary depending on the age of the patient, the location, and the growth rate of the tumor. While headache, nausea, vomiting, and gait/balance problems are common in older children, restlessness, high-pitched crying, and bulging fontanel can be seen in infants.[3] Treatment of CNS tumors requires a multidisciplinary approach. Treatment includes a multimodal surgical approach, radiation therapy (RT), and chemotherapy (CT). Approximately two-thirds of all patients are alive 5 years after diagnosis but at the same time, neurological, cognitive, psychological, and endocrinological sequelae due to both the disease itself and treatments are common in survivors.[4,5] This study aimed to evaluate the outcomes and prognostic factors affecting the overall survival of CNS tumors.

PATIENTS AND METHODS

In this study, 141 childhood CNS tumor patients who were diagnosed and completed their treatments in Ankara Pediatrics Hematology Oncology Training and Research Hospital, Oncology Clinic between the years 2005 and 2019 were included. We aimed to determine the demographic and clinical characteristics, histopathological subgroups, the mean time from the first symptom to diagnosis, and treatment methods and whether there is any association with relapse, event-free survival and overall survival in patients with CNS tumor in the pediatric oncology clinic. We recorded the files retrospectively and we obtained the patients' age, gender, clinical findings, tumor location, the time from the first symptom to diagnosis, treatments, histopathological subtype of the tumor, late side effects, recurrence, 5-year event-free survival, and overall survival rates. The presenting symptoms of the patients before the diagnosis of brain tumor were obtained from the files. The tumors are divided into 3 groups according to their localization supratentorial, infratentorial and spinal. The histopathological diagnosis of patients was made according to the 2007 WHO classification. Patients who completed 5 years of follow-up and treatment without any sequelae are defined as cured, and the patients in remission were the ones being followed up after completing their treatments.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 18 © Copyright SPSS Inc. 1989, 2010 software. Chi-square and Fisher Chi-square significance tests were used in the analysis of categorical variables. Survival probabilities were analyzed by the Kaplan-Meier method. Outcomes and survival analyses were made by the time of diagnosis to recurrence or progression of the disease, death from any cause or the last contact time for event-free survival (EFS), and death from any cause or the last contact time for overall survival (OS). Log-rank test was performed to see if there was a difference between variable levels in terms of survival probabilities, and then Cox regression analysis was performed to identify factors affecting survival. The statistical significance level was accepted as 0.05 in this study.

Table 1. Demographic characteristics of patients

	n	%
Gender		
Female	67	47.5
Male	74	52.5
Age Groups		
< 2 years	15	10.6
2-10 years	80	56.7
>10 years	46	32.6
Histopathological Subtypes		
Pilocytic astrocytoma	26	18.4
Medulloblastoma	28	19.9
Diffuse intrinsic pontine glioma	15	10.6
High-grade glial tumors	8	5.7
AT/RT	6	4.3
Epandimoma	7	5.0
Optic glioma	5	3.5
Craniopharyngioma	5	3.5
Other benign tumors	19	13.5
Spinal cord tumors	14	9.9
Other malign tumors	8	5.7
Type of Surgery		
Total/Gross total	80	56.7
Subtotal	25	17.7
Inoperable	21	14.9
Others	15	10.6
Presence of Relapse		
No	113	80.1
Present	28	19.9
Presence of Metastasis		
No	121	85.8
Present	20	14.2
RT Doses		
No	67	47.5
5400 cGy	39	27.6
6000 cGy	20	14.1
3600 cGy	2	1.4
Unknown dose	8	5.6
Outcomes		
Exitus	48	34.8
Cure	39	28.3
Survival with sequelae	37	26.8
Follow-up in remission	14	10.1

Ethical Approval: This study received University of Health Sciences, Ankara City Hospital Health Application Center Clinical Research Ethics Committee approval with the ID number 2019/089; April, 08, 2019.

RESULTS

Demographic and clinical characteristics of the patients are shown in Table 1. The median age of 141 patients was 7 years (range 1 month-17.6

Table 2. The time from the first symptom to diagnosis of tumors according to histopathological subtypes and location

Histopathological Subtypes	Time from first symptom to diagnosis (month)		
	Median	Min-Max	p
Pilocytic astrocytoma	1.00	0.01-24.00	0.411
Medulloblastoma	1.50	0.10-6.00	
Diffuse intrinsic pontine glioma	0.60	0.10-18.00	
High grade glial tumors	1.00	0.10-36.00	
AT/RT	1.00	0.50-18.00	
Epandimoma	2.00	0.10-2.00	
Optic glioma	2.00	1.00-3.00	
Craniopharyngioma	1.50	0.20-2.00	
Other benign tumors	5.00	0.03-120.0	
Spinal cord tumors	3.00	0.30-36.00	
Other malign tumors	1.75	0.20-12.00	
Tumor Locations			
Supratentorial	1.00	0.03-120.0	0.860
Infratentorial	1.40	0.01-36.0	0.520
Spinal cord	1.75	0.3-12.0	0.421

years) and male to female ratio was 1.1: 1. Out of 141 patients, 15 of them (10,6%) were under age 2, 80 of them were between 2-10 years (56,7%) and 46 of them were above 10 years (32.6%). The most common presenting symptom was a headache, followed by gait/balance problems, nausea and vomiting. Other common symptoms were hemiplegia/hemiparesis, seizures, visual problems, weakness, syncope, somnolence, abducens and facial nerve paralysis. A brain tumor was detected incidentally in four of our patients during the well-child examination. Headache, dizziness and gait/balance problems were more common in patients older than 2 years and were statistically significant ($p< 0.05$). The median time from the first symptom to diagnosis was 1.4 months (range 1 day-120 months). Supratentorial tumors were seen in 53 patients (37.5%), infratentorial tumors in 72 patients (51%), and spinal tumors in 14 patients (9.9%). The most common histopathological subtype was medulloblastoma (19.9%, n= 28), and pilocytic astrocytoma (18.4%, n= 26) respectively (Table 1). There was no association between the time from the first symptom to diagnosis and the location of the tumor or the histopathological subtype of the tumor ($p> 0.05$) (Table 2).

Total/gross total surgery was performed in 80 patients (56,7%), followed by subtotal surgery in 25 patients (17.7%) and 21 patients were inoperable (14,9%). Out of 141 patients, 69 patients received RT (52.5%), and 20 (14.1%) of them received high dose RT (6000 cGy).

A sequela was seen in 55 (39%): neurological sequelae in 33 patients (23.4%), endocrinological sequela in 10 patients (7%), hearing loss in 8 patients (5.6%) and short stature in 4 patients (2.83%). No significant difference was found in terms of neurological sequelae, endocrinological sequelae or hearing loss according to the histopathological subtypes and the type of surgery performed ($p> 0.05$). Out of 69 patients who received RT, 20 of them received high-dose RT and 12 of them survived (60%) (12/20). Short stature was observed in 33.3% (n= 4) of these patients and no short stature was seen in patients who received lower RT doses. The relationship between the high-dose RT and the development of short stature was statistically significant ($p< 0.05$). No significant correlation was observed between other variables and short stature.

Recurrence was seen in 28 patients (80.1%) and the most common tumor with recurrence was atypical teratoid rhabdoid tumor (AT/RT). There was no statistically significant difference between the histopathological subtypes of the tumors and the rate of recurrence ($p> 0.05$). Metastasis was seen in 20 patients (14.2%) (Table 1).

Table 3. The outcomes of patients according to gender, age, histopathological subtypes of tumors, tumor locations, presence of recurrence, presence of postoperative residue in 5 years

	Outcomes n (%)					
Gender	**Exitus**	**Cure**	**Survival with sequelae**	**Follow-up in remission**	**Total**	**p**
Female	17 (25.4)	23 (34.3)	19 (28.4)	8 (11.9)	67 (100.0)	0.136
Male	31 (43.7)	16 (22.5)	18 (25.4)	6 (8.5)	71 (100.0)	
Age Groups						
<2 years	5 (35.7)	4 (28.6)	3 (21.4)	2 (14.3)	14 (100.0)	0.341
2-10 years	31 (39.2)	25 (31.6)	18 (22.8)	5 (6.3)	79 (100.0)	
>10 years	12 (26.7)	10 (22.2)	16 (35.6)	7 (15.6)	45 (100.0)	
Histopathological Subtypes						
Pilocytic astrocytoma	0 (0.0)	15 (57.7)	8 (30.8)	3 (11.5)	26 (100.0)	< 0.001
Medulloblastoma	8 (29.6)	5 (18.5)	13 (48.1)	1 (3.7)	27 (100.0)	
Diffuse intrinsic pontine glioma	15 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (100.0)	
High-grade glial tumors	7 (87.5)	0 (0.0)	1 (12.5)	0 (0.0)	8 (100.0)	
AT/RT	4 (66.7)	0 (0.0)	1 (16.7)	1 (16.7)	6 (100.0)	
Epandimoma	2 (28.6)	2 (28.6)	2 (28.6)	1 (14.3)	7 (100.0)	
Optic glioma	0 (0.0)	1 (20.0)	1 (20.0)	3 (60.0)	5 (100.0)	
Craniopharyngioma	1 (20.0)	0 (0.0)	4 (80.0)	0 (0.0)	5 (100.0)	
Other benign tumors	4 (21.1)	8 (42.1)	4 (21.1)	3 (15.8)	19 (100.0)	
Spinal cord tumors	4 (30.8)	7 (53.8)	1 (7.7)	1 (7.7)	13 (100.0)	
Other malign tumors	3 (42.9)	1 (14.3)	2 (28.6)	1 (14.3)	7 (100.0)	
Tumor Locations						
Supratentorial	13 (24.5)	14 (26.4)	17 (32.1)	9 (17.0)	53 (100.0)	0.056
Infratentorial	30 (41.7)	19 (26.4)	19 (26.4)	4 (5.6)	72 (100.0)	0.146
Spinal cord	6 (42.9)	6 (42.9)	1 (7.1)	1 (7.1)	14 (100.0)	0.278
Presence of Recurrence						
No	12 (26.1)	12 (26.1)	17 (37.0)	5 (10.9)	46 (100.0)	0.231
Present	17 (26.2)	23 (35.4)	18 (27.7)	7 (10.8)	65 (100.0)	
Presence of Postoperative Residue						
No	32 (29.1)	33 (30.0)	32 (29.1)	13 (11.8)	110 (100.0)	0.689
Present	14 (53.8)	6 (23.1)	5 (19.2)	1 (3.8)	26 (100.0)	

The median time of follow-up of all patients was 22 months (range 1 day-132 months). The outcomes of patients according to gender, age, histopathological subtypes, tumor localizations, presence of recurrence, receiving craniospinal RT, sequelae presence and 5-year survival rates are shown in Table 3. There was no significant difference between the survival rates and gender, age groups and tumor location ($p> 0.05$). The cure was achieved in 32.8% (n= 39) of the cases without metastasis, and 28.6% (n= 34) died. Fourteen patients (73.7%) with metastasis died and no cure was achieved in any case with metastasis. The patients with metastatic disease were likely to have lower survival rates than nonmetastatic diseases ($p< 0.05$). The presence of metastasis increased the death status 6.482 times (OR: 6.482; $p= 0.001$) (Table 4). The postoperative residual disease had no significance on recurrence or survival ($p> 0.05$).

The median overall survival time was 54.6 months (range 0.23-190.03 months). The time from the first symptom to diagnosis had no significant effect on survival ($R= 0.003$, $p> 0.05$). In this study, we determined that the 5-year event-free survival rate was 66.2% and the overall 5-year survival rate was 80%. The histopathological subtypes calculated separately for overall survival values are given in Table 5. There was an association between the histopathological subtypes and overall survival rates ($p< 0.05$). The survival rate of pilocytic astrocytoma was 100%. Patients with diffuse intrinsic pontine glioma all died, and mortality of high-grade

Table 4. Five-year event-free and Overall survival rates of tumors according to histopathological subtypes

Histopathological Subtypes	5-year event free survival rates (%)	5-year survival rates (%)	Overall p
Medulloblastoma	72	71	p> 0.05
Standart risk		55	
High risk		27	
Pilocytic astrocytoma	91	100	p< 0.05
Diffuse intrinsic pontine glioma	20	0	
High-grade glial tumors	25	10	
AT/RT	50	30	
Epandimoma	70	71	
Optic glioma	60	100	
Craniopharyngioma	80	80	
Other benign tumors	80	83.3	
Spinal cord tumors	64	65.3	
Other malign tumors	85	66	
Total	66.2	80	

diffuse gliomas was 87.5% (7/8). The overall median survival time of diffuse intrinsic pontine gliomas was 11 months (range 0.4-82.6 months). Exitus was seen 3.27 times more frequently in cases with metastasis. As a result of multivariate analysis, the presence of metastasis increased the risk of death 19.13 times as shown in Table 5 (p< 0.05).

In terms of patients with medulloblastoma, being in the standard or high-risk group had no statistically significant effect on the 5-year overall survival (p< 0.05) (Table 5). In the univariate analysis, death was found to be 1.64 times higher in males and 3.46 times higher in high-risk medulloblastomas, but these differences were not statistically significant (p> 0.05).

DISCUSSION

Malignant CNS tumors are mostly fatal in children and are the most common cause of mortality.[1,2] In the presenting study, the demographic characteristics of patients, male predominancy, the mean time from the first symptom to diagnosis, the prevalence of symptoms at presentation, and the survival rates were found to be compatible with the literature data.[3,4,6,7] Considering the distribution of childhood CNS tumors according to histopathological subtypes, in most studies, pilocytic astrocytomas take the first place, followed by medulloblastomas.[4,6-10] The rate of medulloblastomas and spinal cord tumors is higher in our study than in others.[3,9-12] It may be that our center is a referral center for malign CNS tumors. It is known that approximately 60% of childhood CNS tumors originate from the infratentorial area especially from the posterior fossa, which is comparable to our study.[13] The mean time from the first symptom to diagnosis was similar when compared to other studies and it had no predictive effect on survival (R= 0.003, p> 0.05).[3,7,9] In our study, the most common type of surgery performed on patients was total/gross total resection and it was similar to the literature.[4,9] In the literature, it has been shown that residual disease has negative effects on recurrence and survival[4], but in our study, residual disease had no statistically significant effect on survival (p> 0.05). We assumed that it could be related to the relatively high number of benign tumors in presenting study. Although RT has been shown to have many late side effects, including neurological, developmental, neuroendocrine and hearing loss[5], in presenting study, RT was only statistically associated with short stature (p< 0.05).

As a result of treatments or tumors themselves, neurologic seuqelae are the most common side effects followed by endocrinological seuqelae.[9,14,15] In our study, neurological sequelae were observed in all patients with high-grade glial tumors, AT/RT, optic glioma, and spinal cord tumors. There was no significant difference between neurological sequelae and the type of surgery performed (p> 0.05).

Table 5. Survival analysis according to general clinical characteristics and prognostic factors affecting overall survival – univariate and multivariate Cox regression analysis findings

	Mean Survival (months)	STD ERR	p	Univariate		Multivariate	
				HR (%95 CI)	p	HR (%95 CI)	p
Overall Survival	86.66	5.71	-				
Gender							
Female	94.13	7.10	0.118	1	-	1	-
Male	75.70	8.24		1.64 (0.871-3.108)	0.125	2.03 (0.244-16.970)	0.511
Age Groups							
< 2 years	82.93	15.40	0.240	1	-	1	-
2-10 years	77.88	7.79		1.165 (0.408-3.328)	0.775	0.23 (0.14-3.979)	0.317
> 10 years	91.95	8.13		0.619 (0.190-2.011)	0.425	0.12 (0.004-4.380)	0.128
Medulloblastoma Subtype							
Standart risk	97.55	9.84	0.224	1	-	1	-
High risk	90.78	15.22		3.46 (0.403-29.859)	0.258	0.52 (0.21-13.003)	0.696
Metastasis							
None	94.04	5.83	**< 0.001**	1	-	1	-
Present	31.40	9.88		3.27 (1.637-6.549)	**0.001**	19.13 (1.436-254.773)	**0.025**

In presenting study, metastasis was seen in 14.2% of the patients, and in the spinal imaging and/or LP examinations performed at the time of diagnosis, 30% of the patients had metastasis in the spinal cord. In terms of medulloblastoma, leptomeningeal involvement is expected 1/3 of patients in the intracranial or medulla spinalis in imaging performed at the time of diagnosis.[16,17] In our study, leptomeningeal involvement was detected in 6 patients with medulloblastoma at the time of diagnosis (6/28) (21.4%). The most frequently metastasizing tumor subgroups were medulloblastoma and high-grade glial tumors, consistent with the literature. The exitus rate was found statistically significantly higher in cases with metastasis ($p< 0.05$). In the logistic regression analysis, the presence of metastasis increased the death status by 6.4 times. This shows how important the presence of metastasis is in terms of survival and survival with sequelae.

In this study, the 5-year overall survival rate was 80% which is higher than the other studies.[3,4,8,12,18] This may be due to the relatively high number of patients with benign tumors in our study. The highest survival rates in this study, as expected, belonged to pilocytic astrocytoma and optic glioma, similar to other studies.[1,3,8,18] The 5-year event-free and overall survival rates according to histopathological subtypes were statistically significant in that they differed from each other ($p< 0.05$). The histopathologic subtype with a remarkably poor prognosis was diffuse intrinsic pontine gliomas, followed by high-grade glial tumors and AT/RTs.

In this study, the survival rates of patients with standard or high-risk medulloblastoma, unlike the literature, didn't have a statistically significant effect on the survival rates. When we look at the literature, while there is a decrease in the survival rates of patients in the high-risk classification[17], the reason why this situation was not observed in our study may be due to our insufficient number of patients.

The limitations of our study are that it is retrospective, the cases are heterogeneous, and the number of cases is small. We hope this study will provide a basis for future prospective studies.

In presenting study, a comprehensive evaluation was made of patients with CNS tumors, examining not only their demographic characteristics and presenting symptoms, but also the effects of these parameters on survival and the late side effects of treatment.

As conclusion, it was determined that high-dose craniospinal RT was an important factor in the risk of short stature. On basis of these observed side effects, prospective studies are needed on keeping the RT doses low without affecting overall survival rates. Also, it was concluded that the most important factor affecting reduced survival rate was metastasis and histopathological subtype. In addition, physicians who work in pediatric health and diseases should keep in mind that CNS tumors may present with a wide variety of symptoms and clinical findings.

REFERENCES

1. Osrom QT, de Blank PM, Kruchko C, et al. Alex's Lemonade Stand Foundation Infant and childhood primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro Oncol 16 Suppl 10:x1–x36, 2015.
2. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro Oncol 17(suppl 4): iv1-62, 2015.
3. Stocco C, Pilotto C, Passone E, et al. Presentation and symptom interval in children with central nervous system tumors. A single-center experience. Child's Nerv Syst. 14;33(12):2109–16, 2017 Dec.
4. Pogorzala M, Styczynski J, Wysocki M. Survival and prognostic factors in children with brain tumors: long-term follow-up single center study in Poland. Anticancer Res. 34: 323-326, 2014.
5. Hoffman KE, Yock TI. Radiation therapy for pediatric central nervous system tumors. J Child Neurol. 24: 1387-1396 2009.
6. Pinho RS, Andreoni S, Silva NS, et al. Pediatric central nervous system tumors. J Pediatr Hematol Oncol 33: 605-609, 2011.
7. Azizi AA, Heßler K, Leiss U, et al. From symptom to diagnosis—The prediagnostic symptomatic interval of pediatric central nervous system tumors in Austria. Pediatr Neurol 76: 27-36, 2017.
8. Rivas-Vilela S, Rubió-Casadevall J, Fàbrega-Ribas A, Jet al. Incidence and survival of central nervous system tumors in childhood and adolescence in Girona (Spain) 1990–2013: national and international comparisons. Clin Transl Oncol 21: 1177-1185, 2019.
9. Santos MM, Faria CC, Miguéns J. Pediatric central nervous system tumors: review of a single Portuguese institution. Child's Nerv Syst 32: 1227-1236, 2016.
10. Rosemberg S, Fujiwara D. Epidemiology of pediatric tumors of the nervous system according to the WHO 2000 classification: a report of 1,195 cases from a single institution. Child's Nerv Syst 21: 940–944, 2005.
11. Asirvatham JR, Deepti AN, Chyne R, et al. Pediatric tumors of the central nervous system: a retrospective study of 1,043 cases from a tertiary care center in South India. Child's Nerv Syst. 27(8):1257–63, 2011 Aug 23.
12. Yagci-kupeli B, Okten AI, Gezercan Y, et al. Cocukluk cagi santral sinir sistemi tümörleri: 60 olgunun retrospektif analizi. Cukurova Med J 43: 931-935, 2018.
13. Derek R. Hanson MPA. Lanzkowsky's Manual Of Pediatric Hematology And Oncology. 6th ed. Fish J, Lipton J LP, editor. Cambridge: Elsevier; 2016: 453–472.
14. Packer RJ, Gurney JG, Punyko JA, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood cancer survivor study. J Clin Oncol 21: 3255-3261, 2003.
15. Livesey E, Hindmarsh P, Brook C, et al. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 61: 622-625, 1990.
16. Koob M, Girard N, Cerebral tumors: Specific features in children, Diagn Interv Imaging 95: 965-983, 2014.
17. Millard NE, De Braganca KC. Medulloblastoma. J Child Neurol 2016. Erratum in: Corrigendum J Child Neurol 2016, Sep 15.
18. Karalexi MA, Papathoma P, Thomopoulos TP, et al. Childhood central nervous system tumour mortality and survival in Southern and Eastern Europe (1983–2014): Gaps persist across 14 cancer registries. Eur J Cancer 51: 2665-2677, 2015.

Correspondence:
Dr. Asli GENC
Saglik Bilimleri Universitesi
Ankara Sehir Hastanesi
Pediatri Bolumu
Bilkent
ANKARA / TURKIYE

Tel: (+90-535) 207 25 15
e-mail: asligenc92@gmail.com

ORCIDs:

Asli Genc	0000-0002-3847-1364
Arzu Yazal Erdem	0000-0003-1043-8471
Suna Emir	0000-0002-0702-7869
Derya Ozyoruk	0000-0002-9615-6522