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Surgical Management and Postoperative Outcome in patients with Brain Metastases: Our Surgical Experience

Beyin Metastazı Olan Hastalarda Cerrahi Tedavi ve Postoperatif Sonuç: Cerrahi Deneyimimiz

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ABSTRACT

Aims: Metastatic brain tumors are the most commonly seen intracranial lesion in adults and an important cause of morbidity and mortality in patients with cancer. This study aimed to evaluate the postoperative mortality, morbidity, and survival rates of patients who underwent surgery in our clinic for metastatic brain tumors
Method: Clinical data of 131 patients, including age, sex, symptoms, localization, primer site, surgical methods, resection, complications and recurrence were collected.
Results: Fifty patients (38.1%) were female, and 81 (61.8%) patients were male. The average age of the patients was 54,9. The most common reason for hospital admission was headache (68.7%). Lesions were detected in the cerebral hemisphere in 108 (82.4%) patients and the posterior fossa in 23 (17.5%) patients, and 16 (12.2%) patients had multiple lesions. All patients (n=131) underwent surgery with neuronavigation. Total resection was performed in 25 (19%) patients, gross total resection in 83 (63.3%), subtotal resection in 18 (13.7%), and biopsy in 5 (3.8%). The most commonly seen tumor originated from the lungs (n=63, 48%), according to the histopathological examination. The mean overall survival was 5.3 (range, 1–36) months during the follow-up period. Twelve (9.1%) patients had recurrence and underwent surgery again.
Conclusion: Multidisciplinary treatment methods are used in the treatment of metastatic brain tumors. Effective surgical intervention to eliminate peritumoral edema and increased intracranial pressure improves postoperative survival rates. In addition, post-surgical whole-brain radiotherapy reduces recurrence and improves survival.

Keywords: Brain, metastasis, surgery, prognosis

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ÖZ

Amaç: Metastatik beyin tümörleri erişkinlerde en sık görülen intrakraniyal lezyondur ve kanserli hastalarda önemli bir morbidite ve mortalite nedenidir. Bu çalışmada, kliniğimizde metastatik beyin tümörü nedeniyle ameliyat edilen hastaların postoperatif mortalite, morbidite ve sağkalım oranlarının değerlendirilmesi amaçlandı.
Yöntem: 131 hastanın yaş, cinsiyet, semptomlar, lokalizasyon, primer bölge, cerrahi yöntemler, rezeksiyon, komplikasyonlar ve nüks gibi klinik verileri toplandı.
Bulgular: Hastaların 50'si (%38.1) kadın, 81'i (%61.8) ise erkekti. Hastaların yaş ortalaması 54,9 idi. En sık hastaneye başvuru nedeni baş ağrısıydı (%68.7). 108 (%82.4) hastada serebral hemisferde, 23 (%17.5) hastada posterior fossada ve 16 (%12.2) hastada multisentrik bölgede lezyon saptandı. Tüm hastalara (n=131) nöronavigasyon ile cerrahi uygulandı. Hastaların 25'ine (%19) total rezeksiyon, 83'üne (%63,3) gros total rezeksiyon, 18'ine (%13,7) subtotal rezeksiyon ve 5'ine (%3,8) biyopsi yapıldı. Histopatolojik incelemeye göre en sık görülen tümör akciğer kaynaklı (n=63, %48) idi. Ortalama genel sağkalım, takip süresi boyunca 5.3 (aralık, 1-36) aydı. On iki (%9.1) hastada nüks görüldü ve tekrar ameliyat edildi.
Sonuç: Metastatik beyin tümörlerinin tedavisinde multidisipliner tedavi yöntemleri kullanılmaktadır. Peritümöral ödem ve artan kafa içi basıncını ortadan kaldırmak için etkili cerrahi müdahale, postoperatif sağkalım oranlarını arttırır. Ek olarak, cerrahi sonrası tüm beyin radyoterapisi, nüksü azaltır ve sağkalımı artırır.

Anahtar Kelimeler: Beyin, metastaz, cerrahi, prognoz

INTRODUCTION

Brain metastases are the most common intracranial tumors in adults [11,19,29]. Brain metastasis is the most important cause of morbidity and mortality in patients with cancer [29].

The incidence of brain metastases ranges from 8.3 to 14.3 per 100,000 [29]. These tumors are estimated to occur 10 times more frequently than primary malignant brain tumors [20,29]. However, these incidence rates vary according to the primary tumor, tumor stage, and even the subtype of cancer, among other factors. The most commonly detected brain metastasis originates from the lung upon diagnosis [10]. The incidence of brain metastasis is 15%–40% in adults and 6%–10% in children among all patients with cancer [4]. Brain involvement is a poor prognostic criterion because of its late occurrence in the course of metastatic cancer [2]. In recent years, the number of confirmed brain metastases has increased because of the increased survival of patients with cancer and the widespread use of imaging modalities [3,24]. Brain metastases are mostly seen in the fifth and seventh decades of life and are more common in men [1].

The most common source of brain metastasis is the lung (40%–50%), followed by the breast (15%–25%), malignant melanoma (5%–20%), kidney (5%–10%), and colon (4%–6%) [11,14,20,28,29,34]. Sarcomas metastasizing to the central nervous system are very rare [17]. The primary cancer site could not be identified in 5%–10% of the patients with brain metastases [29,35].

Approximately 80% of the metastases occur in the cerebral hemisphere, with less involvement of the cerebellum and brainstem (10%–15% and 2%–3%, respectively) [30]. Unlike the cerebrum, primary parenchymal metastases to the spinal cord are rare [30].

Symptoms caused by brain metastases may be the only sign of a certain cancer type such as lung cancer, breast cancer, or melanoma [8]. Most brain metastases are diagnosed when they become symptomatic. Patients with brain metastases often present with neurological symptoms such as headache, cognitive impairment, seizure, and focal deficit, all of which accelerate the decline in the quality of life and survival [29]. Brain metastasis usually presents with symptoms localized to that particular area of the brain [22,33]. Seizures

may be seen in 10%–20% of patients with brain metastasis [22]. Seizures are more common in supratentorial and cortical lesions than in infratentorial masses [22].

Frequently used diagnostic tests aim to detect an underlying lesion. Computed tomography (CT) and magnetic resonance imaging (MRI) remain the most widely used imaging techniques. Positron emission tomography (PET) and single-photon emission computed tomography are used to evaluate the primary tumor site and to identify other possible metastases [1,25]. Two MRI sequences, namely, diffusion-weighted MRI and diffusion-tensor imaging, can reveal the microstructure of the brain and its deterioration caused by tumor growth and edema [15]. Histopathological examination is an important diagnostic tool that detects the morphology of metastatic malignancy and possible tumor origin [9].

Patients with brain metastases generally have a poor prognosis and survival of approximately 4 weeks without treatment [37]. Depending on the primary tumor, the mean survival ranges from 2 to 27 months [37].

Radiation therapy, surgery, and chemotherapy are used in the treatment. Radiation therapy includes whole-brain radiotherapy (WBRT), stereotactic radiosurgery, or a combination of these modalities. WBRT has been accepted as the standard treatment of brain metastases [15].

This study aimed to retrospectively evaluate the clinicopathological features and postoperative survival rates of patients who underwent surgery for brain metastases in our clinic.

MATERIALS and METHODS

Patient population

This study was approved by the ethics committee (2020/304). In this study, we retrospectively analyzed 131 patients who were admitted with an intracranial mass and histopathologically confirmed metastasis between September 2016 and November 2020. Of these patients, 50 (38.1%) were female and 81 (61.8%) were male. The mean age was 54.9 (range, 2–82) years.

Clinical and radiological evaluation

The most common reason for admission was headache (68.7%, n=90). In addition, 30 (22.99%) patients were admitted with dizziness, 19 (14.5%) with seizures, and 3 (2.3%) with vision loss. CT and MRI were performed in all patients.

Radiological examination revealed that 108 (82.4%) patients had a supratentorial tumor, while 23 (17.5%) patients had a tumor at the posterior fossa. In addition, 16 (12.2%) patients had more than one lesion in the intracranial region. To reduce intracranial edema and high intracranial pressure caused by the lesion, dexamethasone (16 mg/day) was started in all patients preoperatively.

Tumor resection was classified as total, gross total, subtotal, and biopsy according to intraoperative surgical observation, and MRI was performed in the early postoperative period. Total resection included complete excision of the tumor and capsule, gross total resection meant excision of nearly all tumor tissues and capsule remnants are left, and subtotal resection was defined as cases where the tumor capsule and <10% of the tumor remained.

Surgical strategy

Neuronavigation (featured MRI) was used in all cases in addition to routine surgical preparations. After induction of anesthesia, the patient's head was positioned in accordance with the localization of the lesion by wearing a head clamp.

After the neuronavigation installation, the skin and subcutaneous tissue were passed through an incision made in accordance with the lesion localization in all cases. Craniotomy and craniectomy were performed in cases with lesions located in the cerebral hemisphere and posterior fossa, respectively. Especially in cases with increased intracranial pressure and tight dura mater, mannitol (1 g/kg) was infused rapidly before dural opening [26]. Tumor resection was performed by endoscopic methods (n=20, 15.2%) by placing a thoracoport in deeply located lesions. In other cases, tumor resection was performed by microscopic methods (n=111, 84.7%). After tumor resection, bleeding control was performed in all cases, and the dura was sutured. A bone flap was placed. The skin was properly closed.

RESULTS

Neuronavigation was used in all cases in addition to routine surgical preparations. Especially, in cases with increased intracranial pressure and tight dura mater, mannitol (1 g/kg) was rapidly infused before dural opening [26]. Antiedema treatment (dexamethasone) was continued in all cases in the early postoperative period. In the postoperative period, pulmonary embolism developed in 2 (1.5%) patients, wound infection in 7 (5.3%), and cerebrospinal fluid fistula in 6 (4.5%). In the postoperative period, 3 (2.3%) patients were lost to follow-up because of various complications during the hospitalization period.

Total resection was performed in 25 (19%) patients, gross total resection in 83 (63.3%), subtotal resection in 18 (13.7%), and biopsy in 5 (3.8%) (Figs. 1–3). The patients were discharged after the improvement of the existing preoperative complaints and the wound had healed. The result of histopathological examination revealed that the most common tumor origin was the lung (n=63, 48%) (Table 1). PET was performed after histopathological diagnosis to detect other possible spread of the primary tumor. Subsequently, chemotherapy and radiotherapy treatments were planned.

Table 1. Clinicopathological and postoperative characteristics

Caracteristics	Number	%
Sex		
Male	81	61.8
Female	50	38.1
Symptoms		
Headache	90	68.7
Dizziness	30	22.9
Seizure	19	14.5
Visual lost	3	2.3
Localization		
Cerebral	108	82.4
Posterior fossa	23	17.5
Primer site		
Lung	63	48
Breast	23	17.5
Lenfoma	12	9.1
Gastrointestinal system	9	6.8
Renal	4	3.05
Melanoma	4	3.05
Others	16	12.2
Surgical methods		
Microscopic	111	84.7
Endoscopic	20	15.2
Resection		
Total	25	19
Gros total	83	63.3
Subtotal	18	13.7
Biopsy	5	3.8
Postoperative Complication		
Pulmonary embolism	2	1.5
Wound infection	7	5.3
CSF fistula	6	4.5
Exitus	3	2.3
Relaps	12	9.1

Eight (6.1%) patients died within the first 3 months because of intracranial and primary tumor complications, and 25 (19%) patients were lost to follow-up. The mean overall survival was 5.3 (range, 1–36) months during the follow-up period, and 12 (9.1%) patients had a recurrence and undergo surgery again.

REPRESENTATIVE CASES

Case #1:

A 70-year-old male patient was admitted to our clinic with balance disorder. Neurological examination is normal. He has a history of surgery for gastric adenocarcinoma. On MRI, a 3.5x4 cm mass lesion was detected in the right cerebellar hemisphere. Gross total resection was obtained in the patient who was operated microscopically (Figure 1). Pathological examination was compatible with gastric adenocarcinoma. The patient was discharged on the 5th postoperative day and was referred to radiotherapy. The patient died in the 11th postoperative month due to complications arising from the gastrointestinal system.

Case #2:

A 69-year-old male patient applied to our clinic with complaints of headache and dizziness. In her neurological examination, her right upper and lower extremities were 2/5 paresis. He has a history of right nephrectomy for renal cell carcinoma. Cranial MRI revealed a 3x4 cm mass in the left parietal region. The patient was operated using endoscopic methods and thoracoport. The tumor was grossly excised (Figure 2). Pathological examination was consistent with renal cell carcinoma metastasis. The patient was discharged on the 5th postoperative day and received whole brain radiotherapy. He died at the postoperative 14th month due to non-intracranial complications.

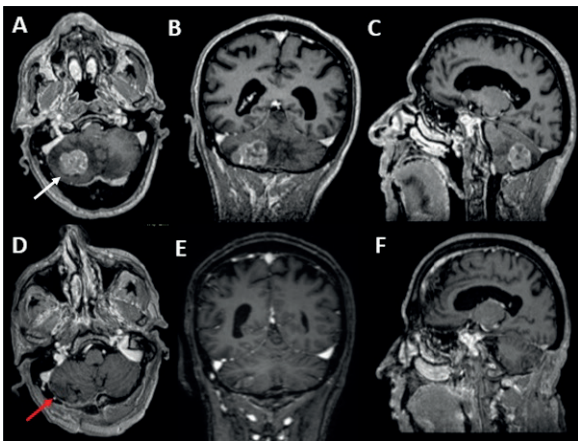

Figure 1. A-C: Preoperative T1-contrast Cranial MRI, D-F: Postoperative sixth month T1-contrast Cranial MRI, White Arrow: Tumor Tıssue, Red Arrow: Tumor cavity

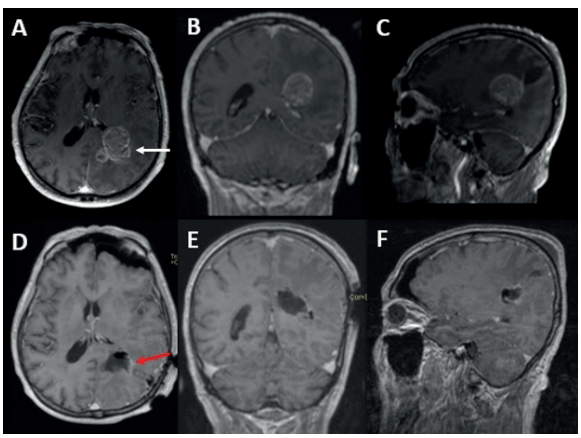

Figure 2. A-C: Preoperative T1-contrast Cranial MRI, D-F: Postoperative 12th month T1-contrast Cranial MRI, White Arrow: Tumor Tıssue, Red Arrow: Tumor cavity

Case #3:

A 61-year-old male patient applied to our clinic with the complaint of dizziness. In her neurological examination, tandem gate was unsuccessful, but other examination findings were normal. There was no significant pathology in his history. Cranial MRI revealed a 3x2.5 cm mass in the left cerebellar hemisphere. The patient was operated with microscopic methods. The tumor was grossly excised (Figure 3). Pathological examination was compatible with high-grade B-cell lymphoma. The patient was discharged on the 4th postoperative day and

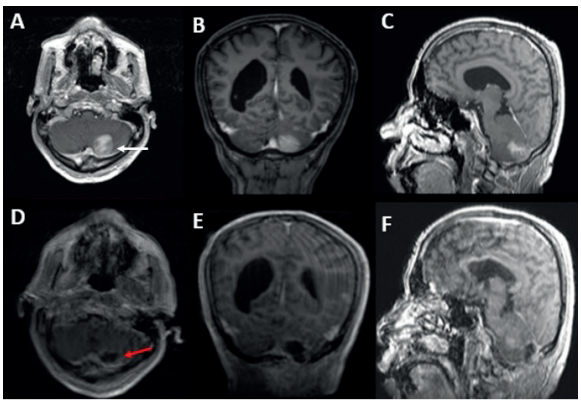

Figure 3. A-C: Preoperative T1-contrast Cranial MRI, D-F: Postoperative 3rd month T1-contrast Cranial MRI, White Arrow: Tumor Tıssue, Red Arrow: Tumor cavity

received whole brain radiotherapy. He died 6 months postoperatively due to complications related to multiple intracranial involvements.

DISCUSSION

Metastasis is the most common type of intracranial neoplasm [39]. Its incidence is 10 times higher than that of primary brain tumors and occurs in approximately 25% of all patients with cancer [24]. This number is expected to increase as more patients develop cancers, imaging technology becomes more common, and there was no progress in finding methods to prevent cancers from metastasizing to the brain [11].

Brain metastases are most commonly detected between ages 50 and 70 years [40]. In this study, the mean patient age was 54.9 years.

The lung is the most common site of origin among all brain metastases. Generally, this is followed by the breast, gastrointestinal tract, lymphomas, renal tumors, and other tumors [5,31,35]. Brain metastases are rare in sarcomas and are more common in undifferentiated sarcomas with previous metastases. The incidence of sarcoma metastasizing to the brain is <1% [14]. In our study, metastases originating from lung cancer (n=63, 48%) were found most frequently. The breast (n=23, 17.5%), lymphoma (n=12, 9.1%), gastrointestinal tract (n=9, 6.8%), kidney (n=4, 3.05%), malignant melanoma (n=3.05%), and other tumors (n=16, 12.2%). The majority of brain metastases (77.7%–85%) are located in the cerebral hemispheres, followed by the cerebellum (15%–20%) and brainstem (2%–5%) (32,38). In this study, similar to the literature, 82.4% (n=108) of the cases were localized in the cerebral hemisphere and 17.5% (n=23) were localized in the posterior fossa.

The most common complaint was headache (49%). Mental changes (32%), focal weakness (30%), and seizures (18%) were other symptoms [32,38]. The most common reason for admission was headache (n=90, 68.7%). Other complaints were dizziness (n=30, 22.9%), seizure (n=19, 14.5%), and vision loss (n=3, 2.3%).

Surgery, Whole Brain RT (WBRT), stereotactic radiosurgery, and chemotherapy are treatment options for brain metastasis [12,36]. Many factors such as age, performance status, number of lesions, and treatment type affect the treatment modality. Aggressive treatment helps improve overall survival. Modi *et al*. reported that resection of metastatic lesions prolongs overall survival [27].

Surgery is an effective treatment modality in increasing survival. Surgical treatment is recommended, especially in brain metastases with large-scale, perilesional edema, neurologic deficits, and unknown histopathological diagnosis [28]. Surgical treatment not only makes adjuvant therapy more effective but also provides benefits such as the alleviation of the mass effect, symptomatic improvement, and histopathological evaluation [21]. However, it is more effective in single lesions [7]. Solitary metastatic lesions have sharp margins and are amenable to surgical resection [23].

Surgery for deep-seated lesions is challenging and postoperative morbidity risk is higher. Such lesions are usually treated to provide palliation [11,21]. Minimally invasive approaches are used to reduce postoperative mortality and morbidity, especially in the surgical intervention of deeply located lesions, but studies on this subject are limited [13,23]. Hong et al. demonstrated the use of minimally invasive methods in 20 patients with deeply located metastatic lesions [23]. Many studies use tubular retractors for minimally invasive approach [6,21,23]. In this study, we also performed tumor resection with endoscopic methods by placing a thoracoport in 20 (15.2%) patients, especially in deeply located cases.

Bakhsheshian et al. reported gross total resection in 80% of 25 patients with deeply located metastatic brain tumors [6]. In the present study, total resection was performed in 25 cases (19%), gross total resection in 83 (63.3%) cases, subtotal resection in 18 (13.7%) cases, and biopsy in 5 (3.8%) cases.

WBRT is a frequently preferred treatment for brain metastases. The role of chemotherapy in the treatment of brain metastases is controversial because of the blood–brain barrier. Most authors argue that most chemotherapeutic drugs are unable to cross the blood–brain barrier; thus, the efficacy of chemotherapy in brain metastatic disease is low or nonexistent [18]. In cases with more than one metastasis, WBRT provided less recurrence in the postoperative period and longer survival than the group that did not receive radiotherapy [18]. In the present study, all (n=98, 74.8%) patients who were followed up in the postoperative period received WBRT.

Five (10%) new cases of neurologic deficits, one case of stroke (2%), and one case (2%) of exitus were reported after resection in a study that included deeply located metastatic brain tumors [21,23]. In another study, new-onset motor weakness and deep-vein thrombosis were reported in one (4%) patient [6]. In this study, pulmonary embolism occurred in 2 (1.5%) patients, wound infection in 7 (5.3%), CSF fistula in 6 (4.5%), and exitus in 3 (2.3%).

Patients with a single metastatic lesion had significantly higher survival rates than patients with multiple metastases [16]. In this study, multiple brain metastases were detected in the intracranial region in 16 (12.2%) patients, and 87.5% (n=7) of the patients who died in the first 3 months after surgery were those with more than one metastasis.

Ekici et al. reported a mean survival of 6.7 months [16]. In the present study, the mean survival during the follow-up period was 5.3 months.

CONCLUSION

Brain metastases are an important cause of morbidity and mortality. The incidence, survival rates, and treatment modalities of brain metastases vary greatly according to the histopathological diagnosis of the primary tumor. Surgical intervention reduces intracranial pressure and eliminates tumor-related edema. Therefore, postoperative survival rates increase. In addition to surgical treatment, adjuvant WBRT reduces recurrence and increases survival in these cases. However, more clinical studies are needed to evaluate the efficacy of single or combined treatments in metastatic brain tumors.

Ethical Approval: This study was approved by the Scientific Research Ethics Committee of the Turkish Republic Health Sciences University (No: 2020-304 / 30.06.2020).
Conflict of interest: There is no conflict of interest in our study.

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REFERENCES

1. Akhavan A, Binesh F, Heidari S. Survival of brain metastatic patients in Yazd, Iran, Asian Pacific J. Cancer Prev. 15 (2014) 3571–3574.
2. Al-Shamy G, Sawaya R. Management of brain metastases: The indispensable role of surgery, J. Neurooncol. 92 (2009) 275–282.
3. American Cancer Society. Cancer Statistics Center. Atlanta, GA: American Cancer Society; 2018.
4. Arnold S.M, Patchell R.A. Diagnosis and management of brain metastases, Hematol. Oncol. Clin. North Am. 15 (2001) 1085–1108.
5. Bachmann S, Schmidt A, Staebler T. et al. CNS metastases in breast cancer patients: prognostic implications of tumor subtype, Med. Oncol. 32 (2015) 1–6.
6. Bakhsheshian J. Strickland B.A, Jackson C. et al. Multicenter investigation of channel-based subcortical trans-sulcal exoscopic resection of metastatic brain tumors: A retrospective case series, Oper. Neurosurg. 16 (2019) 159–166.
7. Baykara M, Kurt G, Buyukberber S. et al. Management of brain metastases from non-small cell lung cancer, J. Cancer Res. Ther. 10 (2014) 915–921.
8. Biswas G, Bhagwat R, Khurana R, Menon H, Prasad N, Parikh P.M. Brain metastasis - Evidence based management, J. Cancer Res. Ther. 2 (2006) 5–13.
9. Brastianos P.K, Carter S.L, Santagata S. et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets, Cancer Discov. 5 (2015) 1164–1177.
10. Cagney D.N, Martin A.M, Catalano P.J. et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: A population-based study, Neuro. Oncol. 19 (2017) 1511–1521.
11. D'Andrea G, Palombi L, Minniti G, Pesce A, Marchetti P. Brain Metastases: Surgical Treatment and Overall Survival, World Neurosurg. 97 (2017) 169–177.
12. Das K.K, Jaiswal S. Brain metastasis and their management: A current perspective, Neurol. India. 66 (2018) 739–742.
13. Day J.D. Transsulcal Parafascicular Surgery Using Brain Path® for Subcortical Lesions, in: Clin. Neurosurg., Oxford University Press, 2017: pp. 151–156.
14. Di Giacomo A.M, Valente M, Cerase A. et al. Immunotherapy of brain metastases: Breaking a "dogma," J. Exp. Clin. Cancer Res. 38 (2019).
15. Duan L, Zeng R, Yang K.H. et al. Whole brain radiotherapy combined with stereotactic radiotherapy versus stereotactic radiotherapy alone for brain metastases: A meta-analysis, Asian Pacific J. Cancer Prev. 15 (2014) 911–915.
16. Ekici K, Temelli O, Dikilitas M, Dursun I.H, Kaplan N.B, Kekilli E. Survival and prognostic factors in patients with brain metastasis: Single center experience, J. B.U.ON. 21 (2016) 958–963.
17. Espat N.J, Bilsky M, Lewis J.J, Leung D, Brennan M.F. Soft tissue sarcoma brain metastases: Prevalence in a cohort of 3829 patients, Cancer. 94 (2002) 2706–2711.
18. Fabi, A. Felici, G. Metro, A. et al. Brain metastases from solid tumors: Disease outcome according to type of treatment and therapeutic resources of the treating center, J. Exp. Clin. Cancer Res. 30 (2011).
19. Fecci P.E, Champion C.D, Hoj J. et al. The evolving modern management of brain metastasis, Clin. Cancer Res. 25 (2019) 6570–6580.
20. Fox B.D, Cheung V.J, Patel A.J, Suki D, Rao G. Epidemiology of metastatic brain tumors, Neurosurg. Clin. N. Am. 22 (2011) 1–6.
21. Gassie K, Alvarado-Estrada K, Bechtle P, Chaichana K.L. Surgical Management of Deep-Seated Metastatic Brain Tumors Using Minimally Invasive Approaches, J. Neurol. Surgery, Part A Cent. Eur. Neurosurg. 80 (2019) 198–204.
22. Glantz MJ, Batten J. Seizures and anti-epileptic drugs in Neuro-Oncology.In:Schiff D, Kesari S, Wen PY, eds. Current Clinical Oncology:Cancer Neurology in Clinical Practice.vol 3.Totowa NJ:Humana Press;2008:33-46 .
23. Hong C.S, Prevedello D.M, Elder J.B. Comparison of endoscope-versus microscope-assisted resection of deep-seated intracranial lesions using a minimally invasive port retractor system, J. Neurosurg. 124 (2016) 799–810.
24. Jung E.W, Rakowski J.T, Delly F. et al. Gamma Knife radiosurgery in the management of brainstem metastases, Clin. Neurol. Neurosurg. 115 (2013) 2023–2028.
25. Madhusoodanan S, Ting M.B, Wilson S.Y. The psychopharmacology of primary and metastatic brain tumors and paraneoplastic syndromes, 1st ed., Elsevier B.V., 2019.
26. Mark S. Greenberg, Handbook of Neurosurgery, Ninth Edition, New York, 2020 .
27. Modi A, Vohra H.A, Weeden D.F. Does surgery for primary non-small cell lung cancer and cerebral metastasis have any impact on survival? Interact. Cardiovasc. Thorac. Surg. 8 (2009) 467–473.
28. Nahed V, Alvarez-Breckenridge C, Brastianos P.K. et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Surgery in the Management of Adults with Metastatic Brain Tumors, Clin. Neurosurg. 84 (2019) E152–E155.

29. Nayak L, Lee E.Q, Wen P.Y. Epidemiology of brain metastases, Curr. Oncol. Rep. 14 (2012) 48–54.
30. Patchell R.A. Brain metastases, Neurol. Clin. 9 (1991) 817–824.
31. Posner J.B. Brain metastases: 1995. A brief review, in: J. Neurooncol., J Neurooncol, 1996: pp. 287–293.
32. Rahmathulla G, Toms S.A, Weil R.J. The molecular biology of brain metastasis, J. Oncol. 2012 (2012).
33. Rostami R, Mittal S, Rostami P, Tavassoli F, Jabbari B. Brain metastasis in breast cancer: a comprehensive literature review, J. Neurooncol. 127 (2016) 407–414.
34. Ryken T.C, Kuo J.S, Prabhu R.S, Sherman J.H, Kalkanis S.N, Olson J.J. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Steroids in the Treatment of Adults with Metastatic Brain Tumors, Clin. Neurosurg. 84 (2019) E189–E191.
35. Saha A, Ghosh S.K, Roy C, Choudhury K.B, Chakrabarty B, Sarkar R. Demographic and clinical profile of patients with brain metastases: A retrospective study, Asian J. Neurosurg. 8 (2013) 157.
36. Singh S, Amirtham U, Premalata C.S, Lakshmaiah K.C, Viswanath L, Kumar R.V. Spectrum of metastatic neoplasms of the brain: A clinicopathological study in a tertiary care cancer centre, Neurol. India. 66 (2018) 733–738.
37. Sundström J.T, Minn H, Lertola K.K, Nordman E. Prognosis of patients treated for intracranial metastases with whole-brain irradiation, Ann. Med. 30 (1998) 296–299.
38. Wong J.J, Hird A, Kirou-Mauro A, Napolskikh J, Chow E. Quality of life in brain metastases radiation trials: A literature review. Curr Oncol (2008) 15:25-45 .
39. Wu J.D, Weingart G.L, Gallia M. et al. Risk Factors for Preoperative Seizures and Loss of Seizure Control in Patients Undergoing Surgery for Metastatic Brain Tumors, World Neurosurg. 104 (2017) 120–128.
40. Yilmazer G, Nart M, Izmirli M, Yavuz A, Can A. Whole brain radiotherapy results of patients with brain metastases and investigation of their prognostic factors. Türk Onkoloji Dergisi. (2014) 29:39-45.