Clinics in Surgery

Research Article
Published: 15 Mar, 2022

Surgical Treatment and Prognosis of Brain Metastases

*Mingtao Feng[#], Changshuai Zhou[#], Huanhaun Cui, Yang Gao and Yiqun Cao**

Department of Neurosurgery, Fudan University Shanghai Cancer Center, China

[#]These authors contributed equally to the work

Abstract

Objective: The traditional view is that patients with Brain Metastases (BMs) are in the end stage and can only receive palliative treatment. However, modern treatment has greatly changed their survival prognosis. The purpose of our study is to determine the curative effect of surgical treatment in patients with different primary tumor brain metastases, and to study the factors influencing the prognosis.

Methods: Continuous retrospective analysis of clinical data of patients with BMs undergoing surgery from December 2015 to January 2019 in Fudan University Shanghai Cancer Center (FUSCC). Analyzing the clinical characteristics, treatment and survival of brain metastases.

Results: A total of 103 patients were included. None worsened after surgery and, two weeks after operation, 18 (17.5%) patients demonstrated an unchanged postoperative neurological examination while 85 patients (82.5%) showed an improvement. Three months after operation, 91 cases (88.3%) were stable, 4 cases progressed (3.9%) and 8 cases died (7.8%). The median survival time was 20 months, nearly two times longer than previously reported. 28 cases (27.2%) had a survival fewer of six months, 62 (60.2%) of 1 year, 36 (35.0%) of 2 years, 17 (16.5%) of 3 years and the longest survival time was 47 months in 1 case, and it is still under follow-up. Univariate analysis identified age over 60 (P=0.045), metastatic tumor size ≥ 3 cm (P=0.002), and high level of tumor markers (P=0.029) as positive prognostic factors. Multivariate analysis identified metastatic tumor size ≥ 3 cm (P=0.009) as an independent negative prognostic factor.

Conclusion: Surgery is a safe and effective option to manage brain metastases which can alleviate clinical symptoms, prolong survival time and improve patients' prognosis. It is not a too aggressive strategy. We suggest surgery as an important part of the comprehensive treatment of BMs, even as the preferred strategy in some cases. Metastasis tumor size ≥ 3 cm (P=0.029) was an independent negative prognostic factor for patients with brain metastases.

Keywords: Brain metastases; Surgical treatment; Prognosis analysis

OPEN ACCESS

Correspondence:
Yiqun Cao, Department of Neurosurgery, Fudan University Shanghai Cancer Center, Shanghai 200433, China,
E-mail: yiqun_fduscc@163.com

Received Date: *27 Jan 2022*
Accepted Date: *07 Mar 2022*
Published Date: *15 Mar 2022*

Citation:
Feng M, Zhou C, Cui H, Gao Y, Cao Y. Surgical Treatment and Prognosis of Brain Metastases. Clin Surg. 2022; 7: 3449.

Introduction

Brain metastases are the most common malignant tumors of the nervous system [1]. About 9% to 26% of patients with malignant tumors develop brain metastases, and brain metastases account for 30% to 40% of intracranial tumors [2,3]. Among the brain metastases, the most common primary lesions are lung, breast, melanoma, and renal tumors, and some brain metastases have unknown sources [4]. Untreated brain metastases tend to progress rapidly, with neurological symptoms occurring in a short period of time, and the median survival time is only 4 to 6 weeks [3]. Traditionally, the prognosis of brain metastases has been considered very poor because they are in advanced stage and can only be treated palliatively. However, the modern treatment of brain metastases has greatly changed their expected prognosis. Current treatments for brain metastases include surgery, radiation therapy, targeted therapy, chemotherapy, and comprehensive therapy. Surgery is still of great importance in treating brain metastases and an essential part of comprehensive treatment. Generally, patients with good condition, symptomatic, isolated and shallow brain metastases are the best surgical indications. Additionally, there are surgical indications for patients who need the pathological diagnosis and those who fail to receive radiotherapy. Recently, due to advances in surgical techniques, surgery can reach deeper lesions than in the past, and the incidence of perioperative complications has decreased. We believe that surgery is a safe and effective method for the treatment of brain metastases and should not be considered an aggressive treatment in such disease. We retrospectively analyzed the clinical data of patients with surgical treatment of BMs in our hospital, and analyzed the clinical outcomes and prognostic factors of surgical treatment for

BMs.

Patients and Methods

The clinical data of patients with BMs in the Department of Neurosurgery, Fudan University Shanghai Cancer Center from December 2015 to January 2019 were retrospectively analyzed.

Inclusion criteria: 1. Patients with single brain metastases who can tolerate surgery 2. Patients with multiple brain metastases with obvious space occupying effect (midline shift >1 cm) had prominent clinical symptoms and were life-threatening 3. Patients with multiple brain metastases had clear responsibility lesions, and the purpose of operation is to prevent the progression of symptoms and intracranial hypertension.

Exclusion criteria: 1. Age >80 years; 2. Patients with other underlying diseases could not tolerate surgery. 3. Incomplete clinical data including general information, imaging, treatment methods, postoperative pathology, follow-up information and lack of consent. A total of 103 cases were included, there were 59 males (57.3%) and 44 females (42.7%), aged 17 to 76 years, with an average age of (57 ± 10) years. Patients were analyzed with respect to age, gender, primary tumor, presence of neurologic symptoms, smoking history, tumor markers, timing of metastasis, preoperative radiotherapy, presence of extracranial metastases at the initial diagnosis, number, location and size of BMs. High level of tumor markers was defined as tumor markers above the upper limit of normal. Complete tumor resection was defined as the absence of significant residual tumor on postoperative MRI. Therefore, there are two main reasons for incomplete resection. One is multiple metastases, and the other is due to location and intraoperative considerations, such as functional areas and close relationship with vital vessels or nerves. The unresectable tumor was treated with radiotherapy after operation. Throughout the analysis, the patient's survival time was defined as the time from brain surgery to death or the end of FU. Most patients are admitted to hospital for surgical treatment as soon as possible after the diagnosis of brain metastases. The study was approved by the ethics committee and patients agreed to use their clinical data for research purposes.

Treatment

All patients underwent a craniotomy to remove the tumor. Conventional craniotomy was performed according to the imaging location. If subcortical tumors are difficult to locate, preoperative or intraoperative navigation or B-ultrasonography was used. After positioning, the cortex is cut in the sulcus along the contour of the tumor to minimize damage to the adjacent gyrus. Dissect and separate the tumor along the edematous zone with the microscope, and the tumor was excised as whole as possible to reduce the chance of intraoperative implantation. If the tumor is huge and complete resection is difficult, the central part of the tumor can be removed by volume reduction, and then the peripheral part of the tumor can be completely separated and removed. The tumor cavity should be carefully hemostatic and covered with hemostatic materials, and the skull should be closed routinely unless intracranial pressure was high.

Follow-up methods

All patients were evaluated by enhanced Magnetic Resonance Imaging (MRI) within 48 h after operation. The general conditions of patients were evaluated 2 weeks after the operation. Three months after surgery, the patients were followed up in the outpatient department for general condition and enhanced MRI. Tumor progression was defined as enhancement of progressive enlargement of the lesion or no change in tumor size, but persistent symptomatic edema.

Statistical analysis

Kaplan-Meier plots (univariate analysis) and Cox regression method (multivariate analysis) were used for statistical analysis. A p value of <0.05 was regarded as significant.

Results

BMs characteristics

Among 103 cases, 94 cases were supratentorial, 9 cases were infratentorial; 78 cases were single brain metastasis and 25 cases were multiple brain metastasis. The primary tumors were 59 cases of lung cancer, 21 cases of breast cancer, 6 cases of renal cancer, 6 cases of colorectal cancer, 5 cases of gastric cancer, 2 cases of liver cancer, 1 case of ovarian cancer, 1 case of cervical cancer, 1 case of melanoma and 1 case of bladder cancer.

Treatment outcomes

All 78 cases of single intracranial lesions were completely resected, 2 cases of multiple lesions were completely removed (divided into two operations), and 23 cases of multiple lesions only underwent responsible lesion resection.

Two weeks after operation, 18 (17.5%) patients demonstrated an

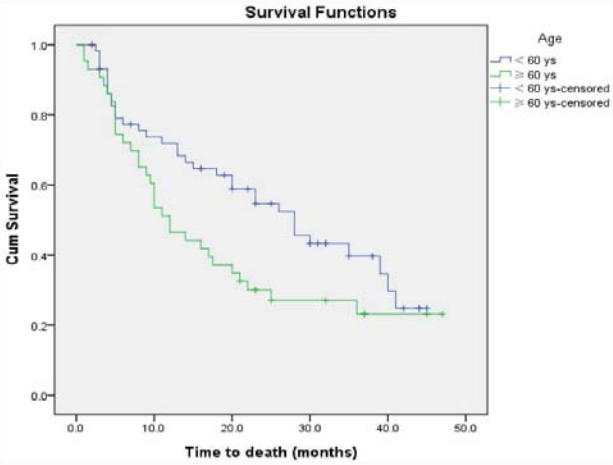

Figure 1: Kaplan–Meier plots for parameters significantly associated with overall survival: Age of patients.

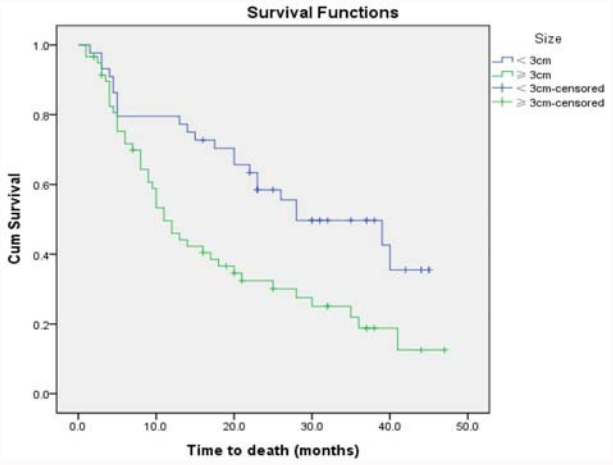

Figure 2: Kaplan–Meier plots for parameters significantly associated with overall survival: Size of BMs.

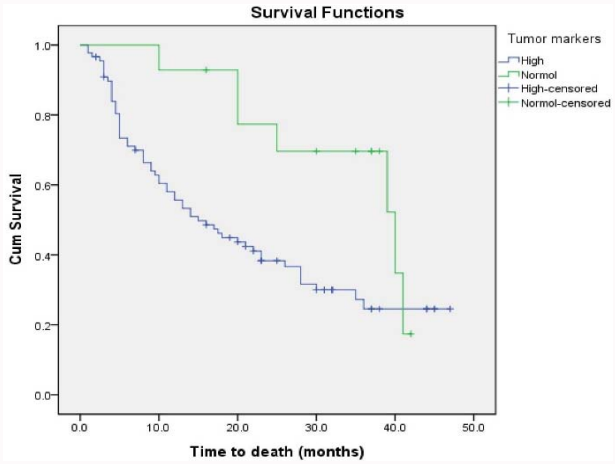

Figure 3: Kaplan–Meier plots for parameters significant associated with overall survival: Level of tumor markers.

unchanged postoperative neurological examination while 85 patients (82.5%) showed an improvement.

Follow up

Three months after operation, 91 cases (88.3%) were stable, 4 cases progressed (3.9%) and 8 cases died (7.8%). Among all cases, 90 cases (87.4%) had good prognosis (Modified Rankin Score, MRS 0-2) and 13 cases (12.6%) were relatively poor (MRS ≥ 3). Among 13 poor prognosis cases, 5 patients had one side of limb hemiplegia before operation, MRS score was 3, and the postoperative score remained unchanged; 3 cases were caused by postoperative tumor progression due to multiple intracranial space occupying lesions; 2 cases had hemiplegia of one limb after operation because of nerve function injury; the remaining 3 cases had poor prognosis due to the progression of metastases in other parts. The median survival time was 20 months, nearly two times longer than previously reported [1]. 28 cases (27.2%) had a survival fewer of six months, 62 (60.2%) of 1 year, 36 (35.0%) of 2 years, 17 (16.5%) of 3 years and the longest survival time was 47 months in 1 case, and it is still under follow-up.

Prognostic analysis

Univariate analysis: In 103 patients with brain metastases, the overall median survival time was 20.0 months (95% CI: 13.372-26.628) from the first day after surgery to the death or follow-up deadline. Kaplan–Meier estimation for clinical parameters showed that patients older than 60 years old (P=0.045) (Figure 1), metastatic tumor size ≥ 3 cm (P=0.002) (Figure 2), and high level of tumor markers (P=0.029) had poor prognosis (Figure 3 and Table 1).

Multivariate analysis: Multivariate Cox proportional hazards regression analysis showed that metastatic tumor size ≥ 3 cm (P=0.009) was an independent negative prognostic factor for patients with brain metastases (Table 2). The size of metastases ≥ 3 cm is a risk factor for death in patients with brain metastases.

Discussion

This study retrospectively analyzed the clinical data of 103 patients with brain metastases who underwent surgical treatment in our hospital. The results confirmed that surgical resection of the

Table 1: Kaplan–Meier estimators for clinical parameters.

Parameter	No. of patients (%)	Median survival (months (95% CI))	χ^2-value	p-value
Gender			0.102	0.794
male	59 (57.3)	20.0 (11.783,28.217)		
female	44 (42.7)	23.0 (9.393,36.607)		
Age			4.008	0.045
<60 ys	60 (58.3)	28.0 (19.193,36.817)		
≥60 ys	43 (41.7)	12.0 (7.879,16.121)		
Primary tumor			2.5	0.475
Lung cancer	55 (53.4)	17.5 (6.252,28.748)		
Breast cancer	19 (18.4)	20.0 (0.000,40.404)		
Digestive system tumor	24 (23.3)	17.0 (0.000,38.604)		
Type is not clear	5 (4.9)	39.0 (10.793,67.207)		
No. of brain metastases			0.005	0.946
<3	93 (90.3)	20.0 (12.754,27.246)		
≥3	10 (9.7)	21.0 (10.471,31.529)		
Size of brain metastases			9.327	0.002
<3cm	44 (42.7)	28.0 (12.433,43.567)		
≥3cm	59 (57.3)	11.0 (7.860,14.140)		
Location			0.340	0.560
Supratentorial	94 (91.3)	20.0 (13.114,26.886)		
Infratentorial	9 (8.7)	17.0 (0.000,46.218)		
Extracranial metastases			1.543	0.214
yes	40 (38.8)	16.0 (9.279,22.721)		
no	63 (61.2)	23.0 (13.962,32.038)		

Tumor markers			4.748	0.029
normal	14 (13.6)	40.0 (24.352,55.648)		
high	89 (86.4)	15.0 (9.075,20.925)		
Timing of metastasis			1.479	0.224
Synchronous	23 (22.3)	17.5 (5.122,29.878)		
Metachronous	80 (77.7)	20.0 (9.976,30.024)		
Clinical presentation			1.798	0.180
Neurologic symptoms	74 (71.8)	15.0 (9.543,20.457)		
No neurologic symptoms	29 (28.2)	30.0 (18.668,41.332)		
Preoperative radiotherapy			0.002	0.964
yes	11 (10.7)	20.0 (1.802,38.198)		
no	92 (89.3)	20.0 (2.219,27.781)		
Smoking history			3.245	0.072
yes	25 (24.3)	8.0 (0.000,16.364)		
no	78 (75.7)	23.0 (15.654,30.346)		

95% CI: 95% Confidence Interval; ys: years old; cm: centimeter

Table 2: Prognostic factors of overall survival based on a Cox' proportional hazard regression model.

Parameter	Regression coefficients	Standard error	Wald value	P value	Hazard ratio	95% CI
Gender	0.312	0.252	1.529	0.216	1.366	0.833, 2.240
Tumor size	0.696	0.265	6.883	0.009	2.005	1.192, 3.372
Tumor marker	0.765	0.404	3.580	0.058	2.149	0.973, 4.747

95% CI: 95% Confidence Interval

responsible lesion can relieve intracranial hypertension and provide an opportunity for the treatment of primary focus and systemic treatment of the whole body. Surgery is not a too aggressive strategy and the median survival time was nearly two times longer than previously reported [1]. The survival analysis demonstrated that the prognosis of surgical treatment for patients with metastases less than 3 cm in diameter is relatively good. In this study, lung cancer and breast cancer accounted for 53.4% and 16.4%, respectively, close to the foreign reports [5]. Lung cancer and breast cancer are the most common primary foci of brain metastases, and their composition directly affects gender composition. In our study, male patients accounted for 57.3%, which higher than females, consistent with literature reports [6]. Male patients have a higher proportion of lung cancer, so there are more men with brain metastases than women. But in recent years, the smoking population of female patients had gradually increased, so did the incidence of female lung cancer. Melanoma and kidney cancer are also common primary lesions, and the source of the digestive system is relatively rare. This study revealed no significant difference in the prognosis of patients with brain metastases caused by different primary foci. However, with the development of targeted and immunotherapy in recent years, the survival time of lung cancer patients with brain metastases is longer than before. The surgical treatment of BMs has bought time for comprehensive treatment, which is very important to prolong the survival time of patients. Besides, we found that age was a prognostic factor. The prognosis of patients over 60 years old is not as good as that of patients younger than 60 years old, which may be related to the elderly patients usually complicated with hypertension, diabetes, low immunity, and even poor general conditions. The brain metastases were mainly located in supratentorial region, and less case were located in infratentorial region. In this series of data, the distribution of supratentorial lesions was further analyzed, the results showed that the frontal and parietal lobes were the most common, and the occipital and temporal lobes were relatively rare. Studies demonstrated that cerebellar metastasis are associated with poor prognosis [7]. Chaichana reported 708 patients, of which 140 (19.8%) had undergone surgery for cerebellar metastases from different primary tumors. The results showed that cerebellar metastasis were associated with poor survival and increased risk of spinal recurrence [5]. There are different possible explanations for the poor prognosis of patients with subcutaneous transfer. Kitaoka reported a higher incidence of meningeal spread in the surgery for metastatic tumors of the posterior fossa, which is attributed to a closer spatial relationship with the ventricular system, leading to poor survival [8,9]. Some studies explained that these factors may also lead to poor survival as the incidence of complications in posterior fossa surgery seemed higher (e.g., hydrocephalus) [9,10]. However, in this study, there was no significant difference in survival between patients with supratentorial and infratentorial metastases. In most cases, surgery is the only viable option for effective treatment of infratentorial metastases, and it had been confirmed that surgery can improve the prognosis of patients compared with radiotherapy alone [5]. Tumor markers are characteristic in malignant tumor cells or produced by the host response to tumor stimulation. It was found that the patients with normal levels of CEA, CA153 and other tumor markers in patients with brain metastasis of breast cancer and lung cancer were significantly better than those with an abnormal increase in progression free survival [11]; suggesting tumor marker levels can be used as a factor in evaluating prognosis. Univariate analysis in this study also found that elevated tumor marker levels are one of the factors that lead to patient's poor prognosis. Although the treatment of brain metastases is controversial, surgery is still a significant method to treat brain metastases and improve the prognosis of patients. Resection of single brain metastases has become the standard

treatment for patients with good functional status and controlled extracranial disease [12,13]. The progress of surgical techniques, microsurgical instruments and intraoperative navigation have led to a decrease in perioperative complications and in-hospital mortality, which is estimated to be as low as 1.8% in large medical centers [14]. There are few reports on surgical indications for multiple brain metastases. In the case of multiple brain metastases, surgery is usually limited to less than three metastases, patients with neurological dysfunction, intracranial hypertension, life-threatening, and those who need pathological diagnosis for systemic treatment. However, two recent single-center retrospective studies claimed that resecting responsible lesions can improve patient outcomes, and patients with two to three metastatic foci can benefit from the same survival benefits as one metastatic foci [15,16]. Our results also showed that the number of brain metastases has no significant impact on the prognosis of patients, while patients with the largest diameter of metastases greater than or equal to 3 m have a relatively poor prognosis. It may be related to the occupation of the metastasis and the cause of neurological symptoms. Moreover, for the patients with larger metastasis size, the tumor growth time was longer, and the metastasis of other extracranial lesions was often combined. Compared with the number and size of metastatic tumors, we pay more attention to the basic situation, the space occupying effect and the location of multiple metastases of patients when formulating the treatment plan. For the lesions with remarkable space occupying effect or located in the posterior fossa, if the primary lesion is controllable and the postoperative survival time is ≥ 6 months, whether the number of lesions is more than 3 or the tumor size is greater than 3 cm, we all actively take surgical treatment. The recurrence of postoperative brain metastases is a problem that cannot be ignored after surgical treatment. Incomplete tumor resection is the main factor for the progress of postoperative pial meninges [9]. Therefore, for surgical treatment of brain metastases, complete resection should be done as much as possible. Studies had shown that WBRT after surgery can reduce 46% to 59% of local recurrences to 28% [17,18]. However, after WBRT, 52% of patients had neurocognitive impairment, while only 24% of patients had neurocognitive impairment without WBRT [19]. Neurotoxicity and reduced quality of life after WBRT are the main concerns of this treatment. Some studies found that the use of stereotactic radiotherapy before surgery, followed by surgical resection of metastatic lesions within 48 h, can reduce neurotoxicity, the risk of meningeal progression and retain a high level of local control [20,21]. Furthermore, many researchers use stereotactic radiotherapy to treat the resectioned tumor cavity, which can avoid the risk of cognitive impairment after WBRT [22]. For patients with local recurrence after brain metastases, re-surgical resection can still benefit some patients. Bindal reported 48 patients with recurrent brain metastases after surgery. The results showed that the median survival time after reoperation was 11.5 months. Among the 48 patients who underwent reoperation, 26 patients relapsed again, and those who chose reoperation had longer median survival time than those who did not (8.6 *vs.* 2.8 months). Therefore, for some selective cases, multiple operations after relapse can benefit patients. Current researches believe that even if the patient's performance is poor or multiple brain metastases have occurred, surgical treatment is still of great significance. On one hand, it can quickly remove the edema caused by the tumor; alleviate space-occupying effects and intracranial hypertension. On the other hand, it can prevent further deterioration of the neurological function. What is more, surgery can also obtain a pathological diagnosis, providing a basis for subsequent systemic treatment. For patients with brain metastases from non-small cell lung cancer with EGFR mutations, EGFR targeted therapy tends to have a better prognosis [23,24]. Besides, several recent studies have reported deviations in EGFR mutation status between primary tumors and metastatic brain lesions, with reported deviations ranging from 27% to 28% [25,26]. The pathological diagnosis obtained by surgery provides the basis for clinical precise treatment. There are certain deficiencies in this study. First of all, it was a retrospective study, a total of 103 cases were included, and the number of cases was not large. The exact conclusion still needs to be confirmed by a multi-center collaborative large-scale prospective randomized controlled study. Second, the time for the inclusion of this study is as of January 2019, and the FU time for this part of cases is not long. Lastly, the patients with metastases included in this study include different primary foci. A separate analysis of the case data of different primary foci will help guide clinical precision treatment.

Conclusion

Surgery is a safe and effective option to manage brain metastases which can alleviate clinical symptoms, prolong survival time and improve patients' prognosis. It is not a too aggressive strategy. We suggest surgery as an important part of the comprehensive treatment of BMs, even as the preferred strategy in some cases. Metastasis tumor size ≥ 3 cm (P=0.029) was an independent negative prognostic factor for patients with brain metastases.

References

1. Giancarlo DA, Lucia P, Giuseppe M. Brain metastases: Surgical treatment and overall survival. World Neurosurg. 2017;97:169-77.
2. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep. 2012;14(1):48-54.
3. Al-Shamy G, Sawaya R. Management of brain metastases: The indispensable role of surgery. J Neurooncol. 2009;92(3):275-82.
4. Ahluwalia MS, Vogelbaum MV, Chao ST, Mehta MM. Brain metastasis and treatment. F1000Prime Rep. 2014;6:114.
5. Chaichana KL, Rao K, Gadkaree S. Factors associated with survival and recurrence for patients undergoing surgery of cerebellar metastases. Neurol Res. 2014;36(1):13-25.
6. Li GW, Guo Y, Zhang X. Brain metastasis: Experience of the Xi-Jing Hospital. Stereotact Funct Neurosurg. 2002;78(2):70-83.
7. Ghods A, Byrne R, Munoz L. Surgical treatment of cerebellar metastases. Surg Neurol Int. 2011;2:159.
8. Siomin VE, Vogelbaum MA, Kanner AA, Lee SY, Suh JH, Barnett GH. Posterior fossa metastases: Risk of leptomeningeal disease when treated with stereotactic radiosurgery compared to surgery. J Neurooncol. 2004;67(1-2):115-21.
9. Ahn JH, Lee SH, Kim S. Risk for leptomeningeal seeding after resection for brain metastases: Implication of tumor location with mode of resection: Clinical article. J Neurosurg. 2012;116(5):984-93.
10. Pompili A, Carapella CM, Cattani F. Metastases to the cerebellum. Results and prognostic factors in a consecutive series of 44 operated patients. J Neurooncol. 2008;88(3):331-7.
11. Nieder C, Marienhagen K, Astner ST, Molls M. Prognostic scores in brain metastases from breast cancer. BMC Cancer. 2009;9:105.
12. Granone P, Margaritora S, D'Andrilli A, Cesario A, Kawamukai K, Meacci E. Non-small cell lung cancer with single brain metastasis: The role of surgical treatment. Eur J Cardio-thoracic Surg. 2001;20:361-6.
13. Bonnette P, Puyo P, Gabriel C. Surgical management of non-small cell

lung cancer with synchronous brain metastases. Chest. 2001;119(5):1469-75.

14. Barker FG. Craniotomy for the resection of metastatic brain tumors in the U.S., 1988-2000: Decreasing mortality and the effect of provider caseload. Cancer. 2004;100(5):999-1007.

15. Paek SH, Audu PB, Sperling MR, Cho J, Andrews DW. Reevaluation of surgery for the treatment of brain metastases: Review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. Neurosurgery. 2005;56(5):1021-34.

16. Stark AM, Tscheslog H, Buhl R, Held-Feindt J, Mehdorn HM. Surgical treatment for brain metastases: Prognostic factors and survival in 177 patients. Neurosurg Rev. 2005;28(2):115-9.

17. Patchell RA, Tibbs PA, Regine WF. Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. J Am Med Assoc. 1998;280(17):1485-9.

18. Vogelbaum MA, Suh JH. Resectable brain metastases. J Clin Oncol. 2006;24(8):1289-94.

19. Chang EL, Wefel JS, Hess KR. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. Lancet Oncol. 2009;10(11):1037-44.

20. Asher AL, Burri SH, Wiggins WF. A new treatment paradigm: Neoadjuvant radiosurgery before surgical resection of brain metastases with analysis of local tumor recurrence. Int J Radiat Oncol Biol Phys. 2014;88(4):899-906.

21. Patel KR, Burri SH, Boselli D. Comparing pre-operative Stereotactic Radiosurgery (SRS) to post-operative Whole Brain Radiation Therapy (WBRT) for resectable brain metastases: A multi-institutional analysis. J Neurooncol. 2017;131(3):611-8.

22. Kondziolka D, Martin JJ, Flickinger JC. Long-term survivors after gamma knife radiosurgery for brain metastases. Cancer. 2005;104(12):2784-91.

23. Abdul-Rahman J, Hanaa B, Ahmet D, Rabab MG, Fady BG, Mansur J, et al. Modification and implementation of NCCN guidelines on non-small cell lung cancer in the Middle East and North Africa region. J Natl Compr Canc Netw. 2010;8:S16-21.

24. Park SJ, Kim HT, Lee DH. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer. 2012;77(3):556-60.

25. Kalikaki A, Koutsopoulos A, Trypaki M. Comparison of EGFR and K-RAS gene status between primary tumours and corresponding metastases in NSCLC. Br J Cancer. 2008;99(6):923-9.

26. Gow CH, Chang YL, Hsu YC. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Ann Oncol. 2009;20(4):696-702.