Research article

Recurrence benefit from supramarginal resection in brain metastases of lung adenocarcinoma

Weizhao Gong *, Taipeng Jiang, Dahui Zuo

Shenzhen Second People's Hospital, Shenzhen 518025, China

ARTICLE INFO

ABSTRACT

Background: There is growing evidence that brain metastases (BM) have no well-defined boundaries and that conventional microsurgical circumferential dissection of BM is often inadequate to prevent local tumor recurrence. Previous studies have suggested that supramarginal resection can significantly improve local tumor control. We retrospectively analyzed the local tumor control in a series of patients with BM from lung adenocarcinoma.
Methods: We retrospectively analyzed 48 patients with BM for lung adenocarcinoma in Shenzhen Second People's Hospital from May 2015 to May 2020. 26 resected lesions were located in eloquent areas and underwent standard gross total resection (GTR group); 22 resected lesions were located in ineloquent areas, after standard gross total resection, the periphery was expanded and resected by 5 mm (MTR group). The postoperative tumor recurrence was compared between the two groups.
Results: During the follow-up period, the local recurrence rates in the GTR group and the MTR group were 61.5% and 27.3% (p = 0.022), respectively. Within 6 months after surgery, the local recurrence rates in the GTR group and the MTR group were 42.3% and 13.6% (p = 0.029), respectively. Within 12 months after surgery, the local recurrence rates in the GTR group and the MTR group were 57.7% and 22.7% (p = 0.014), respectively. The median progression-free survival time after surgery was 7.0 months (95% CI 4.0–10.0 months) in the GTR group and 14.0 months (95% CI 11.4–16.6 months) in the MTR group (Log-Rank p = 0.008). Compared with the MTR group, the HR of local recurrence in the GTR group was 3.74 (95% CI 1.38–10.39, p = 0.010). Cox multivariable analysis showed no other factors associated with local recurrence except for the surgical method (p = 0.012).
Conclusions: On the basis of conventional surgical total resection, expanded peripheral resection of 5 mm around the brain metastases of lung adenocarcinoma can significantly reduce the local recurrence rate and prolongs the progression-free survival time.

1. Introduction

BM are common complications of some solid and even non-solid tumors, occurring in 30% of tumor patients [1]. BM has been considered to be well-defined by the brain parenchyma [2]. Therefore, the traditional standard surgical treatment for metastases in neurosurgery is Gross Total Resection (GTR). However, GTR alone is sometimes clinically insufficient for disease control, as accidental residual tumors may lead to local progression [3, 4]. The incidence of local tumor progression after GTR has been reported as high as 40% [5]. In addition, 10–34% of patients have a recurrence within the surgical cavity one year after treatment, even if they have received GTR and adjuvant radiotherapy [6, 7]. Based on the principle of enlarged resection of BM to reduce recurrence, Yoo H [8] first proposed the "Microscopic Total Resection (MTR)" surgical

approach in 2009, including an additional 5 mm resection of the surrounding normal brain parenchyma after GTR. This enlarged resection significantly reduced the local recurrence rate of the lesion. Lung cancer is the most common primary tumor with BM, among which the most common pathological type is lung adenocarcinoma [9]. This study aimed to investigate whether MTR can reduce the local recurrence rate of BM from lung adenocarcinoma compared with GTR.

2. Material and methods

We retrospectively analyzed 48 patients who underwent surgery for brain metastases from lung adenocarcinoma in Shenzhen Second People's Hospital from May 2015 to May 2020. For metastases in ineloquent areas, we routinely used a tumor circumferential resection followed by

---

* Corresponding author.
E-mail address: wzgong15@163.com (W. Gong).

peripheral expansion of 5 mm (MTR group). Standard gross total resection was used to remove the lesion completely or partly in eloquent areas (GTR group) rather than expand the resection. All patients enrolled in this study met the following criteria: (1) Resection of 1–3 tumors in one case; (2) Tumors in ineloquent areas were resected with 5 mm depth around the expanded resection after GTR, and tumors in eloquent areas were resected with GTR instead of expanded resection (according to surgical records and videos); (3) Preoperative Magnetic Resonance Imaging (MRI) enhancement imaging was completely retained; (4) MRI was completely retained within 72 h postoperatively, and there was no tumor residue in the operative area; (5) The intraoperative distance between the tumor periphery and the meninges was more than 5 mm; (6) Postoperative pathology indicated BM from lung adenocarcinoma; (7) The endpoint of follow-up was tumor recurrence or death; (8) No radiotherapy or chemotherapy prior to tumor recurrence. Patients with other malignancies should also be excluded, such as glioma and brain lymphoma. According to the literature, the eloquent region is defined as the cortical or subcortical brain area, in which intraoperative stimulation are expected to elicit changes in neurologic conditions (especially in movement, tactile sensation and speech) or to trigger responses in electrophysiological recordings of corresponding areas, such as the brainstem, anterior and posterior central gyrus, Broca's area, and Wernicke's area [10]. In this study, tumor recurrence was defined as a suspicious enhancement signal in the surgical area detected by enhanced MRI in the first postoperative examination and an enlarged enhancement signal in the next examination. Neither group received any other treatment (including radiation therapy) prior to the study endpoint.

2.1. Surgical procedures

In this study, all 48 patients underwent preoperative 3.0T MRI enhancement, and relevant sequences were used for the intraoperative neuronavigation system. The data were transferred to the navigation system workstation in D-COM format for 3D reconstruction, and the target arrival area was delineated to design the surgical path. All patients were registered using the laser contour method. The navigation probe was first registered, then the nose tip, eyebrow and the left supraorbital brow at 3.0 cm. Finally, more than 400 registration points were collected by the navigation probe on the skin of face and head. The navigation system matched the patient entity with the imaging data of the workstation based on these registration points. The matching is completed by default if the error is within 2.0 mm. In order to ensure enlarged resection, we designed the surgical scheme under the neuronavigation system, taking into account the peripheral area of about 5 mm. The GTR group also underwent Diffusion Tensor Imaging (DTI) and functional Magnetic Resonance Imaging (fMRI) to protect better essential functions such as motor, sensory, and speech during surgery. Left-handed patients also underwent the Wada test to determine the dominant cerebral hemisphere. Intraoperative Monitoring (IOM) was used to continuously capture real-time motor-evoked potentials (MEPs), sensory-evoked potentials (SEPs), and continuous electroencephalography (EEG) during the procedure. In the MTR group, neither cortical nor subcortical stimulation caused new neurological deficits during surgery. After GTR, the resection depth was extended to approximately 5 mm, which was determined by the neuronavigation system and ruler. In the GTR group, enlarged resection was not performed because the tumor was near the functional area and new postoperative severe complications were avoided. All patients were injected with intravenous methylprednisolone (40 mg Q6H) postoperatively to prevent cerebral edema, and postoperative MRI enhancement was completed within 72 to eliminate tumor remnants.

2.2. Statistical methods

Progression-free survival time was defined as the time from surgical resection to local recurrence or death of the patient. The baseline characteristics of the two groups were compared by t-test and chi-square test.

Pearson's chi-squared test was used to determine the difference in recurrence rates between the two groups. Progression-free survival distribution was assessed using the Kaplan-Meier method. Log-Rank test and Cox regression analysis were used to assess the correlation between variables and tumor recurrence. In addition, we evaluated other factors in relation to local recurrences, such as gender, age, tumor size, maximum tumor diameter, metastasis time, number of intracranial metastases, extracranial metastases, and KPS score. The above statistical analyses were performed using IBM SPSS software version 26. We utilized R software to conduct a Time-dependent receiver operating characteristic curve (ROC). Results were considered statistically significant when the probability value was <0.05.

3. Results

A total of 48 patients were enrolled in this study (Table 1), of which 22 (45.8%) were male and 26 (54.2%) were female, with an average age of 57.6 ± 10.8 years. According to the surgical procedure, the patients were divided into the GTR group and the MTR group. The postoperative pathology of all patients showed BM from lung adenocarcinoma. The surgically resected lesions in the GTR group were located in eloquent areas, while those in the MTR group were ineloquent areas. In the recorded patient data, such as gender (p = 0.594), age (p = 0.092), time to metastasis (p = 0.900), maximum tumor diameter (p = 0.214), tumor volume (p = 0.118), number of brain metastases (p = 0.715), presence of extracranial metastases (p = 0.632), and KPS score (p = 0.055), there were no statistical differences between the two groups.

During the follow-up period, a total of 16 patients (61.5%) in the GTR group and 6 patients (27.3%) in the MTR group experienced in situ tumor recurrence (p = 0.022). The recurrence rate within 6 months after surgery was 42.3% (11 of 26 patients) in the GTR group and 13.6% (3 of 22 patients) in the MTR group (p = 0.029). The recurrence rate within 12 months after surgery was 57.7% (15 of 26) in the GTR group and 22.7% (5 of 22) in the MTR group (p = 0.014; Table 2).

A total of 26 deaths occurred in the GTR group and the MTR groups during the follow-up period, and no recurrence occurred before death.

Table 1. Clinical and demographic characteristics in 48 patients.

Characteristic	Total (n = 48)	GTR (n = 26)	MTR (22)	p Value
Sex				0.594#
male	22 (45.8)	11 (42.3)	11 (50)	
female	26 (54.2)	15 (57.7)	11 (50)	
Age (mean + SD)	57.6 ± 10.8	55.2 ± 11.0	60.5 ± 10.1	0.092#
Timing of metastasis				0.900#
synchronous	17 (35.4)	9 (34.6)	8 (36.4)	
metachronous	31 (64.6)	17 (65.4)	14 (63.6)	
Dmax (cm)*	3.6 ± 1.2	3.8 ± 1.3	3.4 ± 1.1	0.214#
Tumor size (cm³)	39.3 ± 38.8	47.3 ± 45.7	29.7 ± 26.5	0.118#
Number of brain metastases				0.715#
1	21 (43.8)	12 (46.2)	9 (40.9)	
≥2	27 (56.3)	14 (53.8)	13 (59.1)	
Extracranial metastases				0.632#
yes	17 (35.4)	10 (38.5)	7 (31.8)	
no	31 (64.6)	16 (61.5)	15 (68.2)	
KPS				0.055‡
<70	8 (16.7)	7 (26.9)	1 (4.5)	
≥70	40 (83.3)	19 (73.1)	21 (95.5)	

GTR gross total resection, MTR gicroscopic total resection (supramarginal resection).
* Maximum diameter of tumor.
‡ Pearson chi-square test , # t-test , ‡ Fisher exact test.

Table 2. Summary of local recurrence rates, according to treatment protocol.

		GTR	MTR	Pearson Chi-Square	p Value
Recurrence time (months)	≤6	11 (42.3)	3 (13.6)	4.742	0.029
	≤12	15 (57.7)	5 (22.7)	5.994	0.014
	Follow-up period	16 (61.5)	6 (27.3)	7.623	0.022

Therefore, the time from surgery to death was also defined as progression-free survival time. We finally concluded that the median progression-free survival time after surgery was 7.0 months (95% CI 4.0–10.0 months) in the GTR group and 14.0 months (95% CI 11.4–16.6 months) in the MTR group (Log-Rank p = 0.008; Figure 1). The risk of postoperative tumor recurrence or death increased over time in both groups, but it was higher in the GTR group than in the MTR group (Log-Rank p = 0.008; Figure 2).

Cox univariate regression analysis showed that compared with the MTR group, the HR of local recurrence in the GTR group was 3.74 (95% CI 1.38–10.39, p = 0.010). Cox multivariate analysis showed that no factors other than surgical modality were associated with local recurrence (p = 0.012; Table 3).

Moreover, time-dependent receiver operating characteristic curves (ROC) showed free-progression predictive accuracy at 1-year follow-up of the MTR group (red) and GTR group (black) with AUC 0.71 and 0.50 (Figure 3). Which indicated that the probability of progression-free survival at one year after surgery was higher in the MTR group than in the GTR group.
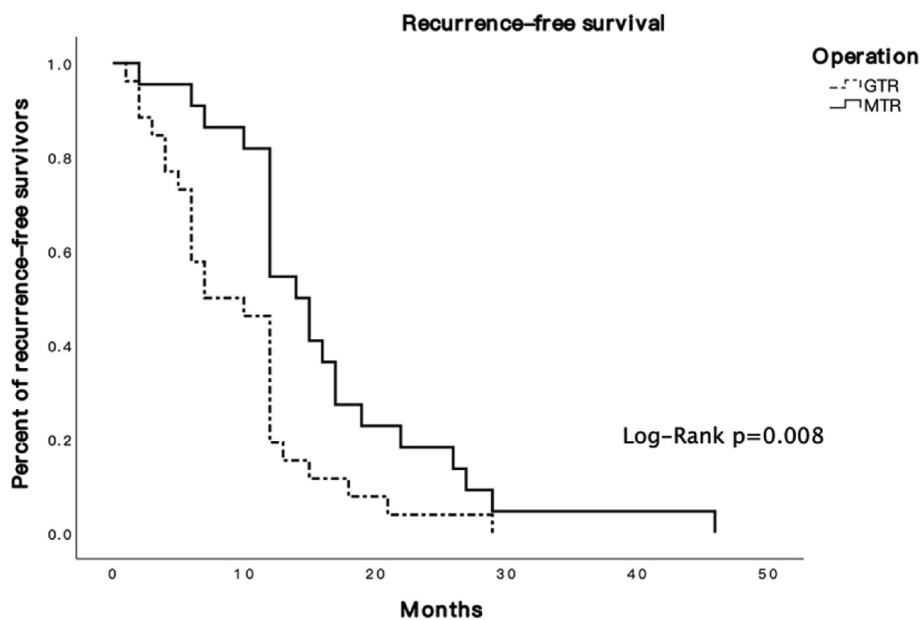

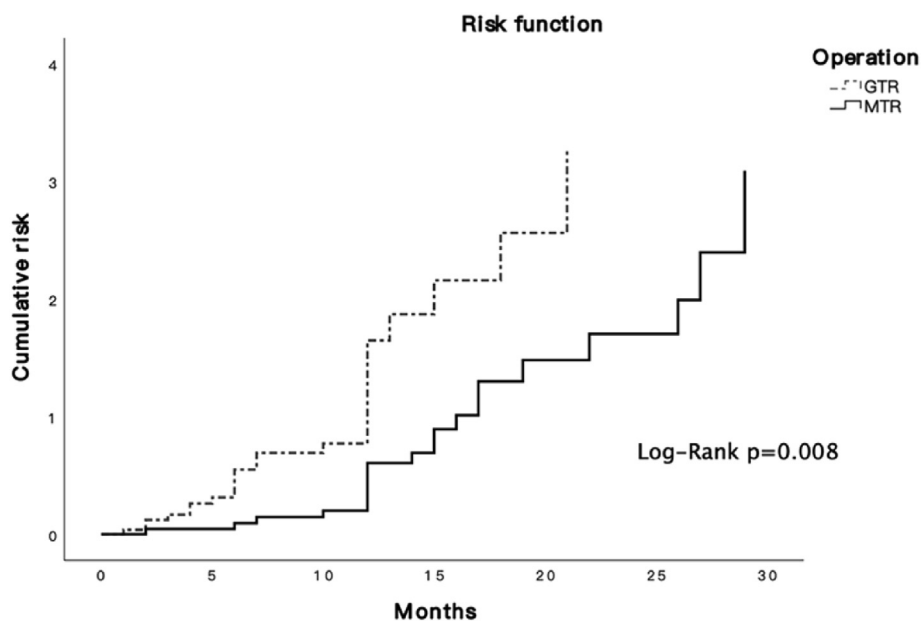**Figure 1.** Graph showing recurrence-free survival of different surgical methods.

Figure 2. Graph showing risk function of recurrence from different surgical methods.

Table 3. Factors affecting local recurrence on univariate and multivariate analysis.*

| Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Sex (male vs female)	0.72 (0.30-1.75)	0.471	–	–
Age	1.01 (0.97–1.05)	0.805	–	–
Timing of metastasis (synchronous vs metachronous)	0.89 (0.36–2.22)	0.807	–	–
Dmax (cm)	0.98 (0.70–1.36)	0.890	–	–
Tumor size (cm^3)	0.99 (0.98–1.01)	0.346	–	–
Number of brain metastases (1 vs ≥2)	0.48 (0.20–1.19)	0.112	0.64 (0.26–1.62)	0.348
Extracranial metastases (yes vs no)	0.50 (1.81–1.39)	0.184	0.50 (1.71–1.45)	0.200
Operation (GTR vs MTR)	3.78 (1.38–10.39)	0.010	3.74 (1.34–10.46)	0.012
KPS (<70 vs ≥70)	0.78 (0.23–2.68)	0.698	–	–

* Cox regression model.
– Not assessed.

4. Discussion

Metastases can occur in various parts of the central nervous system, and classification criteria can be supratentorial or infratentorial, different brain lobes and functions, etc. Among them, the division of eloquent and ineloquent areas according to function seems to be inappropriate. Because any section of the brain has a corresponding function. In this study, we only narrowly defined areas with essential functions as eloquent areas, such as motor and sensory. Besides, there is no evidence of difference in microscopic invasion of BM cells in different brain areas [11]. There is little evidence that eloquent areas predict poorer survival, but there is an intrinsic relationship with neurological function, which can be used to guide management decisions [12]. Although Yoo H et al. have conducted several studies on the effect of MTR and GTR on the postoperative recurrence rate of BM patients, currently, no study has confirmed whether MTR is superior to GTR in the recurrence rate of single pathological BM.

Our study provided the first data on MTR of BM from lung adenocarcinoma. Moreover, we compared the recurrence rate not only one year after surgery but also six months after surgery. The results all suggest a lower rate of recurrence after MTR. Otherwise, we also found that MTR was more likely to have progression-free survival at 1 year postoperatively by time-dependent ROC curve analysis. None of the patients received any adjuvant therapy (such as radiotherapy and chemotherapy) prior to the observation endpoint. Therefore, the postoperative tumor progression mainly depended on the surgical approach. In addition, in order to avoid the prognosis of tumor invasion of meninges, we have included the distance between tumor border and meninges greater than 5 mm as the inclusion criterion. The results showed that MTR could significantly reduce the local recurrence rate. BM is considered to be well-defined from the brain parenchyma and can be easily detached from the surrounding brain tissue. In conventional GTR, the lesions are circumferentially stripped along with the brain-tumor interface without invading its capsule membrane. The reasons for the high local recurrence rate have not been systematically analyzed. Based on the intraoperative evaluation and postoperative MRI, the best explanation is that malignant cells remained despite GTR. A trial showed that 34.7% of tumor cells infiltrated into adjacent brain parenchyma in all biopsies around metastases [13]. During GTR, the residual tumor fractions or infiltrated tumor cells may be invisible, leading to local intracerebral progression.

Through the study of 416 patients with newly diagnosed and recurrent gliomas, M Lacroix proposed the concept of maximum, safe and achievable volume resection, indicating that with the increase of the maximum extent of resection (EOR) from 89%, the survival rate would increase. The most substantial effect of resection on the survival rate was observed at the threshold of 98% [14]. However, there is no similar study on BM. The neuroradiological findings showed a clear demarcation between MRI enhancement areas and peripheral brain tissue. In fact, less than 40% of brain metastases have definable boundaries with the brain parenchyma. In comparison, more than 60% of brain metastases show an irregular tumor-brain interface with a tongue-like extension into the surrounding brain, and even an infiltrative growth pattern [15]. In Justyna Tabaka's study, 66 cases had tumor infiltration beyond the regular margin, with an average distance of 153.8 μm [16]. 63% of cases in the Baumert study showed infiltrative growth beyond the boundaries of BM. The infiltration percentage of non-small cell lung cancer (NSCLC) was the highest (70%), and the maximum infiltration depth of small cell lung cancer (SCLC) was >1 mm. In contrast, the infiltration depth of other histologies was < 1 mm [17]. Sundaresan [18,19] suggested that although some metastatic tumor cells may infiltrate into the surrounding
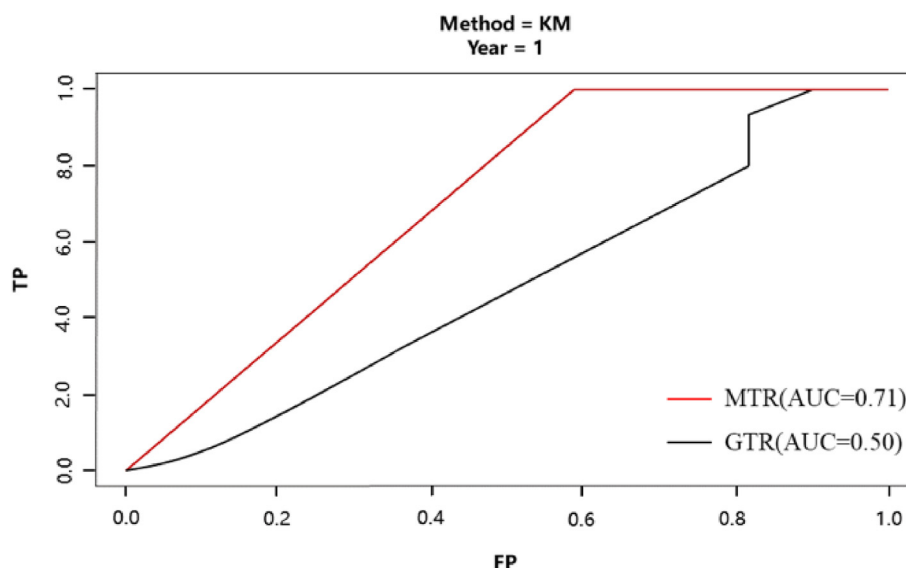
Figure 3. The time-dependent ROC curve analysis with 1 year.

brain, this is usually less than 5 mm. Expanded BM resection may help avoid or delay recurrence based on the available pathological research. Yoo H [8] first introduced the concept of supramarginal resection which mean an additional 5 mm of surrounding normal brain parenchyma was resected after GTR. In the Yoo H study, within one year after MTR, the recurrence rate decreased by more than 50%. However, there was no difference in the median overall survival time between the two groups of patients. This could be explained by the fact that most BM patients die due to the progression of the extracranial disease rather than CNS failure. Our results suggested that MTR of BM from lung adenocarcinoma led to a 28.7% reduction in the 6-month recurrence rate, a 35% reduction in the 12-month recurrence rate, and a 7-month extension in progression-free survival time. This would support the conclusion that the MTR benefited patients with BM of lung adenocarcinoma more than the GTR. There is still tumor recurrence after extended resection, and the causes need further systematic analysis.

Enlarged resection of eloquent areas implies an increased probability of postoperative neurological dysfunction, and MTR was initially only applicable to BM in ineloquent areas. However, there were still some attempts of MTR in eloquent areas. In Marta Rossetto's [20] study, 90% of patients with eloquent areas tumors improved or maintained stable functional impairment after surgery. For patients with dyskinesia, 55% improved postoperatively, while only 16% deteriorated. Barkhoudarian [21] performed the first paracentral lobular deep BM resection with the help of endoscopy. After cerebrospinal fluid release, the contralateral cerebral hemisphere was moved away from the midline, enlarging the interhemispheric space, which facilitated the opening of the cerebral falx and the extensive exposure of the lesions without involving the vital cortex. In addition to neuroendoscopy, advances in digital imaging, WiFi network connectivity, screen technology and optics have also led to the development of exoscopy [22]. The exoscope can enhance the visualization of anatomical details and identify different tissue layers and the tumor-nerve interface to achieve tumor resection while preserving functional fiber bundles [23]. Besides, the exoscopes offer particular advantages in terms of operator comfort, educational purposes, image quality, magnetism, illumination and cost.

However, this study has some limitations. First, as a retrospective study, this is a retrospective experience from a single institution with only a small sample of patients. Second, stereotactic radiation therapy is an important treatment for BM, which significantly impacts the patient's prognosis. However, our study did not establish a control group for stereotactic radiotherapy.

5. Conclusions

Based on the current study results, it is suggested that for brain metastases from lung adenocarcinoma, an expanded peripheral resection of 5 mm based on conventional gross total resection can significantly reduce the local recurrence rate and prolong the progression-free survival time.

Declarations

Author contribution statement

Funding statement

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] R.V. Lukas, P. Gabikian, M. Garza, et al., Treatment of brain metastases, Oncology 87 (6) (2014) 321–329.

[2] A.S. Berghoff, S. Schur, Füreder, M. Lisa, et al., Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers, ESMO Open 1 (2) (2016), e000024.

[3] N. Thon, F.W. Kreth, J.C. Tonn, The role of surgery for brain metastases from solid tumors, Handb. Clin. Neurol. 149 (2018) 113–121.

[4] G.A. Plataniotis, M. Theofanopoulou, K. Sotiriadou, et al., The volume of brain metastases may be of prognostic significance in patients with non-small-cell lung cancer classified as RTOG-RPA classes 2 and 3, Clin. Oncol. 18 (1) (2006) 85–86.

[5] A.J. Patel, D. Suki, M.A. Hatiboglu, et al., Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis, J. Neurosurg. 122 (5) (2015) 1132–1143.

[6] B.J. Williams, D. Suki, B.D. Fox, et al., Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications, J. Neurosurg. 111 (3) (2009) 439.

[7] J. Li, S.M. Bentzen, M. Renschler, et al., Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function, J. Clin. Oncol. 25 (10) (2007) 1260.

[8] H. Yoo, Y.Z. Kim, B.H. Nam, et al., Reduced local recurrence of a single brain metastasis through microscopic total resection, J. Neurosurg. 110 (4) (2009) 730–736.

[9] N.D. Arvold, E.Q. Lee, M.P. Mehta, et al., Updates in the management of brain metastases, Neuro Oncol. 18 (8) (2016) 1043–1065.

[10] H. Duffau, L. Capelle, D. Denvil, et al., Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients, J. Neurosurg. 98 (4) (2003) 764–778.

[11] G. Trude, Simonsen, et al., Intertumor heterogeneity in vascularity and invasiveness of artificial melanoma brain metastases, J. Exp. Clin. Cancer Res. 34 (1) (2015) 150.

[12] K. Pragnan, I. Alexander, C. Susie, et al., The effect of brain metastasis location on clinical outcomes: a review of the literature, Neuro-Oncol. Adv. (1) (2019) 1.

[13] L. Siam, A. Bleckmann, H.N. Chaung, et al., The metastatic infiltration at the metastasis/brain parenchyma-interface is very heterogeneous and has a significant impact on survival in a prospective study, Oncotarget 6 (30) (2015) 29254–29267.

[14] M. Lacroix, D. Abi-Said, D.R. Fourney, et al., A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival, J. Neurosurg. 95 (2) (2001) 190–198.

[15] Incidence of local in-brain progression after supramarginal resection of cerebral metastases, Acta Neurochir. 157 (6) (2015) 905–911.

[16] J. Tabaka, P. Nowacki, J. Pankowski, The interaction between lung cancer metastases to the brain and their surroundings, Folia Neuropathol. (2006).

[17] B.G. Baumert, I. Rutten, C. Dehing-Oberije, et al., A pathology-based substrate for target definition in radiosurgery of brain metastases, Int. J. Radiat. Oncol. Biol. Phys. 66 (1) (2006) 187–194.

[18] N. Sundaresan, J.H. Galicich, Surgical treatment of brain metastases. Clinical and computerized tomography evaluation of the results of treatment, Cancer 55 (6) (1985) 1382–1388.

[19] A. Marcel, KMaxine Dibué, L. Niemann, D.C. Reichelt, et al., Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas, Acta Neurochir. 154 (11) (2012) 1981–1986.

[20] M. Rossetto, P. Ciccarino, G. Lombardi, G. Rolma, D. Cecchin, A. Della Puppa, Surgery on motor area metastasis, Neurosurg. Rev. 39 (1) (2016) 71–78.

[21] G. Barkhoudarian, D. Farahmand, R.G. Louis, et al., Microsurgical endoscope-assisted gravity-aided transfalcine approach for contralateral metastatic deep medial cortical tumors, Operat. Neurosurg. (2017).

[22] G. Trevisi, The exoscope in neurosurgery: an overview of the current literature of intraoperative use in brain and spine surgery, J. Clin. Med. (2021) 11.

[23] I.G. Vetrano, F. Acerbi, J. Falco, et al., High-Definition 4K 3D exoscope (ORBEYE) in peripheral nerve sheath tumor surgery: a preliminary, explorative, pilot study, Operat. Neurosurg. (3) (2020).