Intraoperative radiotherapy after resection of brain metastases located in the posterior fossa. Analysis of postoperative morbidity and mortality in a single center cohort

Philipp Krauss [a,*], Klaus Henning Kahl [b], Maximilian Niklas Bonk [a], Christina Wolfert [a], Bjoern Sommer [a], Georg Stueben [b], Ehab Shiban [a]

[a] *Department of Neurosurgery, University Hospital Augsburg, Stenglinstrasse 2, 86156 Augsburg, Germany*
[b] *Department of Radiooncology, University Hospital Augsburg, Stenglinstrasse 2, 86156 Augsburg, Germany*

1. Introduction

Surgical resection plays an important role in the comprehensive treatment of brain metastases (BM) [1]. Avoidance of perioperative adverse events (AE) is of upmost importance in order to prevent a delay of any adjuvant therapy and ensure the maintenance or improvement of the functional status. Adjuvant stereotactic radiotherapy (RT) of the resection cavity along with systemic treatment represents the standard of care. Adjuvant therapy is usually started after wound healing is ensured, approximately 10–14 days after surgery. Intraoperative radiotherapy (IORT) of the resection cavity in brain tumors has emerged as a treatment option in high grade gliomas (HGG) and BM with the possible advantage of avoiding the delay to postoperative systemic therapy (BM) or enabling a radiation boost without the risk of increased radiotoxicity [2–5]. Previously published small series demonstrate the safety and feasibility of IORT in BM [3,4]. As most knowledge on IORT is based on HGG, detailed data on the use of IORT for lesions in the posterior fossa (PF) is sparse. Nevertheless, depending on the oncologic entity, up to 70% of BMs are located in the PF [6,7]. Due to the specific anatomy and narrow space, surgery of the PF harbors inherent risks such as postoperative hydrocephalus, CSF leakage, pulmonary embolism or brainstem compression in case of rebleeding or infarction. Here we report the largest series of patients undergoing surgery for BM with IORT performed exclusively in the PF. The aim of this study is to evaluate the feasibility, safety, perioperative morbidity and mortality of IORT in the direct postoperative course.

* Corresponding author at: Department of Neurosurgery, University Hospital Augsburg, Stenglinstrasse 2, 86156 Augsburg, Germany.
E-mail address: philippemanuel.krauss@uk-augsburg.de (P. Krauss).

2. Methods

2.1. Ethics approval

The study protocol was approved by the local ethics committee (UKA/LMU) in accordance to the Declaration of Helsinki. For this retrospective observational study, no individual informed consent was necessary according to the ethics committee's guidelines and regulations.

2.2. Study design

We performed a retrospective analysis of patient-specific clinical records in a single tertiary neurosurgical center. The analyzed parameters included age, sex, Karnofsky Performance Scale (KPS) before and after surgery as well as KPS difference (pre/post surgery), the recursive partitioning analysis (RPA) for BMs, length of surgery (LOS), length of radiation (LORT), maximal diameter of the metastasis, diameter of radiation applicator, radiation dose, total number of BMs, length of hospitalization (LOH) and adverse events during hospitalization according to the Clavien Dindo Grading system (CDG) [8–10]. Furthermore, the histopathology of the underlying neoplasm was recorded.

2.3. Patient selection

Electronic data files of all adult patients undergoing a BM resection and receiving IORT therapy between 2014 and 2022 were screened. Patients younger than 18 years of age and patients who underwent resection of a BM outside the posterior fossa were excluded from the analysis.

2.4. Intraoperative radiotherapy

Treatment indication was confirmed by the local multidisciplinary tumor board for all patients. Between 2014 and 2017 IORT was offered on an individual basis based on interdisciplinary consensus. From 2017 onwards, it was applied routinely as an alternative to postoperative external-beam RT following an expert panel of the German Society for Radiation Oncology (DEGRO) guidelines [Expert panel decision DEGRO, inquiry 123, 17.02.2017]. Patients were considered not eligible if 1) the distance between the border of the MRI contrast-enhancing lesion and the brainstem was < 5 mm, 2) there was a history of small-cell lung cancer or 3) the resection trajectory was estimated to not allow a safe introduction of the radiation applicator. All patients signed an informed consent for resection and IORT. After tumor resection, the resection cavity was irradiated with 50-kV x-rays via an INTRABEAM system (ZEISS MEDITEC AG, Oberkochen, Germany) [4]. The device and procedure have been described previously [4]. A suitable spherical applicator was installed according to the size of the resection cavity in order to provide direct contact of the cavity walls to the surface of the applicator. Radiation dose was prescribed to the surface of the applicator corresponding to the target volume/dose concept of postoperative SRS cavity treatment (GTV = CTV = cavity). During the perioperative course, steroids were administered orally following a local standard procedure. The extent of resection was verified via postoperative 3T cMRI-scans using a T1 +/−Gd subtraction sequence.

2.5. Statistics

Statistical analysis was performed using the software SPSS Statistics™ (version 25, IBM Corp, Armonk, New York, USA). Data in text and graphs are shown as mean and standard deviation (SD) for continuous data and as median and interquartile range for ordinal data.

3. Results

3.1. Patient population

In this study, 9 (n = 5 female) patients were identified and met the inclusion criteria. Mean age was 65.8 ± 11.2 years. Median KPS was 80% [70–90%] (see Table 1). No patient had prior cranial RT. Two patients had 2 BMs with the other 7 patients having only a single BM.

3.2. Surgery and outcome

Mean LOS was 163 min including a mean LORT of 9 min. The median radiation dose applied was 20 Gy (16 Gy: n = 1, 18 Gy: n = 1, 20 Gy: n = 7). The median diameter of the radiation applicator was 2 cm (2–2.5 cm; 2 cm: n = 7; 2.5 cm: n = 2). Surgery was performed in sitting (n = 6), supine (n = 2), or prone (n = 1) position according to the lead surgeons preference. After surgery mean LOH was 9.2 days. Patients had a median postoperative KPS of 80% and median decline of 0%. Improvement of a preoperative neurological deficit occurred in one patient resulting in an improvement of KPS from 40% before to 60% after surgery. A new neurological deficit occurred in one patient resulting in a reduction of KPS from 100% before to 60% after surgery. All other patients did not experience a change in their functional status (see Table 2). High RPA values significantly inversely correlated with the functional status before (KPS pre; $r = -0.74$; $p = .02$) and after (KPS post; $r = -0.84$; $p < .01$) surgery as well as with KPS. Further, high preoperative functional status correlated inversely with change in KPS (KPS Δ; $r = -0.76$; $p = .02$). No further significant correlations were found (see Table 3).

3.3. Adverse events

In this study, 2 out of 9 patients experienced each one AEs within 30d after surgery. One patient suffered from postoperative re-bleeding in the PF resulting in a decreased consciousness level needing a revision surgery reflecting an AE grade 3b according to the CDG. The LOH was consequently prolonged (27d).

One patient was readmitted to the hospital within 30 days after discharge due to a surgical site infection (SSI) needing surgical revision and explantation of a cranial alloplasty with subsequent antimicrobiological treatment of a ventriculitis reflecting an AE grade 3b according to the CDG. The patient demonstrated no change of her previously known slight dysarthria, remained otherwise in good functional status (KPS 90%) and was discharged 29 days after revision surgery.

Overall, patients suffering from AEs had longer initial LOH (16.5d)

Table 1
Baseline characteristics: y = years; f/m = female/male; Pre = preoperative; RPA = recursive partitioning analysis; y/n = yes/no; BM = brain metastasis; n = number; RT = radiotherapy; NSCLC = non-small cell lung cancer; SCC = Squamous cell cancer; SNC = Sinunasal cancer; data is shown as (mean ± SD/median [interquartile range]).

	Total patients (n = 9)
Age (y)	65.8 ± 11.2
Sex (f/m)	5/4
Karnofsky Pre (%)	80 [70–90]
RPA	2 [2–3]
Neurological deficit (y/n)	7/2
BM size (max. diam. cm)	3.2 ± 0.9
Total brain BM (n)	1.2 ± 0.4
Prior RT (y/n)	0/9
Oncologic Disease	
NSCLC (Adeno)	1
NSCLC (SCC)	2
Gastrointestinal (Adeno)	2
Breast cancer	3
SNC	1

Table 2
Surgical parameters and outcome: LOS = length of surgery; LORT = length of radiotherapy; RT = radiotherapy; Gy = Gray; LOH = length of hospitalization; d = days; KPS = Karnofsky Performance Score; Post = postoperative; y/n = yes/no; AE = Adverse Event; data is shown as (mean ± SD/median [interquartile range]).

	Total patients (n = 9)
LOS (min.)	163 ± 57
LORT (min.)	9 ± 2
RT Dose (Gy)	20 [18–20]
Applicator size (diam. cm)	2 [2–2.5]
Outcome	
LOH (d)	9.2 ± 7.3
KPS Post (%)	80 [80–90]
KPS Δ (%)	0 [0–0]
Neurological deficit deteriorated (y/n)	1/8
Neurological deficit improved (y/n)	1/8
Patients with AE (y/n)	2/7
AE total (n)	2

Table 3
Functional outcome correlation (Spearman correlation): y = years; KPS = Karnofsky Performance Score; Pre = preoperative; Post = postoperative; RPA = recursive partitioning analysis; BM = brain metastasis; n = number; RT = radiotherapy; Gy = Gray; LOS = length of surgery; LORT = length of radiotherapy; n.s. = non-significant; data is shown as spearman's correlation coefficient R with level of significance p.

correlation	KPS Post	KPS Δ
Age (y)	R = −0.36; n.s.	R = 0.37; n.s.
KPS Pre (%)	R = 0.54; n.s.	**R = −0.76; p = .02**
KPS Post (%)	–	R < 0.01; n.s.
KPS Δ (%)	R < 0.01; n.s.	–
RPA	**R = −0.84; p < .01**	R = 0.35; n.s.
Total BM (n)	R = 0.05; n.s.	R = 0.57; n.s.
BM size (cm)	R = −0.59; n.s.	R = 0.32; n.s.
Applicator size (cm)	R = 0.32; n.s.	R < 0.01; n.s.
RT Dose (Gy)	R < 0.01; n.s.	R < 0.01; n.s.
LOS (min.)	R = 0.30; n.s.	R = −0.64; n.s.
LORT (min.)	R = 0.25; n.s.	R = −0.32; n.s.

compared to patients without AEs (7.1d). Mean LOH was notably skewed by one patient (LOH 27d). Excluding this patient, the mean LOH was 7d (see Table 2).

3.4. Illustrative cases

3.4.1. Case 1

77-year-old male patient with a symptomatic (monoataxia of the upper limb) solitary cerebellar metastasis (maximal diameter 3.7 cm) from NSCLC (Squamous cell cancer) (TNM pT3, pN2 (3/17), M1b, L0, V0, Pn0, G2, R0), UICC: IIIB with a KPS of 80%. He underwent tumor resection via lateral suboccipital craniotomy in supine positioning. During surgery, 20 Gy were locally applied. Length of surgery was 110 min with 9 min of RT. Postoperative cranial 3T MRI shows complete resection of the BM (Fig. 1). There was not change of his KPS postoperatively whilst the preoperative hemiataxia remained. No further AEs occurred during the immediate (30d) postoperative course. The patient was discharged 4 days after the surgery.

3.4.2. Case 2

64-year-old female patient with an incidental solitary cerebellar metastasis (maximal diameter 3 cm) from and underlying breast cancer with an intact functional status (KPS 100%). She underwent resection via a median suboccipital craniotomy in sitting position. During surgery, 20 Gy were locally applied. Length of surgery was 217 min including 9 min of RT. Postoperative cranial 3T MRI showed a complete resection of the metastasis (Fig. 2) with a hematoma in the resection cavity, moderate edema and contrast agent extravasation. On postoperative day 2, the patient experienced a sudden decrease of her consciousness level. Imaging showed a hematoma compressing the IVth ventricle resulting in a consecutive occlusive hydrocephalus. Laboratory analysis showed an acute thrombocytopenia (85/nl). The patient underwent immediate ventriculostomy and hematoma evacuation via suboccipital re-craniotomy. The postoperative functional status was reduced (KPS 60%) and subsequent ventriculoperitoneal shunt insertion was necessary. The patient was discharged 27 days after the initial surgery.

4. Discussion

In this study we describe our experience with IORT during surgery for BMs resection in the PF, analyzed the direct postoperative outcome and AEs. To the best of our knowledge, this is the first series of IORT for infratentorial lesions. Another study included patients with RT in the PF without emphasizing this particular anatomic location. [3].

4.1. Baseline parameters

The study population had a median KPS of 80% [70%-90%] and low metastasis burden as most patients were operated on solitary BMs. Functional status in BM surgery is known to influence postoperative and oncological outcome. [11] In most patients, the operated lesion was symptomatic, which is a major indication for resection of BMs. Furthermore, compression of the IVth ventricle with consecutive occlusive hydrocephalus is an inherent risk of cerebellar lesions. The underlying carcinoma varied, including adeno- and squamous cell carcinomas. These might respond differently to RT. Whether this is analogous in IORT remains unclear and is the topic to future studies. The focus of this study is the direct perioperative reaction to and feasibility of IORT in the PF.

4.2. Surgical/IORT parameters

In our study, patients underwent surgery in various positions (e.g. prone, supine and sitting). The patient number is too small to draw any conclusions on preferred patient positioning for IORT. We demonstrated the feasibility in either position as no major intraoperative AE occurred in any position and the prolongation of surgery because of IORT was similar in all patients. The most favorable for surgery in the PF is a matter of ongoing discussion and depends on the exact location. Surgery of lesions in the PF might be challenging due to narrow exposure and the proximity of cranial nerves. Most patients underwent surgery for medium sized metastasis (maximal diameter 3.2 ± 0.9 cm). An applicator size of 2 cm diameter was used in most patients with a RT dose of 20 Gy using 50 kV x-rays as previously described [4]. Surgery was prolonged by mean 9 ± 2 min. Prior reports of IORT for BMs did not exclusively analyze infratentorial lesions with Cifarelli et al. reporting on six infratentorial BMs [3,12–15]. However, these manuscripts report on a combination of supra- and infratentorial lesions and do not focus on the specific characteristics of PF. The size of supratentorial BMs in prior reports ranged between 3.2 and 3.4 cm in diameter, similar to our cohort (3.2 cm) resulting in the use of applicator sizes from 2 to 2.5 cm diameter [3,12,15]. On the other side, our RT dose lied between 18 and 20 Gy, whereas a broader variability and higher doses are reported by other groups ranging from 16 to 30 Gy, which then results in longer IORT duration [3,12–28,13–15]. This variation is most likely based on local standards as a consensus for dosage in IORT for BMs has not yet been established. Based on the currently available literature it is unclear whether different RT doses are needed for IORT of infratentorial lesions. Further larger studies evaluating the optimal RT dose depending on BM location, especially regarding the radionecrosis rate and radiation induced brain edema are warranted.

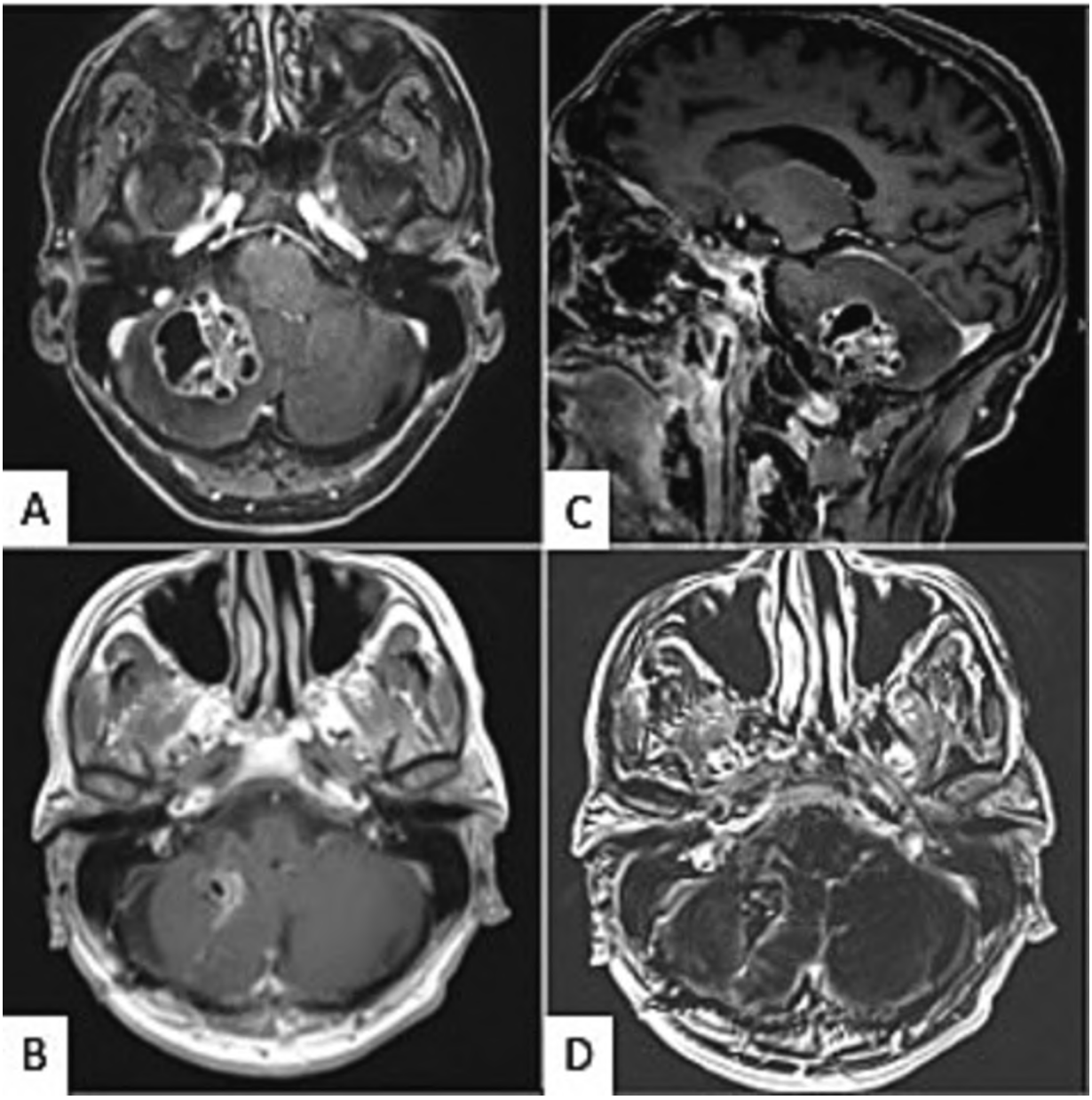

Fig. 1. Preoperative 3T T1 + Gd Imaging (A, C) shows a contrast enhancing cystic mass in the right cerebellar hemisphere. Postoperative resection control (B: T1 + Gd, D: T1 −/+ Gd subtraction) shows complete resection without significant edema.

4.3. Functional outcome

Lesions in the PF can cause severe symptoms due to vertigo, cranial nerve palsy, occlusive hydrocephalus or brainstem compression [16–18]. Therefore, safe resection to maintain a good postoperative functional status is very important in order to enable optimal oncological treatment [8,19]. Prior studies showed no functional decline at discharge compared to the preoperative status [5,14]. We confirmed these findings in our present study. This enables a quick proceeding to adjuvant oncological therapy or even acceleration of the comprehensive therapy as solitary brain lesions do not need additional adjuvant radiotherapy after IORT. Furthermore, no radiation necrosis was detected although no long-term follow-up was available [4]. Whether IORT affects functional or oncological outcome over a longer period cannot be answered at this timepoint. Nevertheless, the present study suggests, that IORT is a safe and viable treatment option not only in supratentorial but also infratentorial BMs.

4.4. Adverse events

Lesions in the posterior fossa are prone to cause symptoms due to the underlying anatomy. Depending on the type of lesion and surgical approach, complications differ and might even require surgical revision [18,20–21]. A previous report on IORT for supratentorial metastasis reported on a complication rate of 11% [14]. In our series 2 out of 9 patients experienced a postoperative AE (22%) requiring revision surgery including one SSI. Current reports do not indicate an increased AE rate in patients undergoing BM surgery with IORT [3–5]. Nevertheless, even in case of AE reducing the functional status and possibly delaying adjuvant systemic therapy, one major part of adjuvant therapy (radiation of the resection cavity) is already applied. Whether IORT influences postoperative AEs and if this leads to better long-term oncological control needs to be addressed in future, larger studies. Wound healing plays an important role in oncological brain surgery as it might delay adjuvant therapy including RT [22,23]. There have been contradictory

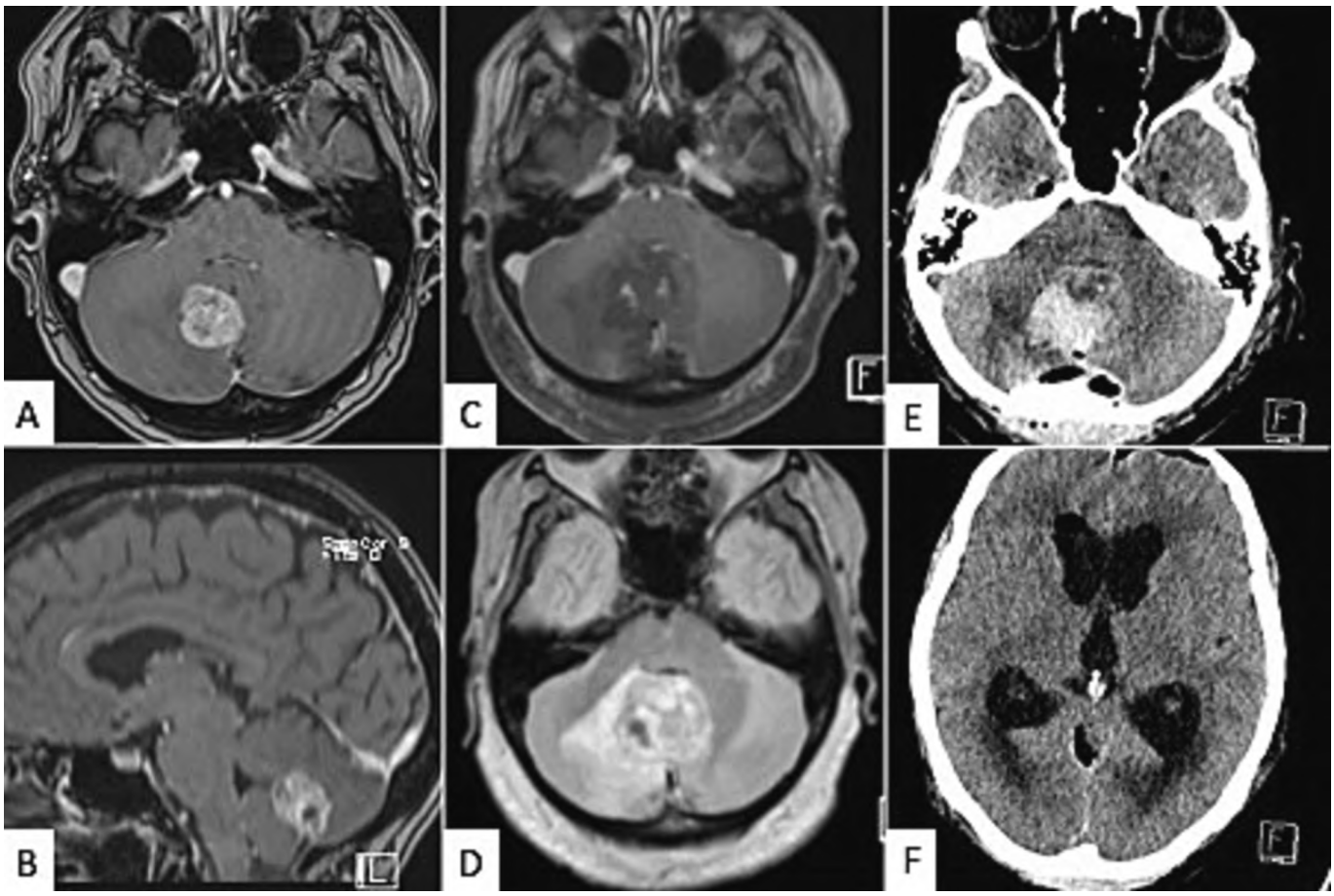

Fig. 2. Preoperative 3T T1 + Gd Imaging (A, B) shows a contrast enhancing mass in the right cerebellar hemisphere. Postoperative resection control (C: T1 + Gd, D: FLAIR) confirms intracavitary hematoma and perifocal edema. After acute decline of vigilance, the emergency CT shows a compressive hematoma (E) with acute occlusive hydrocephalus (F).

results on whether IORT increases SSIs [24,25]. Therefore, especially in IORT for BMs, further larger studies need to be conducted to answer the remaining questions.

4.5. Future perspectives for intraoperative radiotherapy in surgery for brain metastasis

Intraoperative radiotherapy is increasingly applied in oncological surgery including HGG and BMs [2–4]. Whether it improves local control and prevents leptomeningeal disease remains unclear. Interest also exists with regards to whether neoadjuvant RT for BMs reduces the risk of leptomeningeal disease [26,27]. Furthermore, radiation of BMs might create an immune reaction by altering the blood brain barrier and exposing neoplastic tissue [28]. Whether neoadjuvant RT alters the molecular profile of BMs is unknown. If IORT might enhance immune reactions, while keeping the possibility to harvest "fresh" native tissue will need to be answered in future studies.

4.6. Study limitations

This study has several limitations. First, the retrospective nature of the study does not allow to draw any conclusion on causality. Second, the small number of patients limits the meaningfulness of the results. This is due to the relatively low rate of procedures performed eligible to analysis (surgery for BMs in the PF fulfilling the criteria for the application of IORT). Nevertheless, this study allows to claim feasibility of this technique without an increased AE rate. Various types of underlying oncological disease were included in this analysis. Whether our findings ultimately affect the oncological prognosis remains unclear, as no long-term data was collected and the focus of our study was on short term outcome, for which the underlying oncologic disease plays a limited role. This would be more important for long term follow-up looking at progression free survival and mortality. In this study, despite its limitations, we describe the practical use of IORT in the PF to encourage further studies, that can address the long-term oncologic outcome.

5. Conclusion

In this retrospective study, the direct postoperative course, morbidity and mortality of patients undergoing IORT during surgery for intraaxial BM in the PF is reported in detail. Functional outcome and AE rates do indicate safety of IORT during surgery of PF lesions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Le Rhun E, Guckenberger M, Smits M, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021;32(11):1332–47. https://doi.org/10.1016/j.annonc.2021.07.016.

[2] Giordano FA, Brehmer S, Murle B, et al. Intraoperative radiotherapy in newly diagnosed glioblastoma (INTRAGO): An open-label, dose-escalation phase I/II trial. *Neurosurgery* 2019;84(1):41–9. https://doi.org/10.1093/neuros/nyy018.

[3] Cifarelli CP, Brehmer S, Vargo JA, et al. Intraoperative radiotherapy (IORT) for surgically resected brain metastases: outcome analysis of an international cooperative study. J Neurooncol 2019;145(2):391–7. https://doi.org/10.1007/s11060-019-03309-6.
[4] Kahl KH, Balagiannis N, Hock M, et al. Intraoperative radiotherapy with low-energy x-rays after neurosurgical resection of brain metastases-an Augsburg University Medical Center experience. Strahlenther Onkol 2021;197(12):1124–30. https://doi.org/10.1007/s00066-021-01831-z.
[5] Steininger K, Kahl KH, Konietzko I, et al. Intraoperative radiotherapy during awake craniotomies: preliminary results of a single-center case series. Neurosurg Rev 2022. https://doi.org/10.1007/s10143-022-01838-9.
[6] Schroeder T, Bittrich P, Kuhne JF, et al. Mapping distribution of brain metastases: does the primary tumor matter? J Neurooncol 2020;147(1):229–35. https://doi.org/10.1007/s11060-020-03419-6.
[7] Cardinal T, Pangal D, Strickland BA, et al. Anatomical and topographical variations in the distribution of brain metastases based on primary cancer origin and molecular subtypes: a systematic review. Neurooncol Adv 2022;4(1):vdab170. https://doi.org/10.1093/noajnl/vdab170.
[8] Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2(3):187–93. https://doi.org/10.1200/JCO.1984.2.3.187.
[9] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205–13.
[10] Mak PH, Campbell RC, Irwin MG, American Society of A. The ASA Physical Status Classification: inter-observer consistency. American Society of Anesthesiologists. Anaesth Intensive Care 2002;30(5):633–40. https://doi.org/10.1177/0310057X0203000516.
[11] Chambless LB, Kistka HM, Parker SL, Hassam-Malani L, McGirt MJ, Thompson RC. The relative value of postoperative versus preoperative Karnofsky Performance Scale scores as a predictor of survival after surgical resection of glioblastoma multiforme. J Neurooncol 2015;121(2):359–64. https://doi.org/10.1007/s11060-014-1640-x.
[12] Vargo JA, Sparks KM, Singh R, Jacobson GM, Hack JD, Cifarelli CP. Feasibility of dose escalation using intraoperative radiotherapy following resection of large brain metastases compared to post-operative stereotactic radiosurgery. J Neurooncol 2018;140(2):413–20. https://doi.org/10.1007/s11060-018-2968-4.
[13] Diehl CD, Pigorsch SU, Gempt J, et al. Low-energy X-Ray intraoperative radiation therapy (Lex-IORT) for resected brain metastases: A single-institution experience. Cancers (Basel) 2022;15(1). https://doi.org/10.3390/cancers15010014.
[14] Hamed M, Potthoff AL, Layer JP, et al. Benchmarking safety indicators of surgical treatment of brain metastases combined with intraoperative radiotherapy: Results of prospective observational study with comparative matched-pair analysis. Cancers (Basel) 2022;14(6). https://doi.org/10.3390/cancers14061515.
[15] Krauss P, Steininger K, Motov S, et al. Resection of supratentorial brain metastases with intraoperative radiotherapy. Is it safe? Analysis and experiences of a single center cohort. Front Surg 2022;9:1071804. https://doi.org/10.3389/fsurg.2022.1071804.
[16] Roux A, Botella C, Still M, et al. Posterior fossa metastasis-associated obstructive hydrocephalus in adult patients: literature review and practical considerations from the Neuro-Oncology Club of the French Society of Neurosurgery. World Neurosurg 2018;117:271–9. https://doi.org/10.1016/j.wneu.2018.06.084.
[17] Ganslandt O, Merkel A, Schmitt H, et al. The sitting position in neurosurgery: indications, complications and results. a single institution experience of 600 cases. Acta Neurochir (Wien) 2013;155(10):1887–93. https://doi.org/10.1007/s00701-013-1822-x.
[18] Ersoy TF, Mokhtari N, Brainman D, et al. Surgical treatment of cerebellar metastases: survival benefits, complications and timing issues. Cancers (Basel) 2021;13(21). https://doi.org/10.3390/cancers13215263.
[19] Sunderland GJ, Jenkinson MD, Zakaria R. Surgical management of posterior fossa metastases. J Neurooncol 2016;130(3):535–42. https://doi.org/10.1007/s11060-016-2254-2.
[20] Aftahy AK, Jorger AK, Hillebrand S, et al. The bigger the better? Analysis of surgical complications and outcome of the retrosigmoid approach in 449 oncological cases. Front Oncol 2022;12:938703. https://doi.org/10.3389/fonc.2022.938703.
[21] Himes BT, Mallory GW, Abcejo AS, et al. Contemporary analysis of the intraoperative and perioperative complications of neurosurgical procedures performed in the sitting position. J Neurosurg 2017;127(1):182–8. https://doi.org/10.3171/2016.5.JNS152328.
[22] Stienen MN, Moser N, Krauss P, Regli L, Sarnthein J. Incidence, depth, and severity of surgical site infections after neurosurgical interventions. Acta Neurochir (Wien) 2019;161(1):17–24. https://doi.org/10.1007/s00701-018-3745-z.
[23] Dormand EL, Banwell PE, Goodacre TE. Radiotherapy and wound healing. Int Wound J 2005;2(2):112–27. https://doi.org/10.1111/j.1742-4801.2005.00079.x.
[24] Lasso JM, Pinilla C, Vasquez W, Asencio JM. The effect of intraoperative radiotherapy on healing and complications after sacrectomy and immediate reconstruction. Ann Plast Surg 2021;86(6):688–94. https://doi.org/10.1097/SAP.0000000000002571.
[25] Kraus-Tiefenbacher U, Bauer L, Kehrer T, Hermann B, Melchert F, Wenz F. Intraoperative radiotherapy (IORT) as a boost in patients with early-stage breast cancer – acute toxicity. Onkologie 2006;29(3):77–82. https://doi.org/10.1159/000091160.
[26] Takami H, Nassiri F, Moraes FY, et al. A phase II study of neoadjuvant stereotactic radiosurgery for large brain metastases: clinical trial protocol. Neurosurgery 2020;87(2):403–7. https://doi.org/10.1093/neuros/nyz442.
[27] Routman DM, Yan E, Vora S, et al. Preoperative stereotactic radiosurgery for brain metastases. Front Neurol 2018;9:959. https://doi.org/10.3389/fneur.2018.00959.
[28] Lumniczky K, Szatmari T, Safrany G. Ionizing radiation-induced immune and inflammatory reactions in the brain. Front Immunol 2017;8:517. https://doi.org/10.3389/fimmu.2017.00517.