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Management of recurrent malignant glioma – neurosurgical strategies

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Management der rezivierten malignen Gliome – neurochirurgische Strategien

Zusammenfassung. Bei PatientInnen mit rezidivierten malignen Gliomen gibt es auch für das neurochirurgische Vorgehen keine akkordierten Standards. Zur Entscheidungsfindung hat stets der mögliche Benefit für den Patienten/die Patientin im Vordergrund zu stehen. Oft ist unter der Ausnützung der modernen Diagnosemethoden und der optimierten Resektion mit Hilfe von Neuronavigation und Anwendung von 5-Ala *in vivo* Fluoreszenz eine erneute Tumorresektion oder Verkleinerung möglich, die es erlaubt, Symptomverbesserung und eine längere Überlebenszeit zu erreichen.

Schlüsselwörter: Rezidiviertes malignes Gliom, neurochirurgische Intervention, individualisiertes Vorgehen, 5-Ala *in vivo* fluoreszenz

Summary. There is currently no standard for neurosurgical interventions in patients with recurrent high grade gliomas. An individualized approach is recommended as well for decision-making as for planning an intervention with resection of the outmost possible amount of tumor tissue while preserving neurological function and thus quality of life. Recent technical developments of imaging and of neuronavigation and visualization of tumor tissue with *in vivo* fluorescence with 5-Ala have proved helpful in improving symptoms and prolonging survival times also for patients with recurrent malignant gliomas.

Key words: Neurosurgical intervention, recurrent malignant glioma, individualized approach, 5-Ala *in vivo* fluorescence

Introduction

Despite some progress in the treatment of glioblastoma almost all patients will experience disease recurrence and will ultimately die of their disease. Overall survival from recurrence or progression is in the range of 5–10 months, with a 1-year survival rate of 10–15%. Gliomas are still the great challenge for the neurosurgeon, not only from the point of technical skills but also from the point of resecting the outmost possible amount of tumor tissue while preserving neurological function and thus quality of life. Meanwhile there are enough data to demonstrate that a total or gross total resection and a good Karnofsky performance correlate with prolonged survival. Pre- and intraoperative guidance by neuronavigation, ultrasound and fluorescence guided resection and intraoperative photodynamic treatment are the major new achievements in order to facilitate tumor resection and cytoreduction to the outmost extent. In addition, preoperative metabolic imaging by FET or FLT-PET allows to resect the most active part of tumor e.g. in case of location in eloquent areas.

Neurosurgical strategies

In contrast to the primary treatment, there is no "standard of care" for the therapeutic management of recurrent high grade gliomas. The options include reoperation, re-irradiation, alternative schedule Temozolomide (TMZ) regimens, and various regiments of CHT and novel experimental treatment protocols.

There are various reports on the reoperation of recurrent glioblastoma multiforme [1–3]. In over 85% of the cases the tumor recur locally, therefore the reoperation is feasible from the neurosurgical point of view. The rate of reoperation depends on the centers ranging from 10 to 33%.

The median overall survival after reoperation with surgery alone without adjuvant treatment is between 2

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and 3 months, whereas with adjuvant CHT and/or XRT the median survival ranges up to 12 months [4].

In recent years, fluorescence guided tumor resection has emerged as a promising technique for the optimization of surgery in malignant gliomas. Using specifically modified microscopes, intraoperative visualisation of fluorescing (residual) glioma tissue is facilitated. In glioma surgery, frequently 5-aminolevulinic acid (5-ALA) is used for fluorescence guided tumor resection: 5-ALA leads to intracellular accumulation of strongly fluorescing protoporphyrin IX in malignant glioma tissue [5]. Stummer et al. demonstrated in a randomized controlled multicenter phase 3 trial on primary malignant gliomas that the use of 5-ALA leads to a significantly higher frequency of complete resections of the contrast-enhancing tumor area as compared with the conventionally operated white light control group (65% *versus* 36%, respectively) [6]. Patients in the 5-ALA fluorescence-guided resection group revealed as well a significantly prolonged 6-month progression-free survival as compared to the control group (41% *versus* 21%, respectively). Recently, Nabavi et al. demonstrated in a multicenter phase II study that 5-ALA fluorescence has a high predictive value for the visualisation of recurrent gliomas as well [7]. Therefore, 5-ALA fluorescence guided tumor resection plays also an important role in the surgery of recurrent malignant gliomas (median overall survival was 7.9 months). The combination of fluorescence guided resection and intraoperative photodynamic therapy with a chlorine compound named FOSCAN resulted in a significant prolongation of survival in patients with recurrent glioblastoma [8].

In our own series of 320 patients presenting with histological verified GBM, 91 underwent reoperation (28.4%) which was followed by CHT and in some cases re-radiation. The overall survival time of all patients was 12.3 month. The 91 patients who were reoperated demonstrated a median OS of 18.9 month, whereas those patients without reoperation showed a median OS of 9, 7 month respectively [8].

In our cohort of patients the following factors were significant in terms of overall survival; KPS, CHT, XRT, resection grade, and age [9, data in preparation].

Our data correspond favorably with the recent literature, except that our patients had a better outcome.

We recommend reoperation if the following questions could be answered positively.

- Is the patient conditions >KPI 60%, WHO II?
- Is the recurrent tumor not crossing the midline?
- Is the tumor not involving eloquent areas?
- Could the tumor be resected more than >70%?
- Are further CHT and/or re-radiation planed?
- Will the patient condition benefit from reoperation?
- Does the patient wish to receive further treatment?

Conclusion

Surgical treatment of recurrent glioblastoma multiforme should always be considered, if the patient will improve after surgery and adjuvant therapies are further options. Re-surgery as a *standalone treatment* for recurrent high grade gliomas should not be considered.

Conflict of interest

The authors declare that there is no conflict of interest.

Literature

[1] Barbagallo GM, Jenkinson MD, Brodbelt AR. 'Recurrent' glioblastoma multiforme, when should we reoperate? Br J Neurosurg, 22: 452–455, 2008.

[2] Guyotat J, Signorelli F, Frappaz D, et al. Is reoperation for recurrence of glioblastoma justified? Oncol Rep, 7: 899–904, 2000.

[3] Pinsker M, Lumenta C. Experiences with reoperation on recurrent glioblastoma multiforme. Zentralbl Neurochir, 62: 43–47, 2001.

[4] Mandl ES, Dirven CM, Buis DR, et al. Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy. Surg Neurol, 69: 506–509, 2008; discussion 509.

[5] Stummer W, Stocker S, Novotny A, et al. In vitro and in vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid. J Photochem Photobiol B, 45: 160–169, 1998.

[6] Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol, 7: 392–401, 2006.

[7] Nabavi A, Thurm H, Zountsas B, et al.; 5-ALA Recurrent Glioma Study Group. Five-aminolevulinic acid for fluorescence-guided resection of recurrent malignant gliomas: a phase ii study. Neurosurgery, 65: 1070–1076, 2009.

[8] Kostron H, Fiegele Th, Akatuna E. Combination of FOSCAN® mediated fluorescence guided resection and photodynamic treatment as new therapeutic concept for malignant brain tumors. Med Laser Appl, 21: 285–290, 2006.

[9] Bauer R, Kostron H. Influence of reoperation of overall survival in recurrent Glioblastoma multiforme. 2010. (in preparation)