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What’s up in Neurooncology
Update Neuroonkolgie 2017

Handout
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## Glioblastome – klinische Aspekte

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Glioblastome – klinische Aspekte

Prof. Dr. med. Dr. rer. Nat. Ghazaleh Tabatabai (Tübingen)

Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial.

Weller M1, Butowski N2, Tran DD3, Recht LD4, Lim M5, Hirte H6, Ashby L7, Mechtler L8, Goldlust SA9, Iwamoto F10, Drappatz J11, O’Rourke DM12, Wong M13, Hamilton MG14, Finocchiaro G15, Perry J16, Wick W17, Green J18, He Y18, Turner CD18, Yellin MJ18, Keler T18, Davis TA18, Stupp R19, Sampson JH20; ACT IV trial investigators.


BACKGROUND

Rindopepimut (also known as CDX-110), a vaccine targeting the EGFR deletion mutation EGFRvIII, consists of an EGFRvIII-specific peptide conjugated to keyhole limpet haemocyanin. In the ACT IV study, we aimed to assess whether or not the addition of rindopepimut to standard chemotherapy is able to improve survival in patients with EGFRvIII-positive glioblastoma.

METHODS

In this randomised, double-blind, phase 3 trial, we recruited patients aged 18 years and older with glioblastoma from 165 hospitals in 22 countries. Eligible patients had newly diagnosed glioblastoma confirmed to express EGFRvIII by central analysis, and had undergone maximal surgical resection and completion of standard chemoradiation without progression. Patients were stratified by European Organisation for Research and Treatment of Cancer recursive partitioning analysis class, MGMT promoter methylation, and geographical region, and randomly assigned (1:1) with a prespecified randomisation sequence (block size of four) to receive rindopepimut (500 μg admixed with 150 μg GM-CSF) or control (100 μg keyhole limpet haemocyanin) via monthly intradermal injection until progression or intolerance, concurrent with standard oral temozolomide (150-200 mg/m² for 5 of 28 days) for 6-12 cycles or longer. Patients, investigators, and the trial funder were masked to treatment allocation. The primary endpoint was overall survival in patients with minimal residual disease (MRD; enhancing tumour <2 cm² post-chemoradiation by central review), analysed by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01480479.

FINDINGS

Between April 12, 2012, and Dec 15, 2014, 745 patients were enrolled (405 with MRD, 338 with significant residual disease [SRD], and two unevaluable) and randomly assigned to rindopepimut and temozolomide (n=371) or control and temozolomide (n=374). The study
was terminated for futility after a preplanned interim analysis. At final analysis, there was no significant difference in overall survival for patients with MRD: median overall survival was 20.1 months (95% CI 18.5-22.1) in the rindopepimut group versus 20.0 months (18.1-21.9) in the control group (HR 1.01, 95% CI 0.79-1.30; p=0.93). The most common grade 3-4 adverse events for all 369 treated patients in the rindopepimut group versus 372 treated patients in the control group were: thrombocytopenia (32 [9%] vs 23 [6%]), fatigue (six [2%] vs 19 [5%]), brain oedema (eight [2%] vs 11 [3%]), seizure (nine [2%] vs eight [2%]), and headache (six [2%] vs ten [3%]). Serious adverse events included seizure (18 [5%] vs 22 [6%]) and brain oedema (seven [2%] vs 12 [3%]). 16 deaths in the study were caused by adverse events (nine [4%] in the rindopepimut group and seven [3%] in the control group), of which one—a pulmonary embolism in a 64-year-old male patient after 11 months of treatment—was assessed as potentially related to rindopepimut.

INTERPRETATION

Rindopepimut did not increase survival in patients with newly diagnosed glioblastoma. Combination approaches potentially including rindopepimut might be required to show efficacy of immunotherapy in glioblastoma.
Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG.


BACKGROUND

Radiation with concurrent and adjuvant (6 cycles) temozolomide (TMZ) is the established standard of postsurgical care for newly diagnosed glioblastoma (GBM). This regimen has been adopted with variations, including extending TMZ beyond 6 cycles. The optimal duration of maintenance therapy remains controversial.

METHODS

We performed pooled analysis of individual patient data from 4 randomized trials for newly diagnosed GBM. All patients who were progression free 28 days after cycle 6 were included. The decision to continue TMZ was per local practice and standards, and at the discretion of the treating physician. Patients were grouped into those treated with 6 cycles and those who continued beyond 6 cycles. Progression-free and overall survival were compared, adjusted by age, performance status, resection extent, and MGMT methylation.

RESULTS

A total of 2214 GBM patients were included in the 4 trials. Of these, 624 qualified for analysis 291 continued maintenance TMZ until progression or up to 12 cycles, while 333 discontinued TMZ after 6 cycles. Adjusted for prognostic factors, treatment with more than 6 cycles of TMZ was associated with a somewhat improved progression-free survival (hazard ratio [HR] 0.80 [0.65-0.98], P = .03), in particular for patients with methylated MGMT (n = 342, HR 0.65 [0.50-0.85], P < .01). However, overall survival was not affected by the number of TMZ cycles (HR = 0.92 [0.71-1.19], P = .52), including the MGMT methylated subgroup (HR = 0.89 [0.63-1.26], P = .51).

CONCLUSIONS

Continuing TMZ beyond 6 cycles was not shown to increase overall survival for newly diagnosed GBM.
Limited role for extended maintenance temozolomide for newly diagnosed glioblastoma.


OBJECTIVE
To explore an association with survival of modifying the current standard of care for patients with newly diagnosed glioblastoma of surgery followed by radiotherapy plus concurrent and 6 cycles of maintenance temozolomide chemotherapy (TMZ/RT→TMZ) by extending TMZ beyond 6 cycles.

METHODS
The German Glioma Network cohort was screened for patients with newly diagnosed glioblastoma who received TMZ/RT→TMZ and completed ≥6 cycles of maintenance chemotherapy without progression. Associations of clinical patient characteristics, molecular markers, and residual tumor determined by magnetic resonance imaging after 6 cycles of TMZ with progression-free survival (PFS) and overall survival (OS) were analyzed with the log-rank test. Multivariate analyses using the Cox proportional hazards model were performed to assess associations of prolonged TMZ use with outcome.

RESULTS
Sixty-one of 142 identified patients received at least 7 maintenance TMZ cycles (median 11, range 7-20). Patients with extended maintenance TMZ treatment had better PFS (20.5 months, 95% confidence interval [CI] 17.7-23.3, vs 17.2 months, 95% CI 10.2-24.2, p = 0.035) but not OS (32.6 months, 95% CI 28.9-36.4, vs 33.2 months, 95% CI 25.3-41.0, p = 0.126). However, there was no significant association of prolonged TMZ chemotherapy with PFS (hazard ratio [HR] = 0.8, 95% CI 0.4-1.6, p = 0.559) or OS (HR = 1.6, 95% CI 0.8-3.3, p = 0.218) adjusted for age, extent of resection, Karnofsky performance score, presence of residual tumor, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, or isocitrate dehydrogenase (IDH) mutation status.

CONCLUSION
These data may not support the practice of prolonging maintenance TMZ chemotherapy beyond 6 cycles.
CLASSIFICATION OF EVIDENCE

This study provides Class III evidence that in patients with newly diagnosed glioblastoma, prolonged TMZ chemotherapy does not significantly increase PFS or OS.

Prolonged Temozolomide Maintenance Therapy in Newly Diagnosed Glioblastoma.


BACKGROUND

The impact of prolonging temozolomide (TMZ) maintenance beyond six cycles in newly diagnosed glioblastoma (GBM) remains a topic of discussion. We investigated the effects of prolonged TMZ maintenance on progression-free survival (PFS) and overall survival (OS).

PATIENTS AND METHODS

In this retrospective single-center cohort study, we included patients with GBM who were treated with radiation therapy with concomitant and adjuvant TMZ. For analysis, patients were considered who either completed six TMZ maintenance cycles (group B), continued with TMZ therapy beyond six cycles (group C), or stopped TMZ maintenance therapy within the first six cycles (group A). Patients with progression during the first six TMZ maintenance cycles were excluded.

RESULTS

Clinical data from 107 patients were included for Kaplan-Meier analyses and 102 for Cox regressions. Median PFS times were 8.1 months (95% confidence interval [CI] 6.1-12.4) in group A, 13.7 months (95% CI 10.6-17.5) in group B, and 20.9 months (95% CI 15.2-43.5) in group C. At first progression, response rates of TMZ/lomustine rechallenge were 47% in group B and 13% in group C. Median OS times were 12.7 months (95% CI 10.3-16.8) in group A, 25.2 months (95% CI 17.7-55.5) in group B, and 28.6 months (95% CI 24.4-open) in group C. Nevertheless, multivariate Cox regression for patients in group C compared with group B that accounted for imbalances of other risk factors showed no different relative risk (RR) for OS (RR 0.77, p = .46).

CONCLUSION

Our data do not support a general extension of TMZ maintenance therapy beyond six cycles.

The Oncologist 2017;22:570-575 IMPLICATIONS FOR PRACTICE

Radiation therapy with concomitant and adjuvant temozolomide (TMZ) maintenance therapy is still the standard of care in patients below the age of 65 years in newly diagnosed glioblastoma. However, in clinical practice, many centers continue TMZ maintenance therapy
beyond six cycles. The impact of this continuation is controversial and has not yet been addressed in prospective randomized clinical trials. We compared the effect of more than six cycles of TMZ in comparison with exactly six cycles on overall survival (OS) and progression-free survival (PFS) by multivariate analysis and found a benefit in PFS but not OS. Thus, our data do not suggest prolonging TMZ maintenance therapy beyond six cycles, which should be considered in neurooncological practice.
Lomustine and Bevacizumab in Progressive Glioblastoma.


BACKGROUND

Bevacizumab is approved for the treatment of patients with progressive glioblastoma on the basis of uncontrolled data. Data from a phase 2 trial suggested that the addition of bevacizumab to lomustine might improve overall survival as compared with monotherapies. We sought to determine whether the combination would result in longer overall survival than lomustine alone among patients at first progression of glioblastoma.

METHODS

We randomly assigned patients with progression after chemoradiation in a 2:1 ratio to receive lomustine plus bevacizumab (combination group, 288 patients) or lomustine alone (monotherapy group, 149 patients). The methylation status of the promoter of O6-methylguanine-DNA methyltransferase (MGMT) was assessed. Health-related quality of life and neurocognitive function were evaluated at baseline and every 12 weeks. The primary end point of the trial was overall survival.

RESULTS

A total of 437 patients underwent randomization. The median number of 6-week treatment cycles was three in the combination group and one in the monotherapy group. With 329 overall survival events (75.3%), the combination therapy did not provide a survival advantage; the median overall survival was 9.1 months (95% confidence interval [CI], 8.1 to 10.1) in the combination group and 8.6 months (95% CI, 7.6 to 10.4) in the monotherapy group (hazard ratio for death, 0.95; 95% CI, 0.74 to 1.21; P=0.65). Locally assessed progression-free survival was 2.7 months longer in the combination group than in the monotherapy group: 4.2 months versus 1.5 months (hazard ratio for disease progression or death, 0.49; 95% CI, 0.39 to 0.61; P<0.001). Grade 3 to 5 adverse events occurred in 63.6% of the patients in the combination group and 38.1% of the patients in the monotherapy group. The addition of bevacizumab to lomustine affected neither health-related quality of life nor neurocognitive function. The MGMT status was prognostic.

CONCLUSIONS

Despite somewhat prolonged progression-free survival, treatment with lomustine plus bevacizumab did not confer a survival advantage over treatment with lomustine alone in patients with progressive glioblastoma.
Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter-hypermethylation - the NCT Neuro Master Match (N2M2) pilot study.


INTRODUCTION

O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is a predictive biomarker in glioblastoma patients. Glioblastoma without hypermethylated MGMT promoter are largely resistant to treatment with temozolomide. These patients are in particular need of new treatment approaches, which are offered by biomarker-driven clinical trials with targeted drugs based on molecular characterization of individual tumors.

METHODS

In preparation for an upcoming clinical study, a comprehensive molecular profiling approach was undertaken on tissues from 43 glioblastoma patients harboring an unmethylated MGMT promoter at diagnosis. The diagnostic pipeline covered various levels of molecular characteristics including whole-exome sequencing, low-coverage whole-genome sequencing, RNA sequencing as well as microarray-based gene expression profiling and DNA methylation arrays.

RESULTS

Complex multilayer molecular diagnostics were feasible in this setting with a median turn-around time of 4-5 weeks from surgery to the molecular tumor board. In 35% of cases potentially relevant therapeutic decisions were derived from the data. Alterations were most frequently found in receptor tyrosine kinases, members of the phosphoinositide 3-kinase / Akt / mechanistic target of rapamycin and mitogen-activated protein kinase pathway as well as cell cycle control and p53 regulation cascades. Individual tumors harbored clonal alterations such as oncogenic fusions of tyrosine kinases which constitute promising targets for targeted therapies. A prioritization algorithm is proposed to allocate patients with multiple targets to the potentially best treatment option.

CONCLUSION

With this feasibility study, a comprehensive molecular profiling approach for patients with newly diagnosed glioblastoma harboring an unmethylated MGMT promoter is presented. Analyses in this pilot cohort serve as a basis for trials based on targetable alterations and on the question of allocation of patients to the best treatment arm.
Epidermal Growth Factor Receptor Variant III (EGFRvIII) Positivity in EGFR-Amplified Glioblastomas: Prognostic Role and Comparison between Primary and Recurrent Tumors.


PURPOSE

Approximately 40% of all glioblastomas have amplified the EGFR gene, and about half of these tumors express the EGFRvIII variant. The prognostic role of EGFRvIII in EGFR-amplified glioblastoma patients and changes in EGFRvIII expression in recurrent versus primary glioblastomas remain controversial, but such data are highly relevant for EGFRvIII-targeted therapies.

EXPERIMENTAL DESIGN

EGFR-amplified glioblastomas from 106 patients were assessed for EGFRvIII positivity. Changes in EGFR amplification and EGFRvIII status from primary to recurrent glioblastomas were evaluated in 40 patients with EGFR-amplified tumors and 33 patients with EGFR-nonamplified tumors. EGFR single-nucleotide variants (SNV) were assessed in 27 patients. Data were correlated with outcome and validated in 150 glioblastoma patients from The Cancer Genome Atlas (TCGA) consortium.

RESULTS

Sixty of 106 EGFR-amplified glioblastomas were EGFRvIII-positive (56.6%). EGFRvIII positivity was not associated with different progression-free or overall survival. EGFRvIII status was unchanged at recurrence in 35 of 40 patients with EGFR-amplified primary tumors (87.5%). Four patients lost and one patient gained EGFRvIII positivity at recurrence. None of 33 EGFR-nonamplified glioblastomas acquired EGFR amplification or EGFRvIII at recurrence. EGFR SNVs were frequent in EGFR-amplified tumors, but were not linked to survival.

CONCLUSIONS

EGFRvIII and EGFR SNVs are not prognostic in EGFR-amplified glioblastoma patients. EGFR amplification is retained in recurrent glioblastomas. Most EGFRvIII-positive glioblastomas maintain EGFRvIII positivity at recurrence. However, EGFRvIII expression may change in a subset of patients at recurrence, thus repeated biopsy with reassessment of EGFRvIII status is recommended for patients with recurrent glioblastoma to receive EGFRvIII-targeting agents.
Maligne Gliome – experimentell

Prof. Dr. Christian Hartmann (Hannover)

#1 – Glioblastome – Was gibt es noch?

H3-/IDH-wild type pediatric glioblastoma is comprised of molecularly and prognostically distinct subtypes with associated oncogenic drivers.


Pediatric glioblastoma (pedGBM) is an extremely aggressive pediatric brain tumor, accounting for ~6% of all central nervous system neoplasms in children. Approximately half of pedGBM harbor recurrent somatic mutations in histone 3 variants or, infrequently, IDH1/2. The remaining subset of pedGBM is highly heterogeneous, and displays a variety of genomic and epigenetic features. In the current study, we aimed to further stratify an H3-/IDH-wild type (wt) pedGBM cohort assessed through genome-wide molecular profiling. As a result, we identified three molecular subtypes of these tumors, differing in their genomic and epigenetic signatures as well as in their clinical behavior. We designated these subtypes 'pedGBM_MYCN' (enriched for MYCN amplification), 'pedGBM_RTK1' (enriched for PDGFRA amplification) and 'pedGBM_RTK2' (enriched for EGFR amplification). These molecular subtypes were associated with significantly different outcomes, i.e. pedGBM_RTK2 tumors show a significantly longer survival time (median OS 44 months), pedGBM_MYCN display extremely poor outcomes (median OS 14 months), and pedGBM_RTK1 tumors harbor an intermediate prognosis. In addition, the various molecular subtypes of H3-/IDH-wt pedGBM were clearly distinguishable from their adult counterparts, underlining their biological distinctiveness. In conclusion, our study demonstrates significant molecular heterogeneity of H3-/IDH-wt pedGBM in terms of DNA methylation and cytogenetic alterations. The recognition of three molecular subtypes of H3-/IDH-wt pedGBM further revealed close correlations with biological parameters and clinical outcomes and may therefore, be predictive of response to standard treatment protocols, but could also be useful for stratification for novel, molecularly based therapies.
Integrated Molecular Meta-Analysis of 1,000 Pediatric High-Grade and Diffuse Intrinsic Pontine Glioma.


We collated data from 157 unpublished cases of pediatric high-grade glioma and diffuse intrinsic pontine glioma and 20 publicly available datasets in an integrated analysis of >1,000 cases. We identified co-segregating mutations in histone-mutant subgroups including loss of FBXW7 in H3.3G34R/V, TOP3A rearrangements in H3.3K27M, and BCOR mutations in H3.1K27M. Histone wild-type subgroups are refined by the presence of key oncogenic events or methylation profiles more closely resembling lower-grade tumors. Genomic aberrations increase with age, highlighting the infant population as biologically and clinically distinct. Uncommon pathway dysregulation is seen in small subsets of tumors, further defining the molecular diversity of the disease, opening up avenues for biological study and providing a basis for functionally defined future treatment stratification.
H3.3 K27M Cooperates with Trp53 Loss and PDGFRA Gain in Mouse Embryonic Neural Progenitor Cells to Induce Invasive High-Grade Gliomas.


Gain-of-function mutations in histone 3 (H3) variants are found in a substantial proportion of pediatric high-grade gliomas (pHGG), often in association with TP53 loss and platelet-derived growth factor receptor alpha (PDGFRA) amplification. Here, we describe a somatic mouse model wherein H3.3$^{K27M}$ and Trp53 loss alone are sufficient for neoplastic transformation if introduced in utero. H3.3$^{K27M}$-driven lesions are clonal, H3K27me3 depleted, Olig2 positive, highly proliferative, and diffusely spreading, thus recapitulating hallmark molecular and histopathological features of pHGG. Addition of wild-type PDGFRA decreases latency and increases tumor invasion, while ATRX knockdown is associated with more circumscribed tumors. H3.3$^{K27M}$-tumor cells serially engraft in recipient mice, and preliminary drug screening reveals mutation-specific vulnerabilities. Overall, we provide a faithful H3.3$^{K27M}$-pHGG model which enables insights into oncohistone pathogenesis and investigation of future therapies.
Evidence of H3 K27M mutations in posterior fossa ependymomas.


PMID: 27539613

CASE REPORT

Histone 3 (H3) K27M mutations are considered to be a genetic hallmark of diffuse midline gliomas, including high-grade astrocytomas and diffuse intrinsic pontine gliomas (DIPG) [3]. Similar to IDH-mutated gliomas in adults, these mutations are associated with alterations in the epigenetic profile of tumor cells, and are thought to represent a main driving factor in gliomagenesis [2, 8]. In diffuse midline gliomas, H3K27M mutations have been demonstrated to induce de-repression of pro-oncogenic transcription factors by global reduction of histone 3 K27 trimethylation (H3K27me3) [2, 8]. Reportedly, H3K27M mutations are exceedingly rare in tumors other than in diffuse midline gliomas [6, 7, 14].

The possibility of an H3K27M mutation occurring in other brain neoplasms cannot, however, be excluded a priori. We report here the very unexpected finding of H3K27M mutations in two Group A posterior fossa ependymomas (PF-EPN-A), an aggressive subgroup of tumors with relatively stable genomes and no well-characterized oncogenic driving event [9, 10].
H3 K27M mutations are extremely rare in posterior fossa group A ependymoma.


PMID: 28623522

BACKGROUND

Mutations in the tail of histone H3 (K27M) are frequently found in pediatric midline high-grade glioma's but have rarely been reported in other malignancies. Recently, recurrent somatic nucleotide variants in histone H3 (H3 K27M) have been reported in group A posterior fossa ependymoma (EPN_PFA), an entity previously described to have no recurrent mutations. However, the true incidence of H3 K27M mutations in EPN_PFA is unknown.

METHODS

In order to discern the frequency of K27M mutations in histone H3 in EPN_PFA, we analyzed 151 EPN_PFA previously profiled with genome-wide methylation arrays using a validated droplet digital PCR assay.

RESULTS

We identified only 1 case out of 151 EPN_PFA harboring the K27M mutation indicating that histone mutations are extremely rare in EPN_PFA. Morphologically, this single mutated case is clearly consistent with an ependymoma, and the presence of the K27M mutation was confirmed using immunohistochemistry.

DISCUSSION

K27M mutations are extremely rare in EPN_PFA. Routine evaluation of K27M mutations in EPN_PFA is of limited utility, and is unlikely to have any bearing on prognosis and/or future risk stratification.
Primitive neuroectodermal tumors of the central nervous system (CNS-PNETs) are highly aggressive, poorly differentiated embryonal tumors occurring predominantly in young children but also affecting adolescents and adults. Herein, we demonstrate that a significant proportion of institutionally diagnosed CNS-PNETs display molecular profiles indistinguishable from those of various other well-defined CNS tumor entities, facilitating diagnosis and appropriate therapy for patients with these tumors. From the remaining fraction of CNS-PNETs, we identify four new CNS tumor entities, each associated with a recurrent genetic alteration and distinct histopathological and clinical features. These new molecular entities, designated "CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2)," "CNS Ewing sarcoma family tumor with CIC alteration (CNS EFT-CIC)," "CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1)," and "CNS high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)," will enable meaningful clinical trials and the development of therapeutic strategies for patients affected by poorly differentiated CNS tumors.
Immunohistochemical analysis of H3K27me3 demonstrates global reduction in group-A childhood posterior fossa ependymoma and is a powerful predictor of outcome.


PMID: 28733933

Posterior fossa ependymomas (EPN_PF) in children comprise two morphologically identical, but biologically distinct tumor entities. Group-A (EPN_PFA) tumors have a poor prognosis and require intensive therapy. In contrast, group-B tumors (EPN_PFB) exhibit excellent prognosis and the current consensus opinion recommends future clinical trials to test the possibility of treatment de-escalation in these patients. Therefore, distinguishing these two tumor subtypes is critical. EPN_PFA and EPN_PFB can be distinguished based on DNA methylation signatures, but these assays are not routinely available. We have previously shown that a subset of poorly prognostic childhood EPN_PF exhibits global reduction in H3K27me3. Therefore, we set out to determine whether a simple immunohistochemical assay for H3K27me3 could be used to segregate EPN_PFA from EPN_PFB tumors. We assembled a cohort of 230 childhood ependymomas and H3K27me3 immunohistochemistry was assessed as positive or negative in a blinded manner. H3K27me3 staining results were compared with DNA methylation-based subgroup information available in 112 samples [EPN_PFA (n = 72) and EPN_PFB tumors (n = 40)]. H3K27me3 staining was globally reduced in EPN_PFA tumors and immunohistochemistry showed 99% sensitivity and 100% specificity in segregating EPN_PFA from EPN_PFB tumors. Moreover, H3K27me3 immunostaining was sufficient to delineate patients with worse prognosis in two independent, non-overlapping cohorts (n = 133 and n = 97). In conclusion, immunohistochemical evaluation of H3K27me3 global reduction is an economic, easily available and readily adaptable method for defining high-risk EPN_PFA from low-risk posterior fossa EPN_PFB tumors to inform prognosis and to enable the design of future clinical trials.
#5 – Epigenetische Klassifikation von Meningeomen

DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis.


BACKGROUND

The WHO classification of brain tumours describes 15 subtypes of meningioma. Nine of these subtypes are allotted to WHO grade I, and three each to grade II and grade III. Grading is based solely on histology, with an absence of molecular markers. Although the existing classification and grading approach is of prognostic value, it harbours shortcomings such as ill-defined parameters for subtypes and grading criteria prone to arbitrary judgment. In this study, we aimed for a comprehensive characterisation of the entire molecular genetic landscape of meningioma to identify biologically and clinically relevant subgroups.

METHODS

In this multicentre, retrospective analysis, we investigated genome-wide DNA methylation patterns of meningiomas from ten European academic neuro-oncology centres to identify distinct methylation classes of meningiomas. The methylation classes were further characterised by DNA copy number analysis, mutational profiling, and RNA sequencing. Methylation classes were analysed for progression-free survival outcomes by the Kaplan-Meier method. The DNA methylation-based and WHO classification schema were compared using the Brier prediction score, analysed in an independent cohort with WHO grading, progression-free survival, and disease-specific survival data available, collected at the Medical University Vienna (Vienna, Austria), assessing methylation patterns with an alternative methylation chip.

FINDINGS

We retrospectively collected 497 meningiomas along with 309 samples of other extra-axial skull tumours that might histologically mimic meningioma variants. Unsupervised clustering of DNA methylation data clearly segregated all meningiomas from other skull tumours. We generated genome-wide DNA methylation profiles from all 497 meningioma samples. DNA methylation profiling distinguished six distinct clinically relevant methylation classes associated with typical mutational, cytogenetic, and gene expression patterns. Compared with
WHO grading, classification by individual and combined methylation classes more accurately identifies patients at high risk of disease progression in tumours with WHO grade I histology, and patients at lower risk of recurrence among WHO grade II tumours (p=0.0096) from the Brier prediction test. We validated this finding in our independent cohort of 140 patients with meningioma.

INTERPRETATION

DNA methylation-based meningioma classification captures clinically more homogenous groups and has a higher power for predicting tumour recurrence and prognosis than the WHO classification. The approach presented here is potentially very useful for stratifying meningioma patients to observation-only or adjuvant treatment groups. We consider methylation-based tumour classification highly relevant for the future diagnosis and treatment of meningioma.
Metastasen – Grundlagen und Therapie

PD Dr. med. Astrid Weyerbrock (St. Gallen)
Strahlentherapie in der Neuroonkologie

Prof. Dr. med. Dirk Vordermark (Halle / Saale)

#1 Metastasen: postoperative Ganzhirnbestrahlung

Whole brain radiotherapy after stereotactic radiosurgery or surgical resection among patients with one to three brain metastases and favorable prognoses: a secondary analysis of EORTC 22952-26001.

Churilla TM1, Handorf E1, Collette S2, Collette L2, Dong Y1, Aizer AA3, Kocher M4, Soffietti R5, Alexander BM3, Weiss SE1.


BACKGROUND

The absence of a survival benefit for whole brain radiotherapy (WBRT) among randomized trials has been attributed to a competing risk of death from extracranial disease. We re-analyzed EORTC 22952 to assess the impact of WBRT on survival for patients with controlled extracranial disease or favorable prognoses.

PATIENTS AND METHODS

We utilized Cox regression, landmark analysis, and the Kaplan-Meier method to evaluate the impact of WBRT on survival accounting for (i) extracranial progression as a time-dependent covariate in all patients and (ii) diagnosis-specific graded prognostic assessment (GPA) score in patients with primary non-small-cell lung cancer (NSCLC).

RESULTS

A total of 329 patients treated per-protocol were included for analysis with a median follow up of 26 months. One hundred and fifteen (35%) patients had no extracranial progression; 70 (21%) patients had progression <90 days, 65 (20%) between 90 and 180 days, and 79 (24%) patients >180 days from randomization. There was no difference in the model-based risk of death in the WBRT group before [hazard ratio (HR) (95% CI)=0.70 (0.45-1.11), P = 0.133], or after [HR (95% CI)=1.20 (0.89-1.61), P = 0.214] extracranial progression. Among 177 patients with NSCLC, 175 had data available for GPA calculation. There was no significant survival benefit to WBRT among NSCLC patients with favorable GPA scores [HR (95% CI)=1.10 (0.68-1.79)] or unfavorable GPA scores [HR (95% CI)=1.11 (0.71-1.76)].

CONCLUSIONS

Among patients with limited extracranial disease and one to three brain metastases at enrollment, we found no significant survival benefit to WBRT among NSCLC patients with favorable GPA scores or patients with any histology and controlled extracranial disease status. This exploratory analysis of phase III data supports the practice of omitting WBRT for patients with limited brain metastases undergoing SRS and close surveillance.
#2 Metastasen: postoperative stereotaktische Bestrahlung

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial.


BACKGROUND

Whole brain radiotherapy (WBRT) is the standard of care to improve intracranial control following resection of brain metastasis. However, stereotactic radiosurgery (SRS) to the surgical cavity is widely used in an attempt to reduce cognitive toxicity, despite the absence of high-level comparative data substantiating efficacy in the postoperative setting. We aimed to establish the effect of SRS on survival and cognitive outcomes compared with WBRT in patients with resected brain metastasis.

METHODS

In this randomised, controlled, phase 3 trial, adult patients (aged 18 years or older) from 48 institutions in the USA and Canada with one resected brain metastasis and a resection cavity less than 5·0 cm in maximal extent were randomly assigned (1:1) to either postoperative SRS (12-20 Gy single fraction with dose determined by surgical cavity volume) or WBRT (30 Gy in ten daily fractions or 37·5 Gy in 15 daily fractions of 2·5 Gy; fractionation schedule predetermined for all patients at treating centre). We randomised patients using a dynamic allocation strategy with stratification factors of age, duration of extracranial disease control, number of brain metastases, histology, maximal resection cavity diameter, and treatment centre. Patients and investigators were not masked to treatment allocation. The co-primary endpoints were cognitive-deterioration-free survival and overall survival, and analyses were done by intention to treat. We report the final analysis. This trial is registered with ClinicalTrials.gov, number NCT01372774.

FINDINGS

Between Nov 10, 2011, and Nov 16, 2015, 194 patients were enrolled and randomly assigned to SRS (98 patients) or WBRT (96 patients). Median follow-up was 11·1 months (IQR 5·1-18·0). Cognitive-deterioration-free survival was longer in patients assigned to SRS (median 3·7 months [95% CI 3·45-5·06], 93 events) than in patients assigned to WBRT (median 3·0 months [2·86-3·25], 93 events; hazard ratio [HR] 0·47 [95% CI 0·35-0·63]; p<0·0001), and cognitive deterioration at 6 months was less frequent in patients who received SRS than those who received WBRT (28 [52%] of 54 evaluable patients assigned to SRS vs 41 [85%] of 48 evaluable patients assigned to WBRT; difference -33·6% [95% CI -45·3 to -21·8], p<0·00031).
Median overall survival was 12.2 months (95% CI 9.7-16.0, 69 deaths) for SRS and 11.6 months (9.9-18.0, 67 deaths) for WBRT (HR 1.07 [95% CI 0.76-1.50]; p=0.70). The most common grade 3 or 4 adverse events reported with a relative frequency greater than 4% were hearing impairment (three [3%] of 93 patients in the SRS group vs eight [9%] of 92 patients in the WBRT group) and cognitive disturbance (three [3%] vs five [5%]). There were no treatment-related deaths.

**INTERPRETATION**

Decline in cognitive function was more frequent with WBRT than with SRS and there was no difference in overall survival between the treatment groups. After resection of a brain metastasis, SRS radiosurgery should be considered one of the standards of care as a less toxic alternative to WBRT for this patient population.
Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial.


BACKGROUND

After brain metastasis resection, whole brain radiotherapy decreases local recurrence, but might cause cognitive decline. We did this study to determine if stereotactic radiosurgery (SRS) to the surgical cavity improved time to local recurrence compared with that for surgical resection alone.

METHODS

In this randomised, controlled, phase 3 trial, we recruited patients at a single tertiary cancer centre in the USA. Eligible patients were older than 3 years, had a Karnofsky Performance Score of 70 or higher, were able to have an MRI scan, and had a complete resection of one to three brain metastases (with a maximum diameter of the resection cavity ≤4 cm). Patients were randomly assigned (1:1) with a block size of four to either SRS of the resection cavity (within 30 days of surgery) or observation. Patients were stratified by histology of the primary tumour, metastatic tumour size, and number of metastases. The primary endpoint was time to local recurrence in the resection cavity, assessed by blinded central review of brain MRI scans by the study neuroradiologist in the modified intention-to-treat population that analysed patients by randomised allocation but excluded patients found ineligible after randomisation. Participants and other members of the treatment team (excluding the neuroradiologist) were not masked to treatment allocation. The trial is registered with ClinicalTrials.gov, number NCT00950001, and is closed to new participants.

FINDINGS

Between Aug 13, 2009, and Feb 16, 2016, 132 patients were randomly assigned to the observation group (n=68) or SRS group (n=64), with 128 patients available for analysis; four patients were ineligible (three from the SRS group and one from the observation group). Median follow-up was 11.1 months (IQR 4.8-20.4). 12-month freedom from local recurrence was 43% (95% CI 31-59) in the observation group and 72% (60-87) in the SRS group (hazard ratio 0.46 [95% CI 0.24-0.88]; p=0.015). There were no adverse events or treatment-related deaths in either group.

INTERPRETATION

SRS of the surgical cavity in patients who have had complete resection of one, two, or three brain metastases significantly lowers local recurrence compared with that noted for observation alone. Thus, the use of SRS after brain metastasis resection could be an alternative to whole-brain radiotherapy.


PURPOSE

Stereotactic radiosurgery (SRS) dose is limited by brain metastasis (BM) size. The study goal was to retrospectively determine whether there is a benefit for intracranial outcomes and overall survival (OS) for gross total resection with single-fraction SRS versus SRS alone for patients with large BMs.

METHODS AND MATERIALS

A large BM was defined as ≥4 cm³ (2 cm in diameter) prior to the study. We reviewed the records of consecutive patients treated with single-fraction SRS alone or surgery with preoperative or postoperative SRS between 2005 and 2013 from 2 institutions.

RESULTS

Overall, 213 patients with 223 treated large BMs were included; 66 BMs (30%) were treated with SRS alone and 157 (70%) with surgery and SRS (63 preoperatively and 94 postoperatively). The groups (SRS vs surgery and SRS) were well balanced except regarding lesion volume (median, 5.9 cm³ vs 9.6 cm³; P<.001), median number of BMs (1.5 vs 1, P=.002), median SRS dose (18 Gy vs 15 Gy, P<.001), and prior whole-brain radiation therapy (33% vs 5%, P<.001). The local recurrence (LR) rate was significantly lower with surgery and SRS (1-year LR rate, 36.7% vs 20.5%; P=.007). There was no difference in radiation necrosis (RN) by resection status, but there was a significantly increased RN rate with postoperative SRS versus with preoperative SRS and with SRS alone (1-year RN rate, 22.6% vs 5% and 12.3%, respectively; P<.001). OS was significantly higher with surgery and SRS (2-year OS rate, 38.9% vs 19.8%; P=.01). Both multivariate adjusted analyses and propensity score-matched analyses demonstrated similar results.

CONCLUSIONS

In this retrospective study, gross total resection with SRS was associated with significantly reduced LR compared with SRS alone for patients with large BMs. Postoperative SRS was associated with the highest rate of RN. Surgical resection with SRS may improve outcomes in patients with a limited number of large BMs compared with SRS alone. Further studies are warranted.
Consensus Contouring Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases.


PURPOSE

To propose contouring guidelines based on consensus contours generated by 10 international experts for cavity stereotactic radiosurgery (SRS), an emerging treatment option after surgical resection of brain metastases. No guidelines for contouring the surgical cavity volume have been previously reported.

METHODS AND MATERIALS

Ten postoperative completely resected cases with varying clinical scenarios and locations within the brain were selected. For each case, 10 experts independently contoured the surgical cavity clinical target volume (CTV). All the contours were analyzed, and agreement was calculated using the simultaneous truth and performance level estimation (STAPLE) with the kappa statistic. A follow-up survey was also completed by each investigator to summarize their contouring rationale for a number of different clinical scenarios. The results from the survey and the consensus STAPLE contours were both summarized to establish contouring guidelines.

RESULTS

A high level of agreement was found between the expert CTV contours (mean sensitivity 0.75, mean specificity 0.98), and the mean kappa was 0.65. The agreement was statistically significant at P<.001 for all cases. From these results and analyses of the survey answers, the recommendations for CTV include fusion of the preoperative magnetic resonance imaging scan to aid in volume delineation; contouring the entire surgical tract regardless of the preoperative location of the tumor; extension of the CTV 5 to 10 mm along the dura overlying the bone flap to account for microscopic disease extension in cases with preoperative dural contact; and a margin of ≤5 mm into the adjacent sinus when preoperative venous sinus contact was present.

CONCLUSIONS

Consensus contouring guidelines for postoperative completely resected cavity SRS treatment were established using expert contours and clinical practice. However, in the absence of clinical data supporting these recommendations, these guidelines serve as a baseline for further study and refinement.
#3 Metastasen: alleinige stereotaktische Bestrahlung

A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores.

Yamamoto M1, Serizawa T2, Higuchi Y3, Sato Y4, Kawagishi J5, Yamanaka K6, Shuto T7, Akabane A8, Jokura H5, Yomo S9, Nagano O10, Aoyama H11.


PURPOSE

The JLGK0901 study showed the noninferiority of stereotactic radiosurgery (SRS) alone as initial treatment of 5 to 10 brain metastases (BMs) compared with 2 to 4 BMs in terms of overall survival and most secondary endpoints (Lancet Oncol 2014;15:387-95). However, observation periods were not long enough to allow confirmation of the long-term safety of SRS alone in patients with 5 to 10 BMs.

METHODS AND MATERIALS

This was a prospective observational study of Gamma Knife SRS-treated patients with 1 to 10 newly diagnosed BMs enrolled at 23 facilities between March 1, 2009, and February 15, 2012.

RESULTS

The 1194 eligible patients were categorized into the following groups: group A, 1 tumor (n=455); group B, 2 to 4 tumors (n=531); and group C, 5 to 10 tumors (n=208). Cumulative rates of Mini-Mental State Examination (MMSE) score maintenance (MMSE score decrease <3 from baseline) determined with a competing risk analysis of groups A, B, and C were 93%, 91%, and 92%, respectively, at the 12th month after SRS; 91%, 89%, and 91%, respectively, at the 24th month; 89%, 88%, and 89%, respectively, at the 36th month; and 87%, 86%, and 89%, respectively, at the 48th month (hazard ratio [HR] of group A vs group B, 0.719; 95% confidence interval [CI], 0.437-1.172; P=.18; HR of group B vs group C, 1.280; 95% CI, 0.696-2.508; P=.43). During observations ranging from 0.3 to 67.5 months (median, 12.0 months; interquartile range, 5.8-26.5 months), as of December 2014, 145 patients (12.1%) had SRS-induced complications. Cumulative complication incidences by competing risk analysis for groups A, B, and C were 7%, 8%, and 6%, respectively, at the 12th month after SRS; 10%, 11%, and 11%, respectively, at the 24th month; 11%, 11%, and 12%, respectively, at the 36th month; and 12%, 12%, and 13%, respectively, at the 48th month (HR of group A vs group B, 0.850; 95% CI, 0.592-1.220; P=.38; HR of group B vs group C, 1.052; 95% CI, 0.666-1.662, P=.83). Leukoencephalopathy occurred in 12 of the 1074 patients (1.1%) with follow-up magnetic resonance imaging and was detected after salvage whole-brain radiation therapy in 11 of these 12 patients. In these 11 patients, leukoencephalopathy was detected by magnetic resonance imaging 5.2 to 21.2 months (median, 11.0 months; interquartile range, 7.0-14.4 months) after whole-brain radiation therapy.
CONCLUSIONS

Neither MMSE score maintenance nor post-SRS complication incidence differed among groups A, B, and C. This longer-term follow-up study further supports the already-reported noninferiority hypothesis of SRS alone for patients with 5 to 10 BMs versus 2 to 4 BMs.
Whole brain radiotherapy versus stereotactic radiosurgery for 4-10 brain metastases: a phase III randomised multicentre trial.

Zindler JD1,2, Bruynzeel AME3, Eekers DBP4, Hurkmans CW5, Swinnen A4, Lambin P4.


BACKGROUND

Maintenance of quality of life is the primary goal during treatment of brain metastases (BM). This is a protocol of an ongoing phase III randomised multicentre study. This study aims to determine the exact additional palliative value of stereotactic radiosurgery (SRS) over whole brain radiotherapy (WBRT) in patients with 4-10 BM.

METHODS

The study will include patients with 4-10 BM from solid primary tumours diagnosed on a high-resolution contrast-enhanced MRI scan with a maximum lesional diameter of 2.5 cm in any direction and a maximum cumulative lesional volume of 30 cm3. Patients will be randomised between WBRT in five fractions of 4 Gy to a total dose of 20 Gy (standard arm) and single dose SRS to the BMs (study arm) in the range of 15-24 Gy. The largest BM or a localisation in the brainstem will determine the prescribed SRS dose. The primary endpoint is difference in quality of life (EQ5D EUROQOL score) at 3 months after radiotherapy with regard to baseline. Secondary endpoints are difference in quality of life (EQ5D EUROQOL questionnaire) at 6, 9 and 12 months after radiotherapy with regard to baseline. Other secondary endpoints are at 3, 6, 9 and 12 months after radiotherapy survival, Karnofsky ≥ 70, WHO performance status, steroid use (mg), toxicity according to CTCAE V4.0 including hair loss, fatigue, brain salvage during follow-up, type of salvage, time to salvage after randomisation and Barthel index. Facultative secondary endpoints are neurocognition with the Hopkins verbal learning test revised, quality of life EORTC QLQ-C30, quality of life EORTC BN20 brain module and fatigue scale EORTC QLQ-FA13.

DISCUSSION

Worldwide, most patients with more than 4 BM will be treated with WBRT. Considering the potential advantages of SRS over WBRT, i.e. limiting radiation doses to uninvolved brain and a high rate of local tumour control by just a single treatment with fewer side effects, such as hair loss and fatigue, compared to WBRT, SRS might be a suitable alternative for patients with 4-10 BM.

TRIAL REGISTRATION

Trial registration number: NCT02353000 , trial registration date 15th January 2015, open for accrual 1st July 2016, nine patients were enrolled in this trial on 14th April 2017.
Staged Stereotactic Radiosurgery for Large Brain Metastases: Local Control and Clinical Outcomes of a One-Two Punch Technique.

Dohm A1, McTyre ER2, Okoukoni C2, Henson A2, Cramer CK2, LeCompte MC2, Ruiz J3, Munley MT2, Qasem S4, Lo HW5, Xing F5, Watabe K5, Laxton AW1, Tatter SB1, Chan MD1.


BACKGROUND

Treatment options are limited for large, unresectable brain metastases.

OBJECTIVE

To report a single institution series of staged stereotactic radiosurgery (SRS) that allows for tumor response between treatments in order to optimize the therapeutic ratio.

METHODS

Patients were treated with staged SRS separated by 1 mo with a median dose at first SRS of 15 Gy (range 10-21 Gy) and a median dose at second SRS of 14 Gy (range 10-18 Gy). Overall survival was evaluated using the Kaplan-Meier method. Cumulative incidences were estimated for neurological death, radiation necrosis, local failure (marginal or central), and distant brain failure. Absolute cumulative dose-volume histogram was created for each treated lesion. Logistic regression and competing risks regression were performed for each discrete dose received by a certain volume.

RESULTS

Thirty-three patients with 39 lesions were treated with staged radiosurgery. Overall survival at 6 and 12 mo was 65.0% and 60.0%, respectively. Cumulative incidence of local failure at 6 and 12 mo was 3.2% and 13.3%, respectively. Of the patients who received staged therapy, 4 of 33 experienced local failure. Radiation necrosis was seen in 4 of 39 lesions. Two of 33 patients experienced a Radiation Therapy Oncology Group toxicity grade > 2 (2 patients had grade 4 toxicities). Dosimetric analysis revealed that dose (Gy) received by volume of brain (ie, V Dose(Gy) ) was associated with radiation necrosis, including the range V 44.5Gy to V 87.8Gy .

CONCLUSION

Staged radiosurgery is a safe and effective option for large, unresectable brain metastases. Prospective studies are required to validate the findings in this study.
Brain radiation is an important treatment option for malignant and benign brain diseases. The possible acute or chronic impact of radiation therapy on cognitive performance is important for daily functioning and quality of life. A detailed evaluation of cognitive impairment is important in the context of how to control disease progression. The susceptibility of the hippocampus to radiation-induced neuronal damage and its important role in memory highlight that therapeutic strategies require precision medicine.
A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation.

Ma TM1, Grimm J1, McIntyre R1, Anderson-Keightly H1, Kleinberg LR1, Hales RK1, Moore J1, Vannorsdall T2, Redmond KJ3.


BACKGROUND AND PURPOSE

To prospectively evaluate hippocampal radiation dose volume effects and memory decline following cranial irradiation.

MATERIAL AND METHODS

Effects of hippocampal radiation over a wide range of doses were investigated by combining data from three prospective studies. In one, adults with small cell lung cancer received hippocampal-avoidance prophylactic cranial irradiation. In the other two, adults with glioblastoma multiforme received neural progenitor cell sparing radiation or no sparing with extra dose delivered to subventricular zone. Memory was measured by the Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR) at 6 months after radiation. Dose-volume histograms were generated and dose-response data were fitted to a nonlinear model.

RESULTS

Of 60 patients enrolled, 30 were analyzable based on HVLT-R DR testing completion status, baseline HVLT-R DR and intracranial metastasis/recurrence or prior hippocampal resection status. We observed a dose-response of radiation to the hippocampus with regard to decline in HVLT-R DR. D50% of the bilateral hippocampi of 22.1 Gy is associated with 20% risk of decline.

CONCLUSIONS

This prospective study demonstrates an association between hippocampal dose volume effects and memory decline measured by HVLT-R DR over a wide dose range. These data support a potential benefit of hippocampal sparing and encourage continued trial enrollment.
Prospective Study of Hippocampal-Sparing Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer.

Redmond KJ1, Hales RK2, Anderson-Keightly H2, Zhou XC3, Kummerlowe M2, Sair HI4, Duhon M2, Kleinberg L2, Rosner GL3, Vannorsdall T5.


PURPOSE

To prospectively evaluate cognitive function and intracranial failure patterns after hippocampal-sparing prophylactic cranial irradiation (PCI) for limited-stage small cell lung cancer (SCLC).

METHODS AND MATERIALS

Adults with limited-stage SCLC, achieving a complete response to chemoradiotherapy and no brain metastases, were eligible. Patients received PCI 25 Gy/10 fractions, with a mean hippocampal dose limited to <8 Gy and ≥90% of the brain receiving 90% of the prescription. A diverse battery of neuropsychological testing was performed at baseline and 6 and 12 months after PCI. Brain MRI scans were performed at baseline and 6, 12, 18, and 24 months. The primary endpoint was memory measured by the Hopkins Verbal Learning Test-Revised Delayed Recall at 6 months after PCI. The 25-Gy arm of Radiation Therapy Oncology Group protocol 0212 was used as a reference of potential efficacy. Development of intracranial metastases was recorded. Overall survival and progression-free survival were estimated using the Kaplan-Meier method.

RESULTS

Eight men and 12 women with a median age of 61 years enrolled. Two-year overall survival was 88% (95% confidence interval 68%-100%). There was no significant decline in performance between baseline and 6 or 12 months for any of the tests. The association between baseline intelligence quotient and change in performance on testing was not significant. Magnetic resonance imaging revealed asymptomatic brain metastases at a cumulative rate of 20%, with no concurrent extracranial progression. Two patients developed a metastasis in the under-dosed region. Neither involved the dentate gyrus, but 1 involved the avoidance region. Both patients concurrently developed additional metastasis in fully treated brain regions. There were 2 neurologic deaths.

CONCLUSIONS

This prospective study suggests a potential benefit of hippocampal sparing in limiting the neuropsychological sequelae of brain radiation, but with a risk of failures in the spared region. These data strongly support continued enrollment on ongoing cooperative group randomized trials. Clinical Trials registration number: NCT01797159.
#5 GBM / Geriatrische Onkologie

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma.

Perry JR1, Laperriere N1, O’Callaghan CJ1, Brandes AA1, Menten J1, Phillips C1, Fay M1, Nishikawa R1, Cairncross JG1, Roa W1, Osoba D1, Rossiter JP1, Sahgal A1, Hirte H1, Laigle-Donadey F1, Franceschi E1, Chinot O1, Golfinopoulos V1, Fariselli L1, Wick A1, Feuvret L1, Back M1, Tills M1, Winch C1, Baumert BG1, Wick W1, Ding K1, Mason WP1; Trial Investigators.


BACKGROUND

Glioblastoma is associated with a poor prognosis in the elderly. Survival has been shown to increase among patients 70 years of age or younger when temozolomide chemotherapy is added to standard radiotherapy (60 Gy over a period of 6 weeks). In elderly patients, more convenient shorter courses of radiotherapy are commonly used, but the benefit of adding temozolomide to a shorter course of radiotherapy is unknown.

METHODS

We conducted a trial involving patients 65 years of age or older with newly diagnosed glioblastoma. Patients were randomly assigned to receive either radiotherapy alone (40 Gy in 15 fractions) or radiotherapy with concomitant and adjuvant temozolomide.

RESULTS

A total of 562 patients underwent randomization, 281 to each group. The median age was 73 years (range, 65 to 90). The median overall survival was longer with radiotherapy plus temozolomide than with radiotherapy alone (9.3 months vs. 7.6 months; hazard ratio for death, 0.67; 95% confidence interval [CI], 0.56 to 0.80; P<0.001), as was the median progression-free survival (5.3 months vs. 3.9 months; hazard ratio for disease progression or death, 0.50; 95% CI, 0.41 to 0.60; P<0.001). Among 165 patients with methylated O6-methylguanine-DNA methyltransferase (MGMT) status, the median overall survival was 13.5 months with radiotherapy plus temozolomide and 7.7 months with radiotherapy alone (hazard ratio for death, 0.53; 95% CI, 0.38 to 0.73; P<0.001). Among 189 patients with unmethylated MGMT status, the median overall survival was 10.0 months with radiotherapy plus temozolomide and 7.9 months with radiotherapy alone (hazard ratio for death, 0.75; 95% CI, 0.56 to 1.01; P=0.055; P=0.08 for interaction). Quality of life was similar in the two trial groups.

CONCLUSIONS

In elderly patients with glioblastoma, the addition of temozolomide to short-course radiotherapy resulted in longer survival than short-course radiotherapy alone. (Funded by the Canadian Cancer Society Research Institute and others; ClinicalTrials.gov number, NCT00482677.).
Survival Outcomes With Short-Course Radiation Therapy in Elderly Patients With Glioblastoma: Data From a Randomized Phase 3 Trial.


PURPOSE

To perform a subset analysis of survival outcomes in elderly patients with glioblastoma from a randomized phase 3 trial comparing 2 short-course radiation therapy (RT) regimens in elderly and/or frail patients.

METHODS AND MATERIALS

The original trial population included elderly and/or frail patients with a diagnosis of glioblastoma. Patients joined the phase 3, randomized, multicenter, prospective, noninferiority trial; were assigned to 1 of 2 groups in a 1:1 ratio, either short-course RT (25 Gy in 5 fractions, arm 1) or commonly used RT (40 Gy in 15 fractions, arm 2); and were stratified by age (<65 years and ≥65 years), Karnofsky Performance Status (KPS), and extent of surgery. For the subset analysis in this study, only patients aged ≥65 years were evaluated (elderly and frail patients were defined as patients aged ≥65 years with KPS of 50%-70%; elderly and non-frail patients were defined as patients aged ≥65 years with KPS of 80%-100%); 61 of the 98 initial patients comprised the patient population, with 26 patients randomized to arm 1 and 35 to arm 2.

RESULTS

In this unplanned analysis, the short-course RT results were not statistically significantly different from the results of commonly used RT in elderly patients. The median overall survival time was 6.8 months (95% confidence interval [CI], 4.5-9.1 months) in arm 1 and 6.2 months (95% CI, 4.7-7.7 months) in arm 2 (P=.936). The median progression-free survival time was 4.3 months (95% CI, 2.6-5.9 months) in arm 1 and 3.2 months (95% CI, 0.1-6.3 months) in arm 2 (P=.706).

CONCLUSIONS

A short-course RT regimen of 25 Gy in 5 fractions is an acceptable treatment option for patients aged ≥65 years, mainly those with a poor performance status or contraindication to chemotherapy, which would be indicated in cases of methylated O6 methylguanine-DNA-methyltransferase promoter tumors.
Trans sectoral care of geriatric cancer patients based on comprehensive geriatric assessment and patient-reported quality of life - Results of a multicenter study to develop and pilot test a patient-centered interdisciplinary care concept for geriatric oncology patients (PIVOG).

Schmidt H1, Boese S2, Lampe K3, Jordan K4, Fiedler E5, Müller-Werdan U6, Wienke A7, Vordermark D3.


OBJECTIVES

For older patients with cancer the maintenance of independence, functionality and health-related quality of life (HRQOL) is of great importance. Aiming to maintain HRQOL of older patients with cancer we developed an interdisciplinary care program based on comprehensive geriatric assessment (CGA) and patient-reported HRQOL comprising tailored supportive measures and telephone-based counseling during 6month aftercare.

MATERIALS AND METHODS

Pilot-testing of the intervention took place in three centers at the University Hospital Halle to examine feasibility, acceptance and potential benefit. Patients≥70years with confirmed diagnosis of cancer, at least one comorbidity and/or one functional impairment, receiving curative or palliative care were eligible. Primary endpoint was global HRQOL (EORTC QLQ C30).

RESULTS

Mean age of the participants (n=100) was 76.3years (SD 4.8), 47% were female. On average they had 5 comorbidities (SD 2.8, min. 0, max. 15) and took 8 prescribed medications (SD 3.6, min. 0, max. 15). According to predefined treatment pathways, supportive care was triggered by summarized individual assessments that were presented to the treating physicians. Descriptive analyses showed that global HRQOL measured at the 6-month follow-up (n=57) had declined (≥10 points) for n=16 (28%) and improved or remained unchanged for n=41 (72%) patients, although some functional scales (e.g. mobility, role function) and some symptoms (e.g. fatigue, pain) had worsened. The nurse-led telephone-based aftercare was well accepted.

CONCLUSION

The results show feasibility and potential benefit of the combination of CGA and HRQOL to complement standard assessments. Patient-reported symptoms and functioning indicate the need for intensified supportive therapy during aftercare.
Toxicity and efficacy of re-irradiation of high-grade glioma in a phase I dose- and volume escalation trial.

Møller S1, Munck Af Rosenschöld P2, Costa J3, Law I4, Poulsen HS5, Engelholm SA2, Engelholm S6.


INTRODUCTION

The purpose of this study was to evaluate the safety and efficacy of PET and MRI guided re-irradiation of recurrent high-grade glioma (HGG) and to assess the impact of radiotherapy dose, fractionation and irradiated volume.

MATERIAL AND METHODS

Patients with localized, recurrent HGG (grades III-IV) and no other treatment options were eligible for a prospective phase I trial. Gross tumor volumes for radiotherapy were defined using T1-contrast enhanced MRI and 18F-fluoro-ethyl tyrosine PET. Radiotherapy was delivered using volumetric modulated arc therapy with a 2-mm margin. The dose prescription of four consecutive groups was (1) 35 Gy/10fr., (2) 42 Gy/10fr., (3) 29.5 Gy/5fr. and (4) 35 Gy/10fr. to larger tumor volumes (100-300 cm³), respectively.

RESULTS

Thirty-one patients were treated of which 81% had glioblastoma. The median progression-free survival was 2.8 months (95%CI: 2.1-3.5) and the median overall survival was 7.0 months (95%CI: 3.5-10.5). Early side effects were mild and included headache and fatigue. Seven patients were progression-free beyond 10 weeks and were evaluable for late toxicity. Among these patients, three (43%) suffered late adverse events which included radionecrosis and irreversible white matter changes.

CONCLUSION

Re-irradiation showed limited efficacy and 43% of patients achieving disease control suffered late toxicity that was manageable but not negligible.
A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation.

Ma TM1, Grimm J1, McIntyre R1, Anderson-Keightly H1, Kleinberg LR1, Hales RK1, Moore J1, Vannorsdall T2, Redmond KJ3.


BACKGROUND AND PURPOSE

To prospectively evaluate hippocampal radiation dose volume effects and memory decline following cranial irradiation.

MATERIAL AND METHODS

Effects of hippocampal radiation over a wide range of doses were investigated by combining data from three prospective studies. In one, adults with small cell lung cancer received hippocampal-avoidance prophylactic cranial irradiation. In the other two, adults with glioblastoma multiforme received neural progenitor cell sparing radiation or no sparing with extra dose delivered to subventricular zone. Memory was measured by the Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR) at 6 months after radiation. Dose-volume histograms were generated and dose-response data were fitted to a nonlinear model.

RESULTS

Of 60 patients enrolled, 30 were analyzable based on HVLT-R DR testing completion status, baseline HVLT-R DR and intracranial metastasis/recurrence or prior hippocampal resection status. We observed a dose-response of radiation to the hippocampus with regard to decline in HVLT-R DR. D50% of the bilateral hippocampi of 22.1 Gy is associated with 20% risk of decline.

CONCLUSIONS

This prospective study demonstrates an association between hippocampal dose volume effects and memory decline measured by HVLT-R DR over a wide dose range. These data support a potential benefit of hippocampal sparing and encourage continued trial enrollment.
#7 Benigne Tumore (Meningeom, Akustikusneurinom)

Gross total resection and adjuvant radiotherapy most significant predictors of improved survival in patients with atypical meningioma.

Rydzewski NR1, Lesniak MS2, Chandler JP2, Kalapurakal JA1, Pollom E3, Tate MC2, Bloch O2, Kruser T1, Dalal P1, Sachdev S1.


BACKGROUND

Atypical and malignant meningiomas are far less common than benign meningiomas. As aggressive lesions, they are prone to local recurrence and may lead to decreased survival. Although malignant meningiomas typically are treated with maximal surgical resection and adjuvant radiotherapy (RT), to the authors' knowledge the optimal treatment for atypical lesions remains to be defined. There are limited prospective data in this setting.

METHODS

The National Cancer Data Base was queried to investigate cases of histologically confirmed meningiomas diagnosed from 2004 to 2014. This included 7811 patients with atypical meningiomas (World Health Organization grade 2) and 1936 patients with malignant meningiomas (World Health Organization grade 3); during the same period, a total of 60,345 patients were diagnosed with benign meningiomas (World Health Organization grade 1). Data collected included patient and tumor characteristics, extent of surgical resection, and use of RT. Survival analysis was performed using Kaplan-Meier estimates with the log-rank test of significance and Cox univariate and multivariate regression. Logistic regression was used to determine factors associated with use of RT.

RESULTS

The 5-year overall survival rate was 85.5% in patients with benign meningiomas, 75.9% in patients with atypical meningiomas, and 55.4% in patients with malignant meningiomas (P<.0001). In patients with atypical meningiomas, gross (macroscopic) total resection (GTR) and adjuvant RT were found to be associated with significantly improved survival, independently and especially in unison (GTR plus RT: hazard ratio, 0.47; P = .002). On multivariate analysis, the combination of GTR plus RT was found to be the most important factor for improved survival. However, GTR was associated with significantly lower rates of RT use.

CONCLUSIONS

GTR and adjuvant RT appear to be highly associated with improved survival, independent of other factors, in patients with atypical meningiomas.
Overall survival benefit associated with adjuvant radiotherapy in WHO grade II meningioma.
Wang C1, Kaprealian TB1, Suh JH1, Kubicky CD1, Ciporen JN1, Chen Y1, Jaboin JJ1.


BACKGROUND

Adjuvant radiotherapy (RT) after surgical resection of World Health Organization (WHO) grade II meningioma, also known as atypical meningioma (AM), is a topic of controversy. The purpose of this study is to compare overall survival (OS) with or without adjuvant RT after subtotal resection (STR) or gross total resection (GTR) in AM patients diagnosed according to the 2007 WHO classification.

METHODS

The National Cancer Database was used to identify 2515 patients who were diagnosed with AM between 2009 and 2012 and underwent STR or GTR with or without adjuvant RT. Propensity score matching was first applied to balance covariates including age, year of diagnosis, sex, race, histology, and tumor size in STR or GTR cohorts stratified by adjuvant RT status. Multivariate regression according to the Cox proportional hazards model and Kaplan-Meier survival plots with log-rank test were then used to evaluate OS difference associated with adjuvant RT.

RESULTS

GTR is associated with improved OS compared with STR. In the subgroup analysis, adjuvant RT in patients who underwent STR demonstrated significant association with improved OS compared with no adjuvant RT (adjusted hazard ratio [AHR] 0.590, P = .045); however, adjuvant RT is not associated with improved OS in patients who underwent GTR (AHR 1.093, P = .737).

CONCLUSIONS

Despite the lack of consensus on whether adjuvant RT reduces recurrence after surgical resection of AM, our study observed significantly improved OS with adjuvant RT compared with no adjuvant RT after STR.
Population-Based Study of Stereotactic Radiosurgery or Fractionated Stereotactic Radiation Therapy for Vestibular Schwannoma: Long-Term Outcomes and Toxicities.

Lo A1, Ayre G2, Ma R2, Hsu F3, Akagami R4, McKenzie M2, Valev B5, Gete E6, Vallieres I7, Nichol A2.


PURPOSE

To examine long-term local control of vestibular schwannoma and side effects in patients treated with stereotactic radiosurgery (SRS) and fractionated stereotactic radiation therapy (SRT) in British Columbia.

METHODS AND MATERIALS

From August 1998 to May 2009, 207 patients were treated with radiation therapy (RT) at British Columbia Cancer Agency. 136 (66%) received SRS, and 71 (34%) received SRT. Dose prescriptions were 50 Gy/25 fractions for SRT and 12 Gy/1 fraction for SRS. Our multidisciplinary provincial neuro-stereotactic conference recommended SRT for tumors >3 cm and for patients with serviceable hearing (Gardner-Robertson classes I and II).

RESULTS

Median follow-up was 7.7 years to the last MRI and 6.4 years to the last clinical assessment. Local control for SRS versus SRT was 94% versus 87% at 5 years and 90% versus 85% at 10 years (P=.2). Five- and 10-year actuarial rates of RT-induced trigeminal nerve dysfunction were 25% and 25% after SRS, compared with 7% and 12% after SRT (P=.01). Five- and 10-year actuarial rates of RT-induced facial nerve dysfunction were 15% and 15% after SRS, versus 13% and 15% after SRT (P=.93). In the 49 patients with serviceable hearing at baseline who were treated with SRT, hearing preservation was 55% at 3 years, 37% at 5 years, and 29% at 7 years. In multivariable analysis, better pretreatment ipsilateral pure tone average was significantly associated with hearing preservation (hazard ratio 1.03; 95% confidence interval 1.00-1.07; P=.04).

CONCLUSIONS

Both SRS and SRT provided excellent long-term local control of vestibular schwannoma. Stereotactic radiosurgery was associated with higher rates of trigeminal nerve dysfunction. Even with a fractionated course, hearing preservation declined steadily with long-term audiometric follow-up.
Sequential proton boost after standard chemoradiation for high-grade glioma.


PURPOSE

To retrospectively assess the feasibility and safety of a sequential proton boost following conventional chemoradiation in high-grade glioma (HGG).

METHOD AND MATERIALS

Sixty-six consecutive patients with HGG were treated with 50.0 Gy photons (50.0-50.4 Gy) in 2.0 Gy (1.8-2.0 Gy) fractions, followed by a proton boost with 10 Gy equivalent (Gy(RBE)) in 2.0 Gy(RBE) fractions. Patients were matched one to one with 66 patients with HGG undergoing conventional radiation therapy (RT) with 60.0 Gy photons (59.4-60.0 Gy) in 2.0 Gy fractions (1.8-2.0 Gy). Matching criteria were age, WHO grade, Karnofsky's performance status, PTV size, temozolomide therapy (each p > 0.1). The study assessed progression-free survival (PFS), overall survival (OS), acute treatment-related toxicity (CTCAE v.4.03) and pseudoprogession (RANO criteria).

RESULTS

Median PFS and OS were similar in both treatment groups (bimodality RT, PFS: 8.8 months [2-32 months], OS 19.1 months [4-41 months]; photon-only RT, PFS: 7.2 months [2-39 months], 20.9 months [3-53 months]; p = 0.430 and p = 0.125). The median PTV of the proton boost was significantly smaller than the photon plan PTVs (each p < 0.001). Acute toxicity was mild. Toxicity grade 2 was observed in 6 patients (9%) receiving bimodality RT and 9 patients (14%) receiving photon-only RT. Two types of severe adverse events (CTCAE grade 3) occurred solely in the photon-only group: severe increase in intracranial pressure (5%); and generalized seizures (3%). Pseudoprogession was rare, occurring on average 6 weeks after radiotherapy, and was balanced in both treatment groups (n = 4 each; 8%).

CONCLUSION

Delivering a proton boost to significantly smaller target volumes when compared to photon-only plans, yielded comparable progression and survival rates at lower CTCAE grade 3 acute toxicity rates. Pseudoprogession occurred rarely and evenly distributed in both treatment groups. Thus, bimodality RT was at least equivalent regarding outcome and potentially superior with respect to toxicity in patients with HGG.
SUMMARY

Treating patients with HGG with 50.0 Gy photons in 2.0 Gy fractions, followed by a proton boost with 10 Gy(RBE) in 2.0 Gy(RBE) fractions, is safe and feasible. Severe radiation-induced acute toxicity and pseudoprogression were rare in both treatment groups. Therefore, in this clinical setting, combined proton radiotherapy might be beneficial in terms of further risk reduction for treatment-related side effects. Interestingly, treatment volume reduction using a proton boost led to comparable survival and progression rates with decreased severe treatment-related toxicity compared to conventional photon radiotherapy.
Comparing Intelligence Quotient Change After Treatment With Proton Versus Photon Radiation Therapy for Pediatric Brain Tumors.

Kahalley LS1, Ris MD2, Grosshans DR2, Okcu MF2, Paulino AC2, Chintagumpala M2, Moore BD2, Guffey D2, Minard CG2, Stancel HH2, Mahajan A2.


PURPOSE

Compared with photon radiation (XRT), proton beam radiation therapy (PBRT) reduces dose to normal tissues, which may lead to better neurocognitive outcomes. We compared change in intelligence quotient (IQ) over time in pediatric patients with brain tumors treated with PBRT versus XRT.

PATIENTS AND METHODS

IQ scores were available for 150 patients (60 had received XRT, 90 had received PBRT). Linear mixed models examined change in IQ over time since radiation therapy (RT) by RT group, controlling for demographic/clinical characteristics. Craniospinal and focal RT subgroups were also examined.

RESULTS

In the PBRT group, no change in IQ over time was identified (P = .130), whereas in the XRT group, IQ declined by 1.1 points per year (P = .004). IQ slopes did not differ between groups (P = .509). IQ was lower in the XRT group (by 8.7 points) versus the PBRT group (P = .011). In the craniospinal subgroup, IQ remained stable in both the PBRT (P = .203) and XRT groups (P = .060), and IQ slopes did not differ (P = .890). IQ was lower in the XRT group (by 12.5 points) versus the PBRT group (P = .004). In the focal subgroup, IQ scores remained stable in the PBRT group (P = .401) but declined significantly in the XRT group by 1.57 points per year (P = .026). IQ slopes did not differ between groups (P = .342).

CONCLUSION

PBRT was not associated with IQ decline or impairment, yet IQ slopes did not differ between the PBRT and XRT groups. It remains unclear if PBRT results in clinically meaningful cognitive sparing that significantly exceeds that of modern XRT protocols. Additional long-term data are needed to fully understand the neurocognitive impact of PBRT in survivors of pediatric brain tumors.
#1 Diffuse „lower grade“ Gliome IDH wild type

Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study.


**BACKGROUND**

Outcome of low-grade glioma (WHO grade II) is highly variable, reflecting molecular heterogeneity of the disease. We compared two different, single-modality treatment strategies of standard radiotherapy versus primary temozolomide chemotherapy in patients with low-grade glioma, and assessed progression-free survival outcomes and identified predictive molecular factors.

**METHODS**

For this randomised, open-label, phase 3 intergroup study (EORTC 22033-26033), undertaken in 78 clinical centres in 19 countries, we included patients aged 18 years or older who had a low-grade (WHO grade II) glioma (astrocytoma, oligoastrocytoma, or oligodendroglioma) with at least one high-risk feature (aged >40 years, progressive disease, tumour size >5 cm, tumour crossing the midline, or neurological symptoms), and without known HIV infection, chronic hepatitis B or C virus infection, or any condition that could interfere with oral drug administration. Eligible patients were randomly assigned (1:1) to receive either conformal radiotherapy (up to 50.4 Gy; 28 doses of 1.8 Gy once daily, 5 days per week for up to 6.5 weeks) or dose-dense oral temozolomide (75 mg/m² once daily for 21 days, repeated every 28 days [one cycle], for a maximum of 12 cycles). Random treatment allocation was done online by a minimisation technique with prospective stratification by institution, 1p deletion (absent vs present vs undetermined), contrast enhancement (yes vs no), age (<40 vs ≥40 years), and WHO performance status (0 vs ≥1). Patients, treating physicians, and researchers were aware of the assigned intervention. A planned analysis was done after 216 progression events occurred. Our primary clinical endpoint was progression-free survival, analysed by intention-to-treat; secondary outcomes were overall survival, adverse events, neurocognitive function (will be reported separately), health-related quality of life and neurological function (reported separately), and correlative analyses of progression-free survival by molecular
markers (1p/19q co-deletion, MGMT promoter methylation status, and IDH1/IDH2 mutations). This trial is closed to accrual but continuing for follow-up, and is registered at the European Trials Registry, EudraCT 2004-002714-11, and at ClinicalTrials.gov, NCT00182819.

**FINDINGS**

Between Sept 23, 2005, and March 26, 2010, 707 patients were registered for the study. Between Dec 6, 2005, and Dec 21, 2012, we randomly assigned 477 patients to receive either radiotherapy (n=240) or temozolomide chemotherapy (n=237). At a median follow-up of 48 months (IQR 31-56), median progression-free survival was 39 months (95% CI 35-44) in the temozolomide group and 46 months (40-56) in the radiotherapy group (unadjusted hazard ratio [HR] 1·16, 95% CI 0·9-1·5, p=0·22). Median overall survival has not been reached. Exploratory analyses in 318 molecularly-defined patients confirmed the significantly different prognosis for progression-free survival in the three recently defined molecular low-grade glioma subgroups (IDHmt, with or without 1p/19q co-deletion [IDHmt/codel], or IDH wild type [IDHwt]; p=0·013). Patients with IDHmt/non-codel tumours treated with radiotherapy had a longer progression-free survival than those treated with temozolomide (HR 1·86 [95% CI 1·21-2·87], log-rank p=0·0043), whereas there were no significant treatment-dependent differences in progression-free survival for patients with IDHmt/codel and IDHwt tumours. Grade 3-4 haematological adverse events occurred in 32 (14%) of 236 patients treated with temozolomide and in one (<1%) of 228 patients treated with radiotherapy, and grade 3-4 infections occurred in eight (3%) of 236 patients treated with temozolomide and in two (1%) of 228 patients treated with radiotherapy. Moderate to severe fatigue was recorded in eight (3%) patients in the radiotherapy group (grade 2) and 16 (7%) in the temozolomide group. 119 (25%) of all 477 patients had died at database lock. Four patients died due to treatment-related causes: two in the temozolomide group and two in the radiotherapy group.

**INTERPRETATION**

Overall, there was no significant difference in progression-free survival in patients with low-grade glioma when treated with either radiotherapy alone or temozolomide chemotherapy alone. Further data maturation is needed for overall survival analyses and evaluation of the full predictive effects of different molecular subtypes for future individualised treatment choices.
Adult IDH wild-type lower-grade gliomas should be further stratified.

BACKGROUND
Astrocytoma of the isocitrate dehydrogenase (IDH) wild-type gene is described as a provisional entity within the new World Health Organization (WHO) classification. Some groups believe that IDH wild-type lower-grade gliomas, when interrogated for other biomarkers, will mostly turn out to be glioblastoma. We hypothesize that not all IDH wild-type lower-grade gliomas have very poor outcomes and the group could be substratified prognostically.

METHODS
Seven hundred and eighteen adult WHO grades II and III patients with gliomas from our hospitals were re-reviewed and tested for IDH1/2 mutations. One hundred and sixty-six patients with IDH wild-type cases were identified for further studies, and EGFR and MYB amplifications, mutations of histone H3F3A, TERT promoter (TERTp), and BRAF were examined.

RESULTS
EGFR amplification, BRAF, and H3F3A mutations were observed in 13.8%, 6.9%, and 9.5% of patients, respectively, in a mutually exclusive pattern in IDH wild-type lower-grade gliomas. TERTp mutations were detected in 26.8% of cases. Favorable outcome was observed in patients with young age, oligodendroglial phenotype, and grade II histology. Independent adverse prognostic values of older age, nontotal resection, grade III histology, EGFR amplification, and H3F3A mutation were confirmed by multivariable analysis. Tumors were further classified into "molecularly" high grade (harboring EGFR, H3F3A, or TERTp) (median overall survival = 1.23 y) and lower grade (lacking all of the 3) (median overall survival = 7.63 y) with independent prognostic relevance. The most favorable survival was noted in molecularly lower-grade gliomas with MYB amplification.

CONCLUSION
Adult IDH wild-type lower-grade gliomas are prognostically heterogeneous and do not have uniformly poor prognosis. Clinical information and additional markers, including MYB, EGFR, TERTp, and H3F3A, should be examined to delineate discrete favorable and unfavorable prognostic groups.
Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities.


IDH wild type (IDHwt) anaplastic astrocytomas WHO grade III (AA III) are associated with poor outcome. To address the possibilities of molecular subsets among astrocytoma or of diagnostic reclassification, we analyzed a series of 160 adult IDHwt tumors comprising 120 AA III and 40 diffuse astrocytomas WHO grade II (A II) for molecular hallmark alterations and established methylation and copy number profiles. Based on molecular profiles and hallmark alterations the tumors could be grouped into four major sets. 124/160 (78 %) tumors were diagnosed as the molecular equivalent of conventional glioblastoma (GBM), and 15/160 (9 %) as GBM-H3F3A mutated (GBM-H3). 13/160 (8 %) exhibited a distinct methylation profile that was most similar to GBM-H3-K27, however, lacked the H3F3A mutation. This group was enriched for tumors of infratentorial and midline localization and showed a trend towards a more favorable prognosis. All but one of the 120 IDHwt AA III could be assigned to these three groups. 7 tumors recruited from the 40 A II, comprised a variety of molecular signatures and all but one were reclassified into distinct WHO entities of lower grades. Interestingly, TERT mutations were exclusively restricted to the molecular GBM (78 %) and associated with poor clinical outcome. However, the GBM-H3 group lacking TERT mutations appeared to fare even worse. Our data demonstrate that most of the tumors diagnosed as IDHwt astrocytomas can be allocated to other tumor entities on a molecular basis. The diagnosis of IDHwt diffuse astrocytoma or anaplastic astrocytoma should be used with caution.
Use of telomerase promoter mutations to mark specific molecular subsets with reciprocal clinical behavior in IDH mutant and IDH wild-type diffuse gliomas.


ABSTRACT

OBJECTIVE Recent studies have established that hemispheric diffuse gliomas may be grouped into subsets on the basis of molecular markers; these subsets are loosely correlated with the histopathological diagnosis but are strong predictors of clinical tumor behavior. Based on an analysis of molecular and clinical parameters, the authors hypothesized that mutations of the telomerase promoter (TERTp-mut) mark separate oncogenic programs among isocitrate dehydrogenase 1 and/or 2 (IDH) mutant (IDH-mut) and IDH wild-type (IDH-wt) diffuse gliomas independent of histopathology or WHO grade. METHODS Four molecular subsets of the combined statuses of IDH and TERT-promoter mutations (double mutant, IDH only, TERT only, and double negative) were defined. Differences in age, anatomical location, molecular genetics, and survival rates in a surgical cohort of 299 patients with a total of 356 hemispheric diffuse gliomas (WHO Grade II, III, or IV) were analyzed. RESULTS TERTp-mut were present in 38.8% of IDH-mut and 70.2% of IDH-wt gliomas. The mutational status was stable in each patient at 57 recurrence events over a 2645-month cumulative follow-up period. Among patients with IDH-mut gliomas, those in the double-mutant subset had better survival and a lower incidence of malignant degeneration than those in the IDH-only subset. Of patients in the double-mutant subset, 96.3% were also positive for 1p/19q codeletions. All patients with 1p/19q codeletions had TERTp-mut. In patients with IDH-mut glioma, epidermal growth factor receptor or phosphatase and tensin homolog mutations were not observed, and copy-number variations were uncommon. Among IDH-wt gliomas, the TERT-only subset was associated with significantly higher age, higher Ki-67 labeling index, primary glioblastoma-specific oncogenic changes, and poor survival. The double-negative subset was genetically and biologically heterogeneous. Survival analyses (Kaplan-Meier, multivariate, and regression-tree analyses) confirmed that patients in the 4 molecular subsets had distinct prognoses. CONCLUSIONS Molecular subsets result in different tumor biology and clinical behaviors in hemispheric diffuse gliomas.
ATRX immunostaining predicts IDH and H3F3A status in gliomas.


Gliomas are the most frequent intraaxial CNS neoplasms with a heterogeneous molecular background. Recent studies on diffuse gliomas have shown frequent alterations in the genes involved in chromatin remodelling pathways such as α-thalassemia/mental-retardation-syndrome-X-linked gene (ATRX). Yet, the reliability of ATRX in predicting isocitrate dehydrogenase (IDH) and H3 histone, family 3A (H3F3A) mutations in gliomas, is unclear. We analysed the ATRX expression status by immunohistochemistry, in a large series of 1064 gliomas and analysed the results in correlation to IDH, H3F3A and loss of heterozygosity (LOH) 1p/19q status in these tumors. We also investigated the prognostic potential of ATRX concerning the clinical outcome of patients with diffuse gliomas. According to our results, loss of nuclear ATRX expression was accompanied with an astrocytic tumor lineage and a younger age of onset. ATRX loss in astrocytomas was also strongly associated with IDH1/2 and H3F3A mutation (p < 0.0001). Among 196 glial tumors with nuclear ATRX loss, 173 (89 %) had an IDH1 or IDH2 mutation. Among the remaining 23 cases (11 %) with ATRX loss and IDH wild type status, 7 cases had a H3F3A G34R mutation (3 %) and 2 cases had a H3F3A K27M mutation (1 %). ATRX retention in IDH1/2 mutant tumors was strongly associated with LOH 1p/19q and oligodendroglioma histology (p < 0.0001). We also confirmed the significant prognostic role of ATRX. Diffuse gliomas with ATRX loss (n = 137, median: 1413 days, 95 % CI: 1065-1860 days) revealed a significantly better clinical outcome compared with tumors with ATRX retention (n = 335, median: 609, 95 % CI: 539-760 days, HR = 1.81, p < 0.0001). In conclusion, ATRX is a potential marker for prediction of IDH/H3F3A mutations and substratification of diffuse gliomas into survival relevant tumor groups. Such classification is of great importance for further clinical decision making especially concerning the therapeutic options available for diffuse gliomas.
Classification based on mutations of TERT promoter and IDH characterizes subtypes in grade II/III gliomas.


BACKGROUND

Grade II and III gliomas have variable clinical behaviors, showing the distinct molecular genetic alterations from glioblastoma (GBM), many of which eventually transform into more aggressive tumors. Since the classifications of grade II/III gliomas based on the genetic alterations have been recently emerging, it is now a trend to include molecular data into the standard diagnostic algorithm of glioma.

METHODS

Here we sequenced TERT promoter mutational status (TERTp-mut) in the DNA of 377 grade II/III gliomas and analyzed the clinical factors, molecular aberrations, and transcriptome profiles.

RESULTS

We found that TERTp-mut occurred in 145 of 377 grade II and III gliomas (38.5%), mutually exclusive with a TP53 mutation (TP53-mut; P < .001) and coincident with a 1p/19q co-deletion (P = .002). TERTp-mut was an independent predictive factor of a good prognosis in all patients (P = .048). It has been an independent factor associated with a good outcome in the IDH mutation (IDH-mut) subgroup (P = .018), but it has also been associated with a poor outcome in the IDH wild-type (IDH-wt) subgroup (P = .049). Combining TERTp-mut and IDH-mut allowed the grade II/III malignancies to be reclassified into IDH-mut/TERTp-mut, IDH-mut only, TERTp-mut only, and IDH-wt/TERTp-wt. 1p/19q co-deletion, TP53-muts, Ki-67 expression differences, and p-MET expression differences characterized IDH-mut/TERTp-mut, IDH-mut only, TERTp-mut only, and IDH-wt/TERTp-wt subtypes, respectively.

CONCLUSIONS

Our results showed that TERTp-mut combined with IDH-mut allowed simple classification of grade II/III gliomas for stratifying patients and clarifying diagnostic accuracy by supplementing standard histopathological criteria.
Multimodal MRI features predict isocitrate dehydrogenase genotype in high-grade gliomas.

BACKGROUND
High-grade gliomas with mutations in the isocitrate dehydrogenase (IDH) gene family confer longer overall survival relative to their IDH-wild-type counterparts. Accurate determination of the IDH genotype preoperatively may have both prognostic and diagnostic value. The current study used a machine-learning algorithm to generate a model predictive of IDH genotype in high-grade gliomas based on clinical variables and multimodal features extracted from conventional MRI.

METHODS
Preoperative MRIs were obtained for 120 patients with primary grades III (n = 35) and IV (n = 85) glioma in this retrospective study. IDH genotype was confirmed for grade III (32/35, 91%) and IV (22/85, 26%) tumors by immunohistochemistry, spectrometry-based mutation genotyping (OncoMap), or multiplex exome sequencing (OncoPanel). IDH1 and IDH2 mutations were mutually exclusive, and all mutated tumors were collapsed into one IDH-mutated cohort. Cases were randomly assigned to either the training (n = 90) or validation cohort (n = 30). A total of 2970 imaging features were extracted from pre- and postcontrast T1-weighted, T2-weighted, and apparent diffusion coefficient map. Using a random forest algorithm, nonredundant features were integrated with clinical data to generate a model predictive of IDH genotype.

RESULTS
Our model achieved accuracies of 86% (area under the curve [AUC] = 0.8830) in the training cohort and 89% (AUC = 0.9231) in the validation cohort. Features with the highest predictive value included patient age as well as parametric intensity, texture, and shape features.
IDH1/2 mutation status combined with Ki-67 labeling index defines distinct prognostic groups in glioma.


The current World Health Organization (WHO) classification of human gliomas is mainly based on morphology. However, it has limitations in prognostic prediction. We examined whether combining isocitrate dehydrogenase (IDH) 1/2 mutation status with the Ki-67 labeling index would improve the definition of prognostically distinct entities. We investigated the correlation of Ki-67 expression with IDH1/2 mutation status and their impact on clinical outcome in 703 gliomas. Low Ki-67 expression closely overlapped with IDH1/2 mutation in our cohort (P < 0.0001). Patients with IDH1/2 mutation survived significantly longer than patients with wild-type IDH1/2 did (P < 0.0001); higher Ki-67 expression was associated with shorter progression-free survival and overall survival (OS) (P < 0.0001). IDH1/2 combined with Ki-67 was used to re-classify glioma patients into five groups. IDH1/2 mutant patients with low and moderate Ki-67 expression (Group1) had the best prognosis, whereas patients with wild-type IDH1/2 and high Ki-67 expression (Group5) had the worst prognosis (Median OS = 1527 vs. 355 days, P < 0.0001). To summarize, our new classification model distinguishes biologically distinct subgroups and provides prognostic information regardless of the conventional WHO grade. Classification based on IDH1/2 mutation status and Ki-67 expression level could be more convenient for clinical application and guide personalized treatment in malignant gliomas.
The Role of Extent of Resection in IDH1 Wild-Type or Mutant Low-Grade Gliomas.


BACKGROUND

Maximizing extent of resection (EOR) improves outcomes in adults with World Health Organization (WHO) grade II low-grade gliomas (LGG). However, recent studies demonstrate that LGGs bearing a mutation in the isocitrate dehydrogenase 1 (IDH1) gene are a distinct molecular and clinical entity. It remains unclear whether maximizing EOR confers an equivalent clinical benefit in IDH mutated (mtIDH) and IDH wild-type (wtIDH) LGGs.

OBJECTIVE

To assess the impact of EOR on malignant progression-free survival (MPFS) and overall survival (OS) in mtIDH and wtIDH LGGs.

METHODS

We performed a retrospective review of 74 patients with WHO grade II gliomas and known IDH mutational status undergoing resection at a single institution. EOR was assessed with quantitative 3-dimensional volumetric analysis. The effect of predictor variables on MPFS and OS was analyzed with Cox regression models and the Kaplan-Meier method.

RESULTS

Fifty-two (70%) mtIDH patients and 22 (30%) wtIDH patients were included. Median preoperative tumor volume was 37.4 cm³; median EOR of 57.6% was achieved. Univariate Cox regression analysis confirmed EOR as a prognostic factor for the entire cohort. However, stratifying by IDH status demonstrates that greater EOR independently prolonged MPFS and OS for wtIDH patients (hazard ratio [HR] = 0.002 [95% confidence interval {CI} 0.000-0.074] and HR = 0.001 [95% CI 0.00-0.108], respectively), but not for mtIDH patients (HR = 0.84 [95% CI 0.17-4.13] and HR = 2.99 [95% CI 0.15-61.66], respectively).

CONCLUSION

Increasing EOR confers oncologic and survival benefits in IDH1 wtLGGs, but the impact on IDH1 mtLGGs requires further study.
Molecular and histologic characteristics of pseudoprogression in diffuse gliomas.

During the 6 month period following chemoradiotherapy, gliomas frequently develop new areas of contrast enhancement, which are due to treatment effect rather than tumor progression. We sought to characterize this phenomenon in oligodendrogliomas (OG) and mixed oligoastrocytomas (MOA). We reviewed the imaging findings from 143 patients with a WHO grade II or III OG or MOA for evidence of pseudoprogression (PsP) or early tumor progression. We characterized these cases for 1p/19q codeletions by FISH, IDH1 R132H mutation by immunohistochemistry, and TP53, ATRX, and EGFR mutations by next generation sequencing. We then reviewed the pathologic specimens of the patient cases in which a re-resection was performed. We found that OG and MOA that are 1p/19q intact developed PsP at a higher rate than tumors that are 1p/19q codeleted (27 vs. 8 %). Moreover, IDH1 wild-type (WT) tumors developed PsP at a higher rate than IDH1 R132H cases (27 vs. 11 %). Patients with ATRX or TP53 mutations developed PsP at an intermediate rate of 21 %. Ten patients in our cohort underwent a re-resection for early contrast enhancement; these tumors were predominantly 1p/19q intact (90 %) and had a low rate of IDH1 R132H mutation (50 %). 8 of 10 tumors demonstrated primarily treatment effects, while the remaining 2 of 10 demonstrated recurrent/residual tumor of the same grade. Early contrast enhancement that develops during the first 6 months after chemoradiotherapy is typically due to PsP and occurs primarily in OG and MOA that are 1p/19q intact and IDH WT.
IDH mutation is associated with higher risk of malignant transformation in low-grade glioma.

Leu S, von Felten S, Frank S, Boulay JL, Mariani L


Acquisition of IDH1 or IDH2 mutation (IDHmut) is among the earliest genetic events that take place in the development of most low-grade glioma (LGG). IDHmut has been associated with longer overall patient survival. However, its impact on malignant transformation (MT) remains to be defined. A collection of 210 archived adult LGG previously stratified by IDHmut, MGMT methylation (MGMTmet), 1p/19q combined loss of heterozygosity (1p19qloh) and TP53 immunopositivity (TP53pos) status was analyzed. We used multistate models to assess MT-free survival, considering one initial, one transient (MT), and one absorbing state (death). Missing explanatory variables were multiply imputed. Overall, although associated with a lower risk of death (HR(DEATH) = 0.35, P = 0.0023), IDHmut had a non-significantly higher risk of MT (HR(MT) = 1.84; P = 0.1683) compared to IDH wild type (IDHwt). The double combination of IDHmut and MGMTmet and the triple combination of IDHmut, MGMTmet and 1p/19qloh, despite significantly lower hazards for death (HR(DEATH) versus IDHwt: 0.35, P = 0.0194 and 0.15, P = 0.0008, respectively), had non-significantly different hazards for MT. Conversely, the triple combination of IDHmut/MGMTmet/TP53pos, with a non-significantly different hazard for death, had a significantly higher hazard for MT than IDHwt (HR(MT) versus IDHwt: 2.83; P = 0.0452). Although IDHmut status is associated with longer overall patient survival, all IDHmut/MGMTmet subsets consistently showed higher risks of MT than of death, compared to IDHwt LGG. This supports the findings that molecular events relevant to IDH mutations impact early glioma development prior to malignant transformation.
Multi-pronged proteomic analysis to study the glioma pathobiology using cerebrospinal fluid samples.
Gahoi N, Malhotra D, Moiyadi A, Varma SG, Gandhi MN, Srivastava S.

PURPOSE

Gliomas are one of the most aggressive and lethal brain tumors arising from neoplastic transformation of astrocytes and oligodendrocytes. A comprehensive quantitative analysis of proteome level differences in cerebrospinal fluid (CSF) across different grades of gliomas for a better understanding of glioma pathobiology is carried out.

EXPERIMENTAL DESIGN

Glioma patients are diagnosed by radiology and histochemistry-based analyses. Differential proteomic analysis of high (n = 12) and low (n = 8) grade gliomas, and control (n = 3) samples is performed by using two complementary quantitative proteomic approaches; 2D-DIGE and iTRAQ. Further, comparative analysis of three IDH wild-type and five IDH mutants is performed to identify the proteome level differences between these two sub-classes.

RESULTS

Level of several proteins including haptoglobin, transthyretin, osteopontin, vitronectin, complement factor H and different classes of immunoglobulins are found to be considerably increased in CSF of higher grades of gliomas. Subsequent bioinformatics analysis indicated that many of the dysregulated CSF proteins are associated with metabolism of lipids and lipoproteins, complement and coagulation cascades and extracellular matrix remodeling in gliomas. Intriguingly, CSF of glioma patients with IDH mutations exhibite increased levels of multiple proteins involved in response to oxidative stress.

CONCLUSION AND CLINICAL RELEVANCE

To the best of our knowledge, this is the foremost proteome level investigation describing comprehensive proteome profiles of different grades of gliomas using proximal fluid (CSF); and thereby providing insights into disease pathobiology, which aided in identification of grade and sub-type specific alterations. Moreover, if validated in larger clinical cohorts, a panel of differentially abundant CSF proteins may serve as potential disease monitoring and prognostic markers for gliomas.
The new WHO classification of diffuse gliomas has been refined and now includes the 1p/19q codeletion, IDH1/2 mutation, and histone H3-K27M mutation. Our objective was to assess the prognostic value of the updated 2016 WHO classification in the French POLA cohort. All cases of high-grade oligodendrogial tumors sent for central pathological review and included into the French nationwide POLA cohort were reclassified according to the updated 4th WHO classification. In total, 1041 patients were included, with a median age at diagnosis of 50.4 years (range 17.1-84.4). Based on the new histomolecular classification, diagnoses included anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted (32.5 %), anaplastic astrocytoma IDH mutant (IDH (mut)) (11.0 %), anaplastic astrocytoma IDH wild type (IDH (wt)) (5.3 %), glioblastoma IDH (mut) (17.1 %), and glioblastoma IDH (wt) (33.2 %). Ten patients presented with a diffuse midline tumor, H3 K27M mutant. The new WHO classification was prognostic for progression-free survival (PFS) and overall survival (OS) (p < 0.001). We did not find prognosis differences between grades III and IV for IDH (mut) 1p/19q intact and IDH (wt) gliomas in univariate and multivariate analyses. Among anaplastic astrocytoma IDH (wt), cases with chromosome arm 7p gain and 10q loss (55 %) had shorter PFS than the others (p = 0.027). In conclusion, the new WHO histomolecular classification of diffuse gliomas presented with high prognostic value. Grading was not discriminant between grade III and IV high-grade gliomas.
Detection, Characterization, and Inhibition of FGFR-TACC Fusions in IDH Wild-type Glioma.


PURPOSE

Oncogenic fusions consisting of fibroblast growth factor receptor (FGFR) and TACC are present in a subgroup of glioblastoma (GBM) and other human cancers and have been proposed as new therapeutic targets. We analyzed frequency and molecular features of FGFR-TACC fusions and explored the therapeutic efficacy of inhibiting FGFR kinase in GBM and grade II and III glioma.

EXPERIMENTAL DESIGN

Overall, 795 gliomas (584 GBM, 85 grades II and III with wild-type and 126 with IDH1/2 mutation) were screened for FGFR-TACC breakpoints and associated molecular profile. We also analyzed expression of the FGFR3 and TACC3 components of the fusions. The effects of the specific FGFR inhibitor JNJ-42756493 for FGFR3-TACC3-positive glioma were determined in preclinical experiments. Two patients with advanced FGFR3-TACC3-positive GBM received JNJ-42756493 and were assessed for therapeutic response.

RESULTS

Three of 85 IDH1/2 wild-type (3.5%) but none of 126 IDH1/2-mutant grade II and III gliomas harbored FGFR3-TACC3 fusions. FGFR-TACC rearrangements were present in 17 of 584 GBM (2.9%). FGFR3-TACC3 fusions were associated with strong and homogeneous FGFR3 immunostaining. They are mutually exclusive with IDH1/2 mutations and EGFR amplification, whereas they co-occur with CDK4 amplification. JNJ-42756493 inhibited growth of glioma cells harboring FGFR3-TACC3 in vitro and in vivo. The two patients with FGFR3-TACC3 rearrangements who received JNJ-42756493 manifested clinical improvement with stable disease and minor response, respectively.

CONCLUSIONS

RT-PCR sequencing is a sensitive and specific method to identify FGFR-TACC-positive patients. FGFR3-TACC3 fusions are associated with uniform intratumor expression of the fusion protein. The clinical response observed in the FGFR3-TACC3-positive patients treated with an FGFR inhibitor supports clinical studies of FGFR inhibition in FGFR-TACC-positive patients.
Characteristics of H3 K27M-mutant gliomas in adults.


BACKGROUND
Diffuse H3 K27M-mutant gliomas occur primarily in children but can also be encountered in adults. The aim of this study was to describe the characteristics of H3 K27M-mutant gliomas in adults.

METHODS
We analyzed the characteristics of 21 adult H3 K27M-mutant gliomas and compared them with those of 135 adult diffuse gliomas without histone H3 and without isocitrate dehydrogenase (IDH) mutation (IDH/H3 wild type).

RESULTS
The median age at diagnosis in H3 K27M-mutant gliomas was 32 years (range: 18-82 y). All tumors had a midline location (spinal cord n = 6, thalamus n = 5, brainstem n = 5, cerebellum n = 3, hypothalamus n = 1, and pineal region n = 1) and were IDH and BRAF-V600E wild type. The identification of an H3 K27M mutation significantly impacted the diagnosis in 3 patients (14%) for whom the histological aspect initially suggested a diffuse low-grade glioma and in 7 patients (33%) for whom pathological analysis hesitated between a diffuse glioma, ganglioglioma, or pilocytic astrocytoma. Compared with IDH/H3 wild-type gliomas, H3 K27M-mutant gliomas were diagnosed at an earlier age (32 vs 64 y, P < .001), always had a midline location (21/21 vs 21/130, P < .001), less frequently had a methylated MGMT promoter (1/21 vs 52/129, P = .002), and lacked EGFR amplification (0/21 vs 26/128, P = .02). The median survival was 19.6 months in H3 K27M-mutant gliomas and 17 months in IDH/H3 wild-type gliomas (P = .3).

CONCLUSION
In adults, as in children, H3 K27M mutations define a distinct subgroup of IDH wild-type gliomas characterized by a constant midline location, low rate of MGMT promoter methylation, and poor prognosis.
Pilocytic astrocytomas occur rarely in adults and show aggressive tumor behavior. However, their underlying molecular-genetic events are largely uncharacterized. Hence, 59 adult pilocytic astrocytoma (APA) cases of classical histology were studied (MIB-1 LI: 1%-5%). Analysis of BRAF alterations using qRT-PCR, confirmed KIAA1549-BRAF fusion in 11 (19%) and BRAF-gain in 2 (3.4%) cases. BRAF-V600E mutation was noted in 1 (1.7%) case by sequencing. FGFR1-mutation and FGFR-TKD duplication were seen in 7/59 (11.9%) and 3/59 (5%) cases, respectively. Overall 36% of APAs harbored BRAF and/or FGFR genetic alterations. Notably, FGFR related genetic alterations were enriched in tumors of supratentorial region (8/25, 32%) as compared with other locations (P = 0.01). The difference in age of cases with FGFR1-mutation (Mean age ± SD: 37.2 ± 15 years) vs. KIAA1549-BRAF fusion (Mean age ± SD: 25.1 ± 4.1 years) was statistically significant (P = 0.03). Combined BRAF and FGFR alterations were identified in 3 (5%) cases. Notably, the cases with more than one genetic alteration were in higher age group (Mean age ± SD: 50 ± 12 years) as compared with cases with single genetic alteration (Mean age ± SD: 29 ± 10; P = 0.003). Immunoreactivity of p-MAPK/p-MEK1 was found in all the cases examined. The pS6-immunoreactivity, a marker of mTOR activation was observed in 34/39 (87%) cases. Interestingly, cases with BRAF and/or FGFR related alteration showed significantly lower pS6-immunostaining (3/12; 25%) as compared with those with wild-type BRAF and/or FGFR (16/27; 59%) (P = 0.04). Further, analysis of seven IDH wild-type adult diffuse astrocytomas (DA) showed FGFR related genetic alterations in 43% cases. These and previous results suggest that APAs are genetically similar to IDH wild-type adult DAs. APAs harbor infrequent BRAF alterations but more frequent FGFR alterations as compared with pediatric cases. KIAA1549-BRAF fusion inversely correlates with increasing age whereas FGFR1-mutation associates with older age. Activation of MAPK/ERK/mTOR signaling appears to be an important oncogenic event in APAs and may be underlying event of aggressive tumor behavior. The findings provided a rationale for potential therapeutic advantage of targeting MAPK/ERK/mTOR pathway in APAs.


**Adult patients with supratentorial pilocytic astrocytoma: long-term follow-up of prospective multicenter clinical trial NCCTG-867251 (Alliance).**


**BACKGROUND**

Pilocytic astrocytoma is a rare tumor in adults. This report is of a prospective clinical trial with long-term follow-up.

**METHODS**

Between 1986 and 1994, 20 eligible adults with supratentorial pilocytic astrocytomomas were enrolled in a prospective intergroup trial of radiotherapy (RT) after biopsy (3 patients) or observation after gross (11 patients) or subtotal (6 patients) resection.

**RESULTS**

At the time of analysis (median follow-up, 20.8 years), 2 patients (10%) have died and 18 patients (90%) are alive. Neurologic and cognitive function were stable or improved over time for the majority of patients. No toxic effects of treatment or malignant transformations have been recorded at last follow-up. For the entire cohort the 20-year time to progression and overall survival rates are 95% and 90% respectively. The cause of death (2.2 and 16.1 years after enrollment) in both patients was unrelated to tumor although both were biopsy-only patients. One subtotally resected tumor progressed 1 month after enrollment requiring P32 injection into an enlarging cyst. Because of further progression this patient required RT 18 months later. This patient is alive without evidence of progression 18 years after RT.

**CONCLUSION**

The long-term follow-up results of this prospective trial confirm that adults with pilocytic astrocytomomas have a favorable prognosis with regard to survival and neurologic function. Close observation is recommended for adults with pilocytic astrocytomomas, reserving RT for salvage, as the majority remain stable after gross or subtotal resection and no adjuvant therapy.
Brainstem pilocytic astrocytoma with H3 K27M mutation: case report.

Malignant progression of a histone H3.3 K27M-mutated spinal pilocytic astrocytoma in an adult.
Reers S, Krug D, Stummer W, Hasselblatt M
The metabolic genes isocitrate dehydrogenase 1 (IDH1) and IDH2 are commonly mutated in low-grade glioma and in a subset of glioblastoma. These mutations co-occur with other recurrent molecular alterations, including 1p/19q codeletions and tumor suppressor protein 53 (TP53) and alpha thalassemia/mental retardation (ATRX) mutations, which together help to define a molecular signature that aids in the classification of gliomas and helps to better predict clinical behavior. A confluence of research suggests that glioma development in IDH-mutant and IDH wild-type tumors is driven by different oncogenic processes and responds differently to current treatment paradigms. Herein, the authors discuss the discovery of IDH mutations and associated molecular alterations in glioma, review clinical features common to patients with IDH-mutant glioma, and highlight current understanding of IDH mutation-driven gliomagenesis with implications for emerging treatment strategies.
Isocitrate dehydrogenase (IDH) are important enzymes that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG), producing NADPH in the process. More than 80% of low-grade gliomas and secondary glioblastoma (GBM) harbor an IDH mutation. IDH mutations involve a catalytic pocket of the enzyme and lead to a neomorphic ability to produce 2-hydroxyglutarate (2HG) while oxidizing N2HG is considered as an ‘oncometabolite’ which is thought to be responsible for many, if not all, biologic effects of IDH mutations. 2HG accumulation competitively inhibits α-KG-dependent dioxygenases, including histone lysine demethylases and DNA demethylases, resulting in a hypermethylation phenotype with alterations in cellular epigenetic status as well as a block in cellular differentiation. IDH mutations have been suggested as an important early event in tumorigenesis, however it remains unclear whether IDH mutation by itself causes cancer or if it requires other oncogenic events to initiate tumorigenesis. Significant efforts have been made to better understand the mechanisms of IDH mutations in tumor initiation and progression, and to develop targeted therapies for IDH-mutated tumors. This review provides an overview of the function of mutant IDH, and the current understanding of the role IDH mutations play in gliomagenesis. In addition, several potential therapeutic strategies for IDH-mutant gliomas, including mutant IDH inhibitors which have entered clinical evaluation in glioma patients, will be discussed.
Reducing radiation dose to normal brain through a risk adapted dose reduction - protocol for patients with favourable subtype anaplastic glioma


Radiat Oncol. 2017 Mar 2;12(1):46

AIM

In patients with isocitrate dehydrogenase (IDH) mutated anaplastic glioma determine the dosimetric benefits of delivering radiation therapy using a PET guided integrated boost IMRT technique (ib-IMRT) compared with standard IMRT (s-IMRT) in reducing dose to normal brain.

METHODS

Ten patients with anaplastic glioma, identified as a favourable molecular subgroup through presence of IDH mutation, and managed with radiation therapy using an ib-IMRT were enrolled into a dosimetric study comparing two RT techniques: s-IMRT to 59.4Gy or ib-IMRT with 59.4/54Gy regions. Gross Tumour volume (GTV) and Clinical Target Volumes (CTV) were determined by MRI, 18F-Fluoroethyltyrosine (FET) and 18F-Fluorodeoxyglucose (FDG) PET imaging. A standard risk Planning Target Volume (PTVs) receiving 59.4Gy (PTV59.4) in the s-IMRT technique was determined by MRI T2Flair and FET PET. For the ib-IMRT technique this PTVs volume was treated to 54Gy, and the high-risk PTV (PTVhr) receiving 59.4Gy was determined as a higher risk region by FDG PET and MRI gadolinium enhancement. Standard dosimetric criteria and normal tissue constraints based on recent clinical trials were used in target delineation and planning. Normal Brain was defined as Brain minus CTV. Endpoints for dosimetric evaluation related to mean Brain dose (mBrainDose), brain volume receiving 40Gy (Brainv40) and 20Gy (Brainv20). The variation between the dosimetric endpoints for both techniques was examined using Wilcoxon analysis.

RESULTS

The 10 patients had tumours located in temporal (1), parietal (3), occipital (2) and bifrontal (4) regions. In ib-IMRT technique the median volume of PTVhr was 25.5 cm3 compared with PTVs of 300.0 cm3. For dose to PTVhr the two treatments were equivalent (p = 0.33), and although the ibIMRT had a prescribed 10% dose reduction from 59.4Gy to 54Gy the median reduction was only 5.9%. The ib-IMRT dosimetry was significantly improved in normal brain endpoints specifically mBrainDose (p = 0.007), Brainv40 (p = 0.005) and Brainv20 (p = 0.001), with a median reduction of 9.3%, 19.0 and 10.8% respectively. After a median follow-up of 38 months two patients have progressed, with no isolated relapse in the dose reduction region.
CONCLUSION

An approach using ib-IMRT for anaplastic glioma produces significant dosimetric advantages in relation to normal brain dose compared with s-IMRT plan. This is achieved without a significant reduction to the target volume dose despite the reduction in prescribed dose. This technique has advantages to minimise potential late neurocognitive effects from high dose radiation in patients with favorable subtype anaplastic glioma with predicted median survival beyond ten years.
Prospective Longitudinal Analysis of 2-Hydroxyglutarate Magnetic Resonance Spectroscopy Identifies Broad Clinical Utility for the Management of Patients With IDH-Mutant Glioma


J Clin Oncol 34:4030-4039 2016

Proton magnetic resonance spectroscopy (MRS) of the brain can detect 2-hydroxyglutarate (2HG), the oncometabolite produced in neoplasms harboring a mutation in the gene coding for isocitrate dehydrogenase (IDH). We conducted a prospective longitudinal imaging study to determine whether quantitative assessment of 2HG by MRS could serve as a noninvasive clinical imaging biomarker for IDH-mutated gliomas. 2HG MRS was performed in 136 patients using point-resolved spectroscopy at 3 T in parallel with standard clinical magnetic resonance imaging and assessment. Data were analyzed in patient cohorts representing the major phases of the glioma clinical course and were further subgrouped by histology and treatment type to evaluate 2HG. Histologic correlations were performed. Quantitative 2HG MRS was technically and biologically reproducible. 2HG concentration of 1 mM could be reliably detected with high confidence. During the period of indolent disease, 2HG concentration varied by less than 6.1 mM, and it increased sharply with tumor progression. 2HG concentration was positively correlated with tumor cellularity and significantly differed between high- and lower-grade gliomas. In response to cytotoxic therapy, 2HG concentration decreased rapidly in 1p/19q codeleted oligodendrogliomas and with a slower time course in astrocytomas and mixed gliomas. The magnitude and time course of the decrease in 2HG concentration and magnitude of the decrease in tumor volume did not differ between oligodendrogliomas treated with temozolomide or carmustine. Criteria for 2HG MRS were established to make a presumptive molecular diagnosis of an IDH mutation in gliomas technically unable to undergo a surgical procedure. 2HG concentration as measured by MRS was reproducible and reliably reflected the disease state. These data provide a basis for incorporating 2HG MRS into clinical management of IDH-mutated gliomas.
**Pan-mutant IDH1 inhibitor BAY 1436032 for effective treatment of IDH1 mutant astrocytoma in vivo**


*Acta Neuropathol (2017) 133:629–644*

Isocitrate dehydrogenase (IDH)-mutated glioma is a highly attractive brain tumor for targeted treatment. The identification of mutations in codon 132 of IDH1 in a small fraction of glioblastomas was followed by the detection of these mutations in the majority of astrocytoma and oligodendroglioma. Approximately, 70–80% of all diffuse astrocytomas and of all oligodenrogliomas were shown to harbor such mutations in IDH1. These mutations result in a neomorphic enzyme specificity which leads to a dramatic increase of intracellular d-2-hydroxyglutarate (2-HG) in tumor cells. Therefore, mutant IDH1 protein is a highly attractive target for inhibitory drugs. Here, we describe the development and properties of BAY 1436032, a pan-inhibitor of IDH1 protein with different codon 132 mutations. BAY 1436032 strongly reduces 2-HG levels in cells carrying IDH1-R132H, -R132C, -R132G, -R132S and -R132L mutations. Cells not carrying IDH mutations were unaffected. BAY 1436032 did not exhibit toxicity in vitro or in vivo. The pharmacokinetic properties of BAY 1436032 allow for oral administration. In two independent experiments, BAY 1436032 has been shown to significantly prolong survival of mice.
**Volumetric relationship between 2-hydroxyglutarate and FLAIR hyperintensity has potential implications for radiotherapy planning of mutant IDH glioma patients**

Kourosh Jafari-Khouzani, Franziska Loebel, Wolfgang Bogner, Otto Rapalino, Gilberto R. Gonzalez, Elizabeth Gerstner, Andrew S. Chi, Tracy T. Batchelor, Bruce R. Rosen, Jan Unkelbach, Helen A. Shih, Daniel P. Cahill, and Ovidiu C. Andronesi

Neuro-Oncology 18(11), 1569–1578, 2016

**BACKGROUND**

Gliomas with mutant isocitrate dehydrogenase (IDH) produce high levels of 2-hydroxyglutarate (2HG) that can be quantitatively measured by 3D magnetic resonance spectroscopic imaging (MRSI). Current glioma MRI primarily relies upon fluidattenuated inversion recovery (FLAIR) hyperintensity for treatment planning, although this lacks specificity for tumor cells. Here, we investigated the relationship between 2HG and FLAIR in mutant IDH glioma patients to determine whether 2HG mapping is valuable for radiotherapy planning.

**METHODS**

Seventeen patients with mutant IDH1 gliomas were imaged by 3 T MRI. A 3D MRSI sequence was employed to specifically image 2HG. FLAIR imaging was performed using standard clinical protocol. Regions of interest (ROIs) were determined for FLAIR and optimally thresholded 2HG hyperintensities. The overlap, displacement, and volumes of 2HG and FLAIR ROIs were calculated.

**RESULTS**

In 8 of 17 (47%) patients, the 2HG volume was larger than FLAIR volume. Across the entire cohort, the mean volume of 2HG was 35.3 cc (range, 5.3–92.7 cc), while the mean volume of FLAIR was 35.8 cc (range, 6.3–140.8 cc). FLAIR and 2HG ROIs had mean overlap of 0.28 (Dice coefficients range, 0.03–0.57) and mean displacement of 12.2 mm (range, 3.2–23.5 mm) between their centers of mass.

**CONCLUSIONS**

Our results indicate that for a substantial number of patients, the 2HG volumetric assessment of tumor burden is more extensive than FLAIR volume. In addition, there is only partial overlap and asymmetric displacement between the centers of FLAIR and 2HG ROIs. These results may have important implications for radiotherapy planning of IDH mutant glioma.
**Advances in the treatment of newly diagnosed primary central nervous system lymphomas**

Liren Qian, Ciprian Tomuleasa, Ioan-Alexandru Florian, Jianliang Shen, Ioan-Stefan Florian, Mihnea Zdrenghea, Delia Dima

**Blood Research 52(3) 2017**

Primary central nervous system lymphoma (PCNSL) is a type of highly invasive non-Hodgkin lymphoma. With a growing number of organ transplantation and immunosuppressant therapy, the incidence of PCNSL has been growing rapidly in recent years, which is attributed to the increased incidence of HIV/AIDS, a prominent risk factor for developing PCNSL. The rising rate of PCNSL incidence is the highest among the intracranial tumors. In the past 20 years, dozens of clinical trials related to PCNSL have been registered, but adequate therapeutics are still challenging. Currently, the chemotherapy regimens based on high-dose methotrexate and whole-brain radiotherapy are the two main therapeutic options; however, the toxicity associated with those is the main problem that challenges medical researchers. Novel agents and therapeutic strategies have been developed in recent years. In the current review, we describe advances in the treatment of PCNSL and discuss novel therapeutic approaches currently in development, such as the use of rituximab, disruption of the blood-brain barrier, and state-of-the-art radiotherapy.
Diagnostic value of 18F-FDG PET and PET/CT in immunocompetent patients with primary central nervous system lymphoma: A systematic review and meta-analysis

Yaru Zou, Jianjing Tong, Haiyan Leng, Jingwei Jiang, Meng Pan, Zi Chen


BACKGROUND

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) and PET/CT have become two of the most powerful tools for malignant lymphoma exploration, but their diagnostic role in primary central nervous system lymphoma (PCNSL) is still disputed. The purpose of our study is to identify the usefulness of 18F-FDG PET and PET/CT for detecting PCNSL.

RESULTS

A total of 129 patients, obtained from eight eligible studies, were included for this systematic review and meta-analysis. The performance of 18F-FDG PET and PET/CT for diagnosing PCNSL were as follows: the pooled sensitivity was 0.88 (95% CI: 0.80–0.94), specificity was 0.86 (95% CI: 0.73–0.94), positive likelihood ratio (PLR) was 3.99 (95% CI: 2.31–6.90), negative likelihood ratio (NLR) was 0.11 (95% CI: 0.04–0.32), and diagnostic odds ratio (DOR) was 33.40 (95% CI: 10.40–107.3). In addition, the area under the curve (AUC) and Q index were 0.9192 and 0.8525, respectively.

MATERIALS AND METHODS

PubMed/MEDLINE, Embase and Cochrane Library were systematically searched for potential publications (last updated on July 16th, 2016). Reference lists of included articles were also checked. Original articles that reported data on patients who were suspected of having PCNSL were considered suitable for inclusion. The sensitivities and specificities of 18F-FDG PET and PET/CT in each study were evaluated. The Stata software and Meta-Disc software were employed in the process of data analysis.

CONCLUSIONS

18F-FDG PET and PET/CT showed considerable accuracy in identifying PCNSL in immunocompetent patients and could be a valuable radiological diagnostic tool for PCNSL.
Primary Central Nervous System Lymphoma: A Critical Review of the Role of Surgery for Resection
Jonathan Yun, Fabio M. Iwamoto, Adam M. Sonabend
Arch Cancer Res. 2016; 4(2)

BACKGROUND

Primary central nervous system lymphomas (PCNSL) are rare CNS tumors that carry a poor prognosis, with most patients suffering recurrence. Progress has been made in the treatment of this pathology, notably with the widespread use of systemic high dose methotrexate. However, unlike most other malignant CNS neoplasms, surgery for cytoreduction is not routinely performed for this disease, mainly as a result of negative experiences decades ago. Since these studies were published, the availability of intraoperative monitoring, MR imaging and neuro-navigation as well as surgical adjuncts such as fluorescence-guided resection have greatly improved the safety of intracranial procedures. More recent data is suggestive of a potential survival benefit for resection of single PCNSL lesions when patients are subsequently treated with modern regimen high-dose methotrexate, yet this evidence is limited, and should be interpreted conservatively.

METHODS AND FINDINGS

A systematic review of the literature was performed to identify trials evaluating surgical options for the treatment of PCNSL.

CONCLUSION

In this review, we provide a critical overview of the evidence favoring and discouraging resection for PCNSL. This literature suffers from several biases and limitations that must be considered in the context of the extrapolation of this literature into clinical decision-making.
The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

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Abstract The 2016 World Health Organization Classification of Tumors of the Central Nervous System is both a conceptual and practical advance over its 2007 predecessor. For the first time, the WHO classification of CNS tumors uses molecular parameters in addition to histology to define many tumor entities, thus formulating a concept for how CNS tumor diagnoses should be structured in the molecular era. As such, the 2016 CNS WHO presents major restructuring of the diffuse gliomas, medulloblastomas and other embryonal tumors, and incorporates new entities that are defined by both histology and molecular features, including glioblastoma, IDH-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M-mutant; RELA fusion-positive ependymoma; medulloblastoma, WNT-activated and medulloblastoma, SHH-activated; and embryonal tumour with multilayered rosettes, C19MC-altered. The 2016 edition has added newly recognized neoplasms, and has deleted some entities, variants and patterns that no longer have diagnostic and/or biological relevance. Other notable changes include the addition of brain invasion as a criterion for atypical meningioma and the introduction of a soft tissue-type grading system for the now combined entity of solitary fibrous tumor / hemangiopericytoma—a departure from the manner by which other CNS tumors are graded. Overall, it is hoped that the 2016 CNS WHO will facilitate clinical, experimental and epidemiological studies that will lead to improvements in the lives of patients with brain tumors.

Introduction

For the past century, the classification of brain tumors has been based largely on concepts of histogenesis that tumors can be classified according to their microscopic similarities with different putative cells of origin and their presumed levels of differentiation. The characterization of such histological similarities has been primarily dependent on light microscopic features in hematoxylin and eosin-stained sections, immunohistochemical expression of lineage-associated proteins and ultrastructural characterization.
Rapid Determination of Medulloblastoma Subgroup Affiliation With Mass Spectrometry Using a Handheld Picosecond Infrared Laser Desorption Probe

Abstract

Medulloblastoma (MB), the most prevalent malignant childhood brain tumour, consists of at least 4 distinct subgroups each of which possesses a unique survival rate and response to treatment. To rapidly determine MB subgroup affiliation in a manner that would be actionable during surgery, we subjected murine xenograft tumours of two MB subgroups (SHH and Group 3) to Mass Spectrometry (MS) profiling using a handheld Picosecond InfraRed Laser (PIRL) desorption probe and interface developed by our group. This platform provides real time MS profiles of tissue based on laser desorbed lipids and small molecules with only 5-10 seconds of sampling. PIRL-MS analysis of ex vivo MB tumours offered a 98% success rate in subgroup determination, observed over 194 PIRL-MS datasets collected from 19 independent tumours (~10 repetitions each) utilizing 6 different established MB cell lines. Robustness was verified by a 5%-leave-out-and-remodel test. PIRL ablated tissue material was collected on a filter paper and subjected to high resolution LC-MS to provide ion identity assignments for the m/z values that contribute most to the statistical discrimination between SHH and Group 3 MB. Based on this analysis, rapid classification of MB with PIRL-MS utilizes a variety of fatty acid chains, glycerophosphates, glycercophosphoglycerols and glycerophosphocholines rapidly extracted from the tumours. In this work, we provide evidence that 5-10 seconds of sampling from ex vivo MB tissue with PIRL-MS can allow robust tumour subgroup classification, and have identified several biomarker ions responsible for the statistical discrimination of MB Group 3 and the SHH subgroup. The existing PIRL-MS platform used herein offers capabilities for future in vivo use.
Antigen-specific immunoreactivity and clinical outcome following vaccination with glioma-associated antigen peptides in children with recurrent high-grade gliomas: results of a pilot study

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Abstract Recurrent high-grade gliomas (HGGs) of childhood have an increasingly poor prognosis with current therapies. Accordingly, new treatment approaches are needed. We initiated a pilot trial of vaccinations with peptide epitopes derived from glioma-associated antigens (GAAs) overexpressed in these tumors in HLA-A2+ children with recurrent HGGs that had progressed after prior treatments. Peptide epitopes for three GAAs (EphA2, II.13Ra2, survivin), expressed in Montana-ISA-51, were administered subcutaneously adjacent to intramuscular injections of poly-I:CLC every 3 weeks for 8 courses, followed by booster vaccinations every 6 weeks. Primary endpoints were safety and T-cell responses against the GAA epitopes, assessed by enzyme-linked immunospot (ELISPOT) analysis. Treatment response was evaluated clinically and by magnetic resonance imaging. Twelve children were enrolled, 6 with glioblastoma, 5 with anaplastic astrocytoma, and one with malignant gliomatosis cerebri. No dose-limiting non-CNS toxicity was encountered. ELISPOT analysis, in ten children, showed GAA responses in 9 to II.13Ra2 in 4, EphA2 in 9, and survivin in 3. One child had presumed symptomatic pseudoprogression, discontinued vaccine therapy, and responded to subsequent treatment. One other child had a partial response that persisted throughout 2 years of vaccine therapy, and continues at >39 months. Median progression-free survival (PFS) from the start of vaccination was 4.1 months and median overall survival (OS) was 12.9 months. 6-month PFS and OS were 33 and 73%, respectively. GAA peptide vaccination in children with recurrent malignant gliomas is generally well tolerated, and has preliminary evidence of immunological and modest clinical activity.

Keywords Astrocytoma · Glioma · Immunotherapy · Pediatric brain tumor · Vaccine therapy

Introduction

Children with malignant gliomas have high rates of disease progression after initial therapy with irradiation and adjuvant chemotherapy, with 5-year survival rates less than 20%
Rationale and Design of a Phase 1 Clinical Trial to Evaluate HSV G207 Alone or with a Single Radiation Dose in Children with Progressive or Recurrent Malignant Supratentorial Brain Tumors

CLINICAL PROTOCOL

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Primary central nervous system tumors are the most common solid neoplasm of childhood and the leading cause of cancer-related death in pediatric patients. Survival rates for children with malignant supratentorial brain tumors are poor despite aggressive treatment with combinations of surgery, radiation, and chemotherapy, and survivors often suffer from damaging lifelong sequelae from current therapies. Novel innovative treatments are greatly needed. One promising new approach is the use of a genetically engineered, conditionally replicating herpes simplex virus (HSV) that has shown tumor-specific tropism and potential efficacy in the treatment of malignant brain tumors. G207 is a genetically engineered HSV-1 lacking genes essential for replication in normal brain cells. Safety has been established in preclinical investigations involving intracranial inoculation in the highly HSV-sensitive owl monkey (Aotus nancymai), and in three adult phase I trials in recurrent/progressive high-grade gliomas. No dose-limiting toxicities were seen in the adult studies and a maximum tolerated dose was not reached. Approximately half of the 35 treated adults had radiographic or neuropathologic evidence of response at a minimum of one time point. Preclinical studies in pediatric brain tumor models indicate that a variety of pediatric tumor types are highly sensitive to killing by G207. This clinical protocol outlines a first in human children study of intratumoral inoculation of an oncolytic virus via catheters placed directly into recurrent or progressive supratentorial malignant tumors.

Keywords: HSV, oncolytic, virotherapy, pediatric, brain tumors, G207
Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: a systematic review and meta-analysis

Hadeel Hassain12, Anne Pinches2, Susan V. Pilton2, Robert S. Phillips12

Abstract  Diagnosis of a pediatric high grade brain stem glioma is devastating with dismal outcomes. This systematic review and meta-analysis was undertaken to determine the survival rates and assess potential prognostic factors including selected interventions. Studies included involved pediatric participants with high grade brain stem gliomas diagnosed by magnetic resonance imaging or biopsy reporting overall survival rates. Meta-analysis was undertaken using a binomial random effects model. Sixty-five studies (2336 participants) were included. Meta-analysis showed 1 year overall survival (OS) of 41% (95% confidence interval (CI) 38-44%, 1-sq 52%, 2083 participants), 2 year OS 15.3% (95% confidence interval 12-20%, 1-sq 73.1%, 1329 participants) and 3 year OS of 7.3% (95% confidence interval 5.2-10%, 1-sq 26%, 584 participants). Meta-analyses of median overall survival results was not possible due to the lack of reported measures of variance. Subgroup analysis comparing date of study, classification of tumor, use of temozolomide, non-standard interventions or phase 1/2 versus other studies demonstrated no difference in survival outcomes. There was insufficient data to undertake subgroup meta-analysis of patient age, duration of symptoms, K27M histone mutations and AVCR1 mutations. Survival outcomes of high grade brain stem gliomas have remained very poor, and do not clearly vary according to classification, phase of study or use of different therapeutic interventions. Future studies should harmonize outcome and prognostic variable reporting to enable accurate meta-analysis and better exploration of prognosis.

Keywords  Pediatrics - Brain stem glioma - DIPG - Prognostic - Survival and systematic review

Abbreviations  DIPG - Diffuse intrinsic pontine glioma
BSG - Brain stem glioma
RCT - Randomised-controlled trial
CNS - Central nervous system
WHO - World Health Organisation
MRI - Magnetic resonance imaging
CENTRAL - The Cochrane Central Register of Controlled Trials
OS - Overall survival
USA - United States of America
UK - United Kingdom

Introduction
Targeted detection of genetic alterations reveal the prognostic impact of H3K27M and MAPK pathway aberrations in paediatric thalamic glioma

Abstract
Paediatric brain tumours arising in the thalamus present significant diagnostic and therapeutic challenges to physicians due to their sensitive midline location. As such, genetic analysis for biomarkers to aid in the diagnosis, prognosis and treatment of these tumours is needed. Here, we identified 64 thalamic gliomas with clinical follow-up and characterized targeted genomic alterations using newly optimized droplet digital and NanoString-based assays. The median age at diagnosis was 9.25 years (range 0.63–17.55) and median survival was 6.43 (range 0.01–27.63) years. Our cohort contained 42 and 22 tumours reviewed as low and high grade gliomas, respectively. Five (12.5%) low grade and 11 (50%) high grade gliomas were positive for the H3F3A/HIST1H3B H27M (H3K27M) mutation. Kaplan-Meier survival analysis revealed significantly worse overall survival for patients harbouring the H3K27M mutation versus H3F3A/ HIST1H3B wild type (H3WT) samples (log-rank \( p < 0.0001 \)) with a median survival of 1.02 vs. 9.12 years. Mitogen-activated protein kinase (MAPK) pathway activation via BRAF or FGFR1 hotspot mutations or fusion events were detected in 44% of patients, and was associated with long-term survival in the absence of H3K27M (log-rank \( p < 0.0001 \)). Multivariate analysis demonstrated H3K27M status and high grade histology to be the most significant independent predictors of poor overall survival with hazard ratios of 6.945 and 7.721 (\( p < 0.0001 \)), respectively. In contrast, MAPK pathway activation is a predictor of favourable patient outcome, although not independent of other clinical factors. Importantly, we show that low grade malignancies may harbour H3K27M mutations and that these tumours show a dismal survival compared to low grade H3WT cases. Our data strongly supports the inclusion of targeted genetic testing in childhood thalamic tumours to most accurately stratify patients into appropriate risk groups.

Keywords: Thalamic glioma, Pediatric, H3K27M, MAPK, BRAF, Prognostic
Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study

Summary

Background International consensus recognises four medulloblastoma molecular subgroups: WNT (MBWNT), SHH (MBSHH), group 3 (MBG3), and group 4 (MBG4), each defined by their characteristic genome-wide transcriptomic and DNA methylation profiles. These subgroups have distinct clinicopathological and molecular features, and underpin current disease subclassification and initial subgroup-directed therapies that are underway in clinical trials. However, substantial biological heterogeneity and differences in survival are apparent within each subgroup, which remain to be resolved. We aimed to investigate whether additional molecular subgroups exist within childhood medulloblastoma and whether these could be used to improve disease subclassification and prognosis predictions.

Methods In this retrospective cohort study, we assessed 428 primary medulloblastoma samples collected from UK Children’s Cancer and Leukaemia Group (CCLG) treatment centres (UK), collaborating European institutions, and the UKCCSG-SIOP-PNET5 European clinical trial. An independent validation cohort (n=276) of archival tumour samples was also analysed. We analysed samples from patients with childhood medulloblastoma who were aged 0–16 years at diagnosis, and had central review of pathology and comprehensive clinical data. We did comprehensive molecular profiling, including DNA methylation microarray analysis, and did unsupervised class discovery of test and validation cohorts to identify consensus primary molecular subgroups and characterise their clinical and biological significance. We modelled survival of patients aged 3–16 years in patients (n=215) who had craniospinal irradiation and had been treated with a curative intent.

Findings Seven robust and reproducible primary molecular subgroups of childhood medulloblastoma were identified. MBWNT remained unchanged and each remaining consensus subgroup was split in two. MBSHH was split into age-dependent subgroups corresponding to infant (<4.3 years; MBWNT, n=65) and childhood patients (≥4.3 years; MBWNT, n=38). MBG3 and MBG4 were each split into high-risk (MBWNT, n=65) and low-risk (MBWNT, n=50) and MBG3 (n=73) subgroups. These biological subgroups were validated in the independent cohort. We identified features of the seven subgroups that were predictive of outcome. Cross-validated subgroup-dependent survival models, incorporating these novel subgroups along with secondary clinicopathological and molecular features and established disease risk-factors, outperformed existing disease risk-stratification schemes. These subgroup-dependent models stratified patients into four clinical risk groups for 5-year progression-free survival: favourable risk (34% [25%] of 215 patients; 91% survival [95% CI 82–100%]; standard risk [50% [23%] patients; 81% survival [70–94%]; high-risk (82% [35%] patients; 42% survival [31–56%]; and very high-risk (29% [13%] patients; 23% survival [14–56%]).

Interpretation The discovery of seven novel, clinically significant subgroups improves disease risk-stratification and could inform treatment decisions. These data provide a new foundation for future research and clinical investigations.

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The whole-genome landscape of medulloblastoma subtypes


Current therapies for medulloblastoma, a highly malignant childhood brain tumour, impose debilitating effects on the developing child, and highlight the need for molecularly targeted treatments with reduced toxicity. Previous studies have been unable to identify the full spectrum of driver genes and molecular processes that operate in medulloblastoma subgroups. Here we analyse the somatic landscape across 491 sequenced medulloblastoma samples and the molecular heterogeneity among 1,236 epigenetically analysed cases, and identify subgroup-specific driver alterations that include previously undiscovered actionable targets. Driver mutations were confidently assigned to most patients belonging to Group 3 and Group 4 medulloblastoma subgroups, greatly enhancing previous knowledge. New molecular subtypes were differentially enriched for specific driver events, including hotspot in-frame insertions that target KIF6 and ‘enhancer hijacking’ events that activate PRDM6. Thus, the application of integrative genomics to an extensive cohort of clinical samples derived from a single childhood cancer entity revealed a series of cancer genes and biologically relevant subtype diversity that represent attractive therapeutic targets for the treatment of patients with medulloblastoma.
Spinale Tumoren

Prof. Dr. med. Stefan Zausinger (München)

Patient-reported outcomes after surgical stabilization of spinal tumors: symptom-based validation of the Spinal Instability Neoplastic Score (SINS) and surgery

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The Spine Journal, in press

BACKGROUND CONTEXT

Neoplastic spinal instability is movement-related pain or neurologic compromise under physiologic loads with the Spinal Instability Neoplastic Score (SINS) developed to facilitate diagnosis. There is a paucity of evidence that mechanical instability correlates with patient reported symptoms and that surgical stabilization significantly improves these patient-reported outcomes (PROs).

PURPOSE

The objective of this study was to determine if SINS correlates with patient-reported preoperative pain and disability, and if surgical stabilization significantly improves PRO.

STUDY DESIGN

A single-institution prospective cohort study was carried out.

PATIENT SAMPLE

A total of 131 patients who underwent stabilization for metastatic spinal tumor treatment between July 2014 and August 2016 were included.

OUTCOMES MEASURES

Preoperative baseline and mean difference in perioperative PROs as assessed by the Brief Pain Inventory (BPI) and MD Anderson Symptom Inventory (MDASI) were the outcome measures.

METHODS

The SINS was analyzed as a continuous, ordinal, and categorical variable (Stable: 0–6, Indeterminate: 7–12, Unstable: 13–18). Statistical analysis was performed using Spearman rank coefficient (rho), the Kruskal-Wallis test, and an extension of the Cochran-Armitage trend
test. The SINS and association between the mean differences in post- and preoperative PRO scores was analyzed using the Wilcoxon signed-rank test.

RESULTS

There was a statistically significant positive correlation between increasing SINS and severity of preoperative pain with BPI average pain (rho=0.20; p=.03) and MDASI pain (rho=0.19; p=.03). Increasing SINS correlated with severity of preoperative disability with BPI walking (rho=0.19; p=.04), MDASI activity (rho=0.24; p=.006), and MDASI walking (rho=0.20; p=.03). Similar associations were noted when SINS was analyzed as an ordinal categorical variable. Stabilization significantly improved nearly all PRO measures for patients with indeterminate and unstable SINS. Significant correlations persisted when controlling for neurologic status and were not affected based on the technique of surgical stabilization used.
The timing of surgical intervention in the treatment of complete motor paralysis in patients with spinal metastasis

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Eur Spine J (2016) 25:4060–4066

PURPOSE

The timing of surgical intervention is important for ambulatory patients with metastatic epidural spinal cord compression (MESCC), while limited studies have focused on non-ambulant patients. The aim of this study was to investigate the proper timing of surgical intervention for paraplegic patients with MESCC.

METHODS

Forty-three non-ambulant patients with MESCC who underwent posterior decompression were retrospectively reviewed. The neurological outcomes for pre-operative Frankel B patients with different interval window were further compared.

RESULTS

Neurologic deficit improved by at least 1 Frankel grade in 37 patients who underwent surgery within 72 h (86.0 %). Overall, 18 pre-operative Frankel B patients became ambulatory again with an interval of less than 48 h, 15 pre-operative Frankel B patients remained nonambulatory post-operatively with an interval longer than 48 h besides one with an interval of 8 h ($P<0.001$). All nine pre-operative Frankel A patients remained non-ambulatory even though the interval window was less than 24 h.

CONCLUSION

The timing of surgical intervention was key to predicting the post-operative outcome, and 48 h was suggested as the proper interval window for pre-operative.
Thirty-day readmission and reoperation after surgery for spinal tumors: a National Surgical Quality Improvement Program analysis

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Neurosurg Focus 41 (2):E5, 2016

OBJECTIVE

The goal of this study was to use a large national registry to evaluate the 30-day cumulative incidence and predictors of adverse events, readmissions, and reoperations after surgery for primary and secondary spinal tumors.

METHODS

Data from adult patients who underwent surgery for spinal tumors (2011–2014) were extracted from the prospective National Surgical Quality Improvement Program (NSQIP) registry. Multivariable logistic regression was used to evaluate predictors of reoperation, readmission, and major complications (death, neurological, cardiopulmonary, venous thromboembolism [VTE], surgical site infection [SSI], and sepsis). Variables screened included patient age, sex, tumor location, American Society of Anesthesiologists (ASA) physical classification, preoperative functional status, comorbidities, preoperative laboratory values, case urgency, and operative time. Additional variables that were evaluated when analyzing readmission included complications during the surgical hospitalization, hospital length of stay (LOS), and discharge disposition.

RESULTS

Among the 2207 patients evaluated, 51.4% had extradural tumors, 36.4% had intradural extramedullary tumors, and 12.3% had intramedullary tumors. By spinal level, 20.7% were cervical lesions, 47.4% were thoracic lesions, 29.1% were lumbar lesions, and 2.8% were sacral lesions. Readmission occurred in 10.2% of patients at a median of 18 days (interquartile range [IQR] 12–23 days); the most common reasons for readmission were SSIs (23.7%), systemic infections (17.8%), VTE (12.7%), and CNS complications (11.9%). Predictors of readmission were comorbidities (dyspnea, hypertension, and anemia), disseminated cancer, preoperative steroid use, and an extended hospitalization. Reoperation occurred in 5.3% of patients at a median of 13 days (IQR 8–20 days) postoperatively and was associated with preoperative steroid use and ASA Class 4–5 designation. Major complications occurred in 14.4% of patients: the most common complications and their median time to occurrence were VTE (4.5%) at 9 days (IQR 4–19 days) postoperatively, SSIs (3.6%) at 18 days (IQR 14–25 days), and sepsis (2.9%) at 13 days (IQR 7–21 days). Predictors of major complications included dependent functional status, emergency case status, male sex, comorbidities (dyspnea, bleeding disorders, preoperative systemic inflammatory response syndrome, preoperative leukocytosis), and ASA Class 3–5 designation (p < 0.05). The median hospital LOS was 5 days.
(IQR 3–9 days), the 30-day mortality rate was 3.3%, and the median time to death was 20 days (IQR 12.5–26 days).

CONCLUSIONS

In this NSQIP analysis, 10.2% of patients undergoing surgery for spinal tumors were readmitted within 30 days, 5.3% underwent a reoperation, and 14.4% experienced a major complication. The most common complications were SSIs, systemic infections, and VTE, which often occurred late (after discharge from the surgical hospitalization). Patients were primarily readmitted for new complications that developed following discharge rather than exacerbation of complications from the surgical hospital stay. The strongest predictors of adverse events were comorbidities, preoperative steroid use, and higher ASA classification. These models can be used by surgeons to risk-stratify patients preoperatively and identify those who may benefit from increased surveillance following hospital discharge.
A multicenter cohort study of spinal osteoid osteomas: results of surgical treatment and analysis of local recurrence

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The Spine Journal 17 (2017) 401–408

CONTEXT

As a relatively rare spinal neoplasm, the natural history and outcomes of treatment for symptomatic osteoid osteoma are not well characterized. In this context, the authors present clinical data on patients treated for this condition across a number of centers.

CONTRIBUTION

The study included 84 patients treated over a 22-year timeperiod. Follow-up exceeded 2.5 years on average. A total of six patients (7%) experienced local recurrence. An intralesional resection had occurred in all of these individuals.

IMPLICATIONS

The findings of this study emphasize the importance of complete resection of the nidus. En-bloc resection may increase surgical morbidity and piece-meal excision appears to be effective as long as removal of the nidus is achieved. However the authors may wish to refer to their study design, this paper should be viewed as a retrospective review with clear implications for confounding by selection and indication. Advantages include a relatively large number of cases given the rarity of this condition treated at different medical centers. The evidence presented should be viewed as Level IV nonetheless.
Osteoblastomas of the spine: a comprehensive review
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Neurosurg Focus 41 (2):E4, 2016

Osteoblastomas are primary bone tumors with an affinity for the spine. They typically involve the posterior elements, although extension through the pedicles into the vertebral body is not uncommon. Histologically, they are usually indistinguishable from osteoid osteomas. However, there are different variants of osteoblastomas, with the more aggressive type causing more pronounced bone destruction, soft-tissue infiltration, and epidural extension. A bone scan is the most sensitive radiographic examination used to evaluate osteoblastomas. These osseous neoplasms usually present in the 2nd decade of life with dull aching pain, which is difficult to localize. At times, they can present with a painful scoliosis, which usually resolves if the osteoblastoma is resected in a timely fashion. Neurological manifestations such as radiculopathy or myelopathy do occur as well, most commonly when there is mass effect on nerve roots or the spinal cord itself. The mainstay of treatment involves surgical intervention. Curettage has been a surgical option, although marginal excision or wide en bloc resection are preferred options. Adjuvant radiotherapy and chemotherapy are generally not undertaken, although some have advocated their use after less aggressive surgical maneuvers or with residual tumor. In this manuscript, the authors have aimed to systematically review the literature and to put forth an extensive, comprehensive overview of this rare osseous tumor.
A Systematic Review With Consensus Expert Opinion of Best Reconstructive Techniques After Osseous En Bloc Spinal Column Tumor Resection

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SPINE Volume 41, Number 20S, pp S205–S211

STUDY DESIGN

Systematic literature review and consensus expert opinion.

OBJECTIVE

To provide recommendations on reconstructive constructs for large tumor resections of the spinal column. Four questions were studied: (1) What are the best reconstructive options for single versus multilevel resections? (2) Should short segment fixation be considered in primary tumor reconstruction? (3) How should reconstructive techniques differ at various regions of the spine? (4) Does planned postoperative radiation change the fusion strategy?

SUMMARY OF BACKGROUND DATA

Primary spinal tumors requiring en bloc resection are rare. Most studies focus on disease-free survival and local recurrence rates. Few studies focus on reconstructive options and outcomes with respect to fusion rates and need for revision.

METHODS

A literature search was performed from January 1990 to December 2013. Data were combined and construct survivorship summarized. A survey was administered to international spine tumor surgeons, evaluating reconstructive preferences.

RESULTS

The search yielded 381 articles, 12 included in the final analysis. Revision rates for anterior reconstruction were similar for autogenous strut grafts (10%), cages (7.7%), and allograft strut grafts (8.3%). There were two reports of revision from short to long segment constructs and three reports of broken pedicle screws, one requiring revision. Expert survey results revealed that most surgeons preferred cages packed with morcelized allograft and autograft (75%) for anterior reconstruction of single-level vertebrectomies, and strut bone grafting at the cervicothoracic junction (65%) and when more than one vertebrae was resected in the mid-thoracic spine (75%). Surgeons may alter their fusion technique if postoperative radiation is planned.
CONCLUSION

Posterior reconstruction with at least two vertebral levels above and below is recommended. Cages should be used for single-level defects and structural bone graft alone, or in combination with a cage, should be used when spanning a defect greater than two vertebral bodies. Planned postoperative radiation may affect fusion strategy.
Association of tumor location, extent of resection, and neurofibromatosis status with clinical outcomes for 221 spinal nerve sheath tumors

Michael Safaee, MD,1 Andrew T. Parsa, MD, PhD,2 Nicholas M. Barbaro, MD,3 Dean Chou, MD,1 Praveen V. Mummaneni, MD,1 Philip R. Weinstein, MD,1 Tarik Tihan, MD, PhD,4 and Christopher P. Ames, MD 1,5


OBJECT

Intradural extramedullary spine tumors represent two-thirds of all primary spine neoplasms. Approximately half of these are peripheral nerve sheath tumors, mainly neurofibromas and schwannomas. Given the rarity of this disease and, thus, the limited analyses of clinical outcomes, the authors examined the association of tumor location, extent of resection, and neurofibromatosis (NF) status with clinical outcomes.

METHODS

Patients were identified through a search of the University of California, San Francisco, neuropathology database and a separate review of current procedural terminology codes. Data recorded included patient age, patient sex, clinical presentation, presence of NF, tumor type, tumor location, extent of resection (gross-total resection [GTR] or subtotal resection [STR]), and clinical follow-up.

RESULTS

Of 221 tumors in 199 patients (mean age 45 years), 53 were neurofibromas, 163 were schwannomas, and 5 were malignant peripheral nerve sheath tumors. The most common presenting symptom was spinal pain (76%), followed by weakness (36%) and sensory abnormalities (34%). Mean symptom duration was 16 months. In terms of spinal location, neurofibromas were more common in the cervical spine (74% vs 27%, p < 0.001), and schwannomas were more common in the thoracic and lumbosacral spine (73% vs 26%, p < 0.001). Rates of GTR were lower for neurofibromas than schwannomas (51% vs 83%, p < 0.001), regardless of location. Rates of GTR were lower for cerebral (54%) than thoracic (90%) and lumbosacral (86%) lesions (p < 0.001). NF was associated with lower rates of GTR among all tumors (43% vs 86%, p < 0.001). The mean follow-up time was 32 months. Recurrence/progression was more common for neurofibromas than schwannomas (17% vs 7%, p = 0.03), although the mean time to recurrence/progression did not differ according to tumor type (45 vs 53 months, p = 0.63). As expected, GTR was associated with lower recurrence rates (4% vs 22%, p < 0.001). According to multivariate analysis, cervical location (OR 0.239, 95% CI 0.110–0.520) and presence of NF (OR 0.166, 95% CI 0.054–0.507) were associated with lower rates of GTR. In a separate model, only GTR (OR 0.141, 95% CI 0.046–0.429) was associated with tumor recurrence.
CONCLUSIONS

Resection is an effective treatment for spinal nerve sheath tumors. Neurofibromas were found more commonly in the cervical spine than in other regions of the spine and were associated with higher rates of recurrence and lower rates of GTR than other tumor types, particularly in patients with NF Types 1 or 2. According to multivariate analysis, both cervical location and presence of NF were associated with lower rates of GTR. According to a second multivariate model, the only variable associated with tumor recurrence was extent of resection. Maximal safe resection remains ideal for these.
Novel dural incision and closure procedure for preventing postoperative cerebrospinal fluid leakage during the surgical removal of dumbbell-shaped spinal tumors: technical note

Kiyoshi Ito, MD, Tatsuro Aoyama, MD, Takuya Nakamura, MD, Yoshiki Hanaoka, MD, Tetsuyoshi Horiuchi, MD, and Kazuhiro Hongo, MD


The authors report on a new method for removing dumbbell-shaped spinal tumors that avoids the risk for postoperative cerebrospinal fluid (CSF) leakage. Adequate visualization of the intra- and extradural components of the tumor is achieved with the use of separate dural incisions. First, the dura mater is opened along the dural theca to provide adequate visualization of the intradural portion of the mass; then, a second incision is made along the nerve root to remove the extradural component. Meticulous suturing is essential in intradural lesion cases; however, the dura mater is usually thin and fragile in such cases. During suturing with a needle and thread, the dura mater can become lacerated proximal to the needle holes and result in CSF leakage. In the authors’ technique, instead of using a needle and thread, nonpenetrating vascular clips were used to close the dural incisions. When operating on dumbbell-shaped spinal tumors, the authors found that the “separate-dural-incision method” was preferable to the conventional T-shaped dural incision method because no dural defects occurred after the intradural procedure and meticulous dural closure with vascular clips was achieved. The authors conclude that the novel separate-dural-incision method for removing dumbbell-shaped tumors and the use of nonpenetrating vascular clips permits reliable dural closure, prevents postoperative CSF leakage, and promises good postoperative clinical results.
Ewing’s Sarcoma of the Spine: Prognostic Variables for Survival and Local Control in Surgically Treated Patients

Raphaële Charest-Morin, MD1, Michael S Dirks, MD2, Shreyaskumar Patel, MD3, Stefano Boriani, MD4, Alessandro Luzzati, MD5, Michael G Fehlings, MD, PhD6, Charles G Fisher, MD, MHSc7, Mark B Dekutoski, MD8, Richard Williams, MD9, Nasir A Quraishi, MD10, Ziya L Gokaslan, MD11, Chetan Bettegowda, MD, PhD12, Alessandro Luzzati, MD5, Michael G Fehlings, MD, PhD6, Charles G Fisher, MD, MHSc7, Mark B Dekutoski, MD8, Richard Williams, MD9, Nasir A Quraishi, MD10, Ziya L Gokaslan, MD11, Chetan Bettegowda, MD, PhD12, Niccole M Germscheid, MSc13, Peter P Varga, MD14 and Laurence D Rhines, MD15, AOSpine Knowledge Forum Tumor

SPINE An International Journal for the study of the spine Publish Ahead Of Print

STUDY DESIGN

Multicenter, ambispective observational study.

Objectives: To quantify mortality and local recurrence after surgical treatment of spinal Ewing’s sarcoma (ES) and to determine whether an Enneking appropriate procedure and surgical margins (en bloc resection with wide/marginal margins) are associated with improved prognosis.

SUMMARY OF BACKGROUND DATA

Treatment of primary ES of the spine is complex. Ambiguity remains regarding the role and optimal type of surgery in the treatment of spinal ES.

METHODS

The AOSpine Knowledge Forum Tumor developed a multicenter database including demographics, diagnosis, treatment, mortality, and recurrence rate data for spinal ES. Patients were stratified based on surgical margins and Enneking appropriateness. Survival and recurrence were analyzed using Kaplan-Meier curves and log-rank tests.

RESULTS

Fifty-eight patients diagnosed with primary spinal ES underwent surgery. Enneking appropriateness of surgery was known for 55 patients; 24 (44%) treated Enneking appropriately (EA) and 31 (56%) treated Enneking inappropriately (EI). A statistically significant difference in favor of EA-treated patients was found with regards to survival ($p = 0.034$). Neoadjuvant and postoperative chemotherapy was significantly associated with increased survival ($p = 0.008$). Local recurrence occurred in 22% ($N = 5$) of patients with an EA procedure versus 38% ($N = 11$) of patients with an EI procedure. The timing of chemotherapy treatment was significantly different between the Enneking cohorts ($p < 0.001$) and all EA-treated patients received chemotherapy treatment. Although, local recurrence was not significantly different between Enneking cohorts ($p = 0.140$), intrallesional surgical margins and patients who received a previous spine tumor operation were associated with increased local recurrence ($p = 0.025$ and $p = 0.018$, respectively).
CONCLUSION

Surgery should be undertaken when an en bloc resection with wide/marginal margins is feasible. An EA surgery correlates with improved survival, but the impact of other prognostic factors needs to be evaluated. En bloc resection with wide/marginal margins is associated with local control.
Spinal cord hemangioblastomas: significance of intraoperative neurophysiological monitoring for resection and long-term outcome

Sebastian Siller, MD, Andrea Szelényi, MD, Lisa Herlitz, Joerg Christian Tonn, MD, and Stefan Zausinger, MD


OBJECTIVE

Spinal cord hemangioblastomas are rare benign tumors developing either sporadically or as part of von Hippel-Lindau (VHL) disease. Generally, resection is the treatment of choice. However, the significance of intraoperative neurophysiological monitoring (IONM) for resection and postoperative outcome is still controversial. The authors analyzed the surgical and clinical courses of patients who had undergone resection of spinal cord hemangioblastoma, with special attention to preoperative imaging, the use of IONM, and short- and long-term outcomes.

METHODS

A series of 24 patients (male/female 1:1, lesion sporadic/associated with VHL 2.4:1) who had undergone 26 operations for the resection of 27 spinal cord hemangioblastomas was analyzed. All patients had undergone pre- and postoperative contrast-enhanced MRI. In all cases, microsurgical tumor removal had been performed under continuous IONM of both somatosensory and transcranial motor evoked potentials as well as electromyographic recording. Clinical characteristics, imaging findings, and operative records were retrospectively analyzed. Outcome parameters included short- and long-term status as regards sensorimotor deficits and a questionnaire on general performance, patient satisfaction, and Oswestry Disability Index (ODI) at the end of the follow-up period. The impact of IONM findings on postoperative deficits and outcome parameters as well as risk factors affecting functional prognosis was statistically assessed.

RESULTS

Preoperative symptoms (mean duration 16.2 ± 22.0 months) included sensory changes (100.0%), pain (66.7%), spinal ataxia (66.7%), motor deficit (41.7%), and bladder/bowel dysfunction (12.5%). Average age at the first operation was 36.8 ± 12.8 years. Most tumors (21 intramedullary, 6 intra- and/or extramedullary) were located dorsally (92.6%) and cervically (77.8%) and were accompanied by peritumoral edema and/or syringomyelia (81.5%). Tumor resection was achieved via laminectomy for 15 tumors, hemilaminectomy for 5, laminoplasty for 6, and interlaminar approach for 1. Gross-total resection was accomplished for 26 tumors (96.3%) with no local tumor recurrence during follow-up. Intraoperative neurophysiological monitoring was nonpathological in 11 operations (42.3%) and pathological in 15 (57.7%). Patients with nonpathological IONM had significantly fewer new sensorimotor deficits (p = 0.005). Long-term follow-up evaluation (mean 7.9 ± 4.0 years postoperatively, 7 patients lost to follow-up) revealed a stable or improved McCormick myelopathy grade in

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88.2% of the patients, and 88.2% reported a stable or improved overall outcome according to Odom’s criteria. Long-term general performance was excellent with 88.2% having a WHO/Eastern Cooperative Oncology Group (ECOG) Performance Status grade ≤ 1, 76.5% a Karnofsky Performance Scale score ≥ 80, and 70.6% a Barthel Index (BI) of 100. The mean ODI (11.4% ± 12.5%) indicated only minimal disability. There was a significant correlation between pathological IONM findings and a worse long-term status according to the BI and ODI (p = 0.011 and 0.024, respectively). Additionally, VHL disease was a risk factor affecting functional prognosis (p = 0.044).

CONCLUSIONS

Microsurgical removal of spinal cord hemangioblastomas with IONM facilitates a satisfying long-term outcome for patients. Nonpathological IONM findings are associated with a lower risk of new sensorimotor deficits and correlate with a better overall long-term outcome. von Hippel–Lindau disease is a risk factor for a worse long-term prognosis.
Optimal Timing of Surgery for Intramedullary Cavernous Hemangioma of the Spinal Cord in Relation to Preoperative Motor Paresis, Disease Duration, and Tumor Volume and Location

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Global Spine Journal 2017, Vol. 7(3) 246-253

STUDY DESIGN
Prospective study.

OBJECTIVE
Investigate factors associated with preoperative motor paresis, recovery, ambulatory status, and intraoperative neurophysiological monitoring (IONM) among patients with no preoperative paresis (N group), complete preoperative motor recovery (CR group), and no complete recovery (NCR group) in patients with intramedullary spinal cavernous hemangioma to determine the optimal timing of surgery.

METHODS
The study evaluated 41 surgical cases in our institute. Disease duration, tumor lesion, manual muscle testing (MMT), and gait at onset, just before surgery, and final follow-up (FU), tumor and lesion volume, IONM, extent of tumor resection, and tumor recurrence were evaluated among N, CR, and NCR groups.

RESULTS
Motor paresis at onset was found in 26 patients (63%), with 42% of those in CR group. Disease duration from onset negatively affected stable gait just before surgery and FU as well as lower preoperative MMT (P < .05). Thoracic tumors were associated with patients with unstable gait before surgery (P < .05). Tumor volume was larger in NCR group (P < .05). IONM significantly decreased in NCR and CR groups than in N group (P < .05). The NCR group had residual mild motor paresis at FU (P < .05). Stable gait at FU was similar in N group and CR group, though lower in NCR group (P < .05).

CONCLUSIONS
Early surgery is generally recommended for thoracic tumors and large tumors during stable gait without motor paresis before long disease duration. Surgery may be postponed until patients recover from preoperative motor paresis to allow optimal surgical outcome. IONM should be carefully monitored in patients with a history of preoperative paresis even with preoperative complete motor recovery.
Meningiome und Neurinome

Prof. Dr. med. Matthias Simon (Bonn)

#1 Meningeome

DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis.


BACKGROUND

The WHO classification of brain tumours describes 15 subtypes of meningioma. Nine of these subtypes are allotted to WHO grade I, and three each to grade II and grade III. Grading is based solely on histology, with an absence of molecular markers. Although the existing classification and grading approach is of prognostic value, it harbours shortcomings such as ill-defined parameters for subtypes and grading criteria prone to arbitrary judgment. In this study, we aimed for a comprehensive characterisation of the entire molecular genetic landscape of meningioma to identify biologically and clinically relevant subgroups.

METHODS

In this multicentre, retrospective analysis, we investigated genome-wide DNA methylation patterns of meningiomas from ten European academic neuro-oncology centres to identify distinct methylation classes of meningiomas. The methylation classes were further characterised by DNA copy number analysis, mutational profiling, and RNA sequencing. Methylation classes were analysed for progression-free survival outcomes by the Kaplan-Meier method. The DNA methylation-based and WHO classification schema were compared using the Brier prediction score, analysed in an independent cohort with WHO grading, progression-free survival, and disease-specific survival data available, collected at the Medical University Vienna (Vienna, Austria), assessing methylation patterns with an alternative methylation chip.

FINDINGS

We retrospectively collected 497 meningiomas along with 309 samples of other extra-axial skull tumours that might histologically mimic meningioma variants. Unsupervised clustering of
DNA methylation data clearly segregated all meningiomas from other skull tumours. We generated genome-wide DNA methylation profiles from all 497 meningioma samples. DNA methylation profiling distinguished six distinct clinically relevant methylation classes associated with typical mutational, cytogenetic, and gene expression patterns. Compared with WHO grading, classification by individual and combined methylation classes more accurately identifies patients at high risk of disease progression in tumours with WHO grade I histology, and patients at lower risk of recurrence among WHO grade II tumours (p=0.0096) from the Brier prediction test. We validated this finding in our independent cohort of 140 patients with meningioma.

**INTERPRETATION**

DNA methylation-based meningioma classification captures clinically more homogenous groups and has a higher power for predicting tumour recurrence and prognosis than the WHO classification. The approach presented here is potentially very useful for stratifying meningioma patients to observation-only or adjuvant treatment groups. We consider methylation-based tumour classification highly relevant for the future diagnosis and treatment of meningioma.

*Wie bei den Gliomen – demnächst auch integrierte Diagnosen für Meningeome?*
The Simpson grading revisited: aggressive surgery and its place in modern meningioma management.

Gousias K, Schramm J, Simon M.

Neurosurg. 2016 Sep;125(3):551-60.

OBJECTIVE

Recent advances in radiotherapy and neuroimaging have called into question the traditional role of aggressive resections in patients with meningiomas. In the present study the authors reviewed their institutional experience with a policy based on maximal safe resections for meningiomas, and they analyzed the impact of the degree of resection on functional outcome and progression-free survival (PFS).

METHODS

The authors retrospectively analyzed 901 consecutive patients with primary meningiomas (716 WHO Grade I, 174 Grade II, and 11 Grade III) who underwent resections at the University Hospital of Bonn between 1996 and 2008. Clinical and treatment parameters as well as tumor characteristics were analyzed using standard statistical methods.

RESULTS

The median follow-up was 62 months. PFS rates at 5 and 10 years were 92.6% and 86.0%, respectively. Younger age, higher preoperative Karnofsky Performance Scale (KPS) score, and convexity tumor location, but not the degree of resection, were identified as independent predictors of a good functional outcome (defined as KPS Score 90-100). Independent predictors of PFS were degree of resection (Simpson Grade I vs II vs III vs IV), MIB-1 index (< 5% vs 5%-10% vs >10%), histological grade (WHO I vs II vs III), tumor size (≤ 6 vs > 6 cm), tumor multiplicity, and location. A Simpson Grade II rather than Grade I resection more than doubled the risk of recurrence at 10 years in the overall series (18.8% vs 8.5%). The impact of aggressive resections was much stronger in higher grade meningiomas.

CONCLUSIONS

A policy of maximal safe resections for meningiomas prolongs PFS and is not associated with increased morbidity.

Viel hilft viel.
Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539.


OBJECTIVE

This is the first clinical outcomes report of NRG Oncology RTOG 0539, detailing the primary endpoint, 3-year progression-free survival (PFS), compared with a predefined historical control for intermediate-risk meningioma, and secondarily evaluating overall survival (OS), local failure, and prospectively scored adverse events (AEs).

METHODS

NRG Oncology RTOG 0539 was a Phase II clinical trial allocating meningioma patients to 1 of 3 prognostic groups and management strategies according to WHO grade, recurrence status, and resection extent. For the intermediate-risk group (Group 2), eligible patients had either newly diagnosed WHO Grade II meningioma that had been treated with gross-total resection (GTR; Simpson Grades I-III) or recurrent WHO Grade I meningioma with any resection extent. Pathology and imaging were centrally reviewed. Patients were treated with radiation therapy (RT), either intensity modulated (IMRT) or 3D conformal (3DCRT), 54 Gy in 30 fractions. The RT target volume was defined as the tumor bed and any nodular enhancement (e.g., in patients with recurrent WHO Grade I tumors) with a minimum 8-mm and maximum 15-mm margin, depending on tumor location and setup reproducibility of the RT method. The primary endpoint was 3-year PFS. Results were compared with historical controls (3-year PFS: 70% following GTR alone and 90% with GTR + RT). AEs were scored using NCI Common Toxicity Criteria.

RESULTS

Fifty-six patients enrolled in the intermediate-risk group, of whom 3 were ineligible and 1 did not receive RT. Of the 52 patients who received protocol therapy, 4 withdrew without a recurrence before 3 years leaving 48 patients evaluable for the primary endpoint, 3-year PFS, which was actuarially 93.8% (p = 0.0003). Within 3 years, 3 patients experienced events affecting PFS: 1 patient with a WHO Grade II tumor died of the disease, 1 patient with a WHO Grade II tumor had disease progression but remained alive, and 1 patient with recurrent WHO Grade I meningioma died of undetermined cause without tumor progression. The 3-year actuarial local failure rate was 4.1%, and the 3-year OS rate was 96%. After 3 years, progression occurred in 2 additional patients: 1 patient with recurrent WHO Grade I meningioma and 1 patient with WHO Grade II disease; both remain alive. Among 52 evaluable patients who received protocol treatment, 36 (69.2%) had WHO Grade II tumors and underwent GTR, and 16 (30.8%) had recurrent WHO Grade I tumors. There was no significant difference in PFS between these subgroups (p = 0.52, HR 0.56, 95% CI 0.09-3.35), validating
their consolidation. Of the 52 evaluable patients, 44 (84.6%) received IMRT, and 50 (96.2%) were treated per protocol or with acceptable variation. AEs (definitely, probably, or possibly related to protocol treatment) were limited to Grade 1 or 2, with no reported Grade 3 events.

**CONCLUSIONS**

This is the first clinical outcomes report from NRG Oncology RTOG 0539. Patients with intermediate-risk meningioma treated with RT had excellent 3-year PFS, with a low rate of local failure and a low risk of AEs. These results support the use of postoperative RT for newly diagnosed gross-totally resected WHO Grade II or recurrent WHO Grade I meningioma irrespective of resection extent. They also document minimal toxicity and high rates of tumor control with IMRT. Clinical trial registration no.: NCT00895622 (clinicaltrials.gov).

The estimate of disease control rate ranged from 87.0% to 100.0% at 5 years and from 67.0% to 100.0% at 10 years. The PFS rate ranged 78.0%-98.9% and 53.1%-97.2% at 5 and 10 years, respectively. The overall symptom control was 92.3%, the overall toxicity was 8.1%.

RS can be considered a safe and effective treatment. Efforts are needed in standardizing the definition of local and symptom control and toxicity in order to properly compare different treatment schedules.

*Immerhin eine prospektive Studie. Aber wo ist die Kontrollgruppe?*
Factors Associated With Pre- and Postoperative Seizures in 1033 Patients Undergoing Supratentorial Meningioma Resection.

Chen WC, Magill ST, Englot DJ, Baal JD, Wagle S, Rick JW, McDermott MW.

Neurosurgery. 2017 Aug 1;81(2):297-306

BACKGROUND

Risk factors for pre- and postoperative seizures in supratentorial meningiomas are understudied compared to other brain tumors.

OBJECTIVE

To report seizure frequency and identify factors associated with pre- and postoperative seizures in a large single-center population study of patients undergoing resection of supratentorial meningioma.

METHODS

Retrospective chart review of 1033 subjects undergoing resection of supratentorial meningioma at the author’s institution (1991-2014). Multivariate regression was used to identify variables significantly associated with pre- and postoperative seizures.

RESULTS

Preoperative seizures occurred in 234 (22.7%) subjects. At 5 years postoperative, probability of seizure freedom was 89.9% among subjects without preoperative seizures and 62.2% with preoperative seizures. Multivariate analysis identified the following predictors of preoperative seizures: presence of ≥1 cm peritumoral edema (odds ratio [OR]: 4.45, 2.55-8.50), nonskull base tumor location (OR: 2.13, 1.26-3.67), greater age (OR per unit increase: 1.03, 1.01-1.05), while presenting symptom of headache (OR: 0.50, 0.29-0.84) or cranial nerve deficit (OR: 0.36, 0.17-0.71) decreased odds of preoperative seizures. Postoperative seizures after discharge were associated with preoperative seizures (OR: 5.70, 2.57-13.13), in-hospital seizure (OR: 4.31, 1.28-13.67), and among patients without preoperative seizure, occurrence of medical or surgical complications (OR 3.39, 1.09-9.48). Perioperative anti-epileptic drug use was not associated with decreased incidence of postoperative seizures.

CONCLUSIONS

Nonskull base supratentorial meningiomas with surrounding edema have the highest risk for preoperative seizure. Long-term follow-up showing persistent seizures in meningioma patients with preoperative seizures raises the possibility that these patients may benefit from electrocorticographic mapping of adjacent cortex and resection of noneloquent, epileptically active cortex.

Epilepsie beim Meningeom – ein völlig unterschätztes Thema.
EANO guidelines for the diagnosis and treatment of meningiomas.

Although meningiomas are the most common intracranial tumours, the level of evidence to provide recommendations for the diagnosis and treatment of meningiomas is low compared with other tumours such as high-grade gliomas. The meningioma task force of the European Association of Neuro-Oncology (EANO) assessed the scientific literature and composed a framework of the best possible evidence-based recommendations for health professionals. The provisional diagnosis of meningioma is mainly made by MRI. Definitive diagnosis, including histological classification, grading, and molecular profiling, requires a surgical procedure to obtain tumour tissue. Therefore, in many elderly patients, observation is the best therapeutic option. If therapy is deemed necessary, the standard treatment is gross total surgical resection including the involved dura. As an alternative, radiosurgery can be done for small tumours, or fractionated radiotherapy in large or previously treated tumours. Treatment concepts combining surgery and radiosurgery or fractionated radiotherapy, which enable treatment of the complete tumour volume with low morbidity, are being developed. Pharmacotherapy for meningiomas has remained largely experimental. However, antiangiogenic drugs, peptide receptor radionuclide therapy, and targeted agents are promising candidates for future pharmacological approaches to treat refractory meningiomas across all WHO grades.

Schwannomas are common peripheral nerve sheath tumors that can cause debilitating morbidities. We performed an integrative analysis to determine genomic aberrations common to sporadic schwannomas. Exome sequence analysis with validation by targeted DNA sequencing of 125 samples uncovered, in addition to expected NF2 disruption, recurrent mutations in ARID1A, ARID1B and DDR1. RNA sequencing identified a recurrent in-frame SH3PXD2A-HTRA1 fusion in 12/125 (10%) cases, and genomic analysis demonstrated the mechanism as resulting from a balanced 19-Mb chromosomal inversion on chromosome 10q. The fusion was associated with male gender predominance, occurring in one out of every six men with schwannoma. Methylation profiling identified distinct molecular subgroups of schwannomas that were associated with anatomical location. Expression of the SH3PXD2A-HTRA1 fusion resulted in elevated phosphorylated ERK, increased proliferation, increased invasion and in vivo tumorigenesis. Targeting of the MEK-ERK pathway was effective in fusion-positive Schwann cells, suggesting a possible therapeutic approach for this subset of tumors.

*Neue Gene! Aber andere als beim Meningeom.*
Long-term risk of recurrence and regrowth after gross-total and subtotal resection of sporadic vestibular schwannoma.

Nakatomi H, Jacob JT, Carlson ML, Tanaka S, Tanaka M, Saito N, Lohse CM, Driscoll CLW, Link M.


OBJECTIVE

The management of vestibular schwannoma (VS) remains controversial. One commonly cited advantage of microsurgery over other treatment modalities is that tumor removal provides the greatest chance of long-term cure. However, there are very few publications with long-term follow-up to support this assertion. The purpose of the current study is to report the very long-term risk of recurrence among a large historical cohort of patients who underwent microsurgical resection.

METHODS

The authors retrospectively reviewed the medical records of patients who had undergone primary microsurgical resection of unilateral VS via a retrosigmoid approach performed by a single neurosurgeon-neurotologist team between January 1980 and December 1999. Complete tumor removal was designated gross-total resection (GTR), and anything less than complete removal was designated subtotal resection (STR). The primary end point was radiological recurrence-free survival. Time-to-event analyses were performed to identify factors associated with recurrence.

RESULTS

Four hundred fourteen patients met the study inclusion criteria and were analyzed. Overall, 67 patients experienced recurrence at a median of 6.9 years following resection (IQR 3.9-12.1, range 1.2-22.5 years). Estimated recurrence-free survival rates at 5, 10, 15, and 20 years following resection were 93% (95% CI 91-96, 248 patients still at risk), 78% (72-85, 88), 68% (60-77, 47), and 51% (41-64, 22), respectively. The strongest predictor of recurrence was extent of resection, with patients who underwent STR having a nearly 11-fold greater risk of recurrence than the patients treated with GTR (HR 10.55, p < 0.001). Among the 18 patients treated with STR, 15 experienced recurrence at a median of 2.7 years following resection (IQR 1.9-8.9, range 1.2-18.7). Estimated recurrence-free survival rates at 5, 10, 15, and 20 years following GTR were 96% (95% CI 93-98, 241 patients still at risk), 82% (77-89, 86), 73% (65-81, 46), and 56% (45-70, 22), respectively. Estimated recurrence-free survival rates at 5, 10, and 15 years following STR were 47% (95% CI 28-78, 7 patients still at risk), 17% (5-55, 2), and 8% (1-52, 1), respectively.

CONCLUSIONS

Long-term surveillance is required following microsurgical resection of VS even after GTR. Subtotal resection alone should not be considered a definitive long-term cure. These data emphasize the importance of long-term follow-up when reporting tumor control outcomes for VS.

Viel hilft viel! Schon wieder ...
Microsurgical resection of vestibular schwannomas: complication avoidance.
Rahimpour S, Friedman AH, Fukushima T, Zomorodi AR.


Vestibular schwannoma (VS) surgery requires appropriate patient selection, meticulous microsurgical technique and optimal post-operative care. Focused radiation is an effective alternative for the treatment of smaller VSs. For VS surgery to remain a reasonable option, surgery must be performed with a limited number of complications. Complication rates for VS surgery have increased over the last decade. This is likely due to (1) decreased surgical volume and as a result decreased microsurgical experience, (2) larger tumors undergoing surgery while smaller tumors are reserved for radiation, and (3) surgery for previously radiated tumors resulting in more difficult anatomic dissection. Appropriate management of complications is paramount. Herein, we discuss complications related to VS microsurgery and methods of avoidance. Specifically, we discuss the most frequently encountered complications, intraoperative monitoring and finally, methods of addressing these complications. With meticulous microsurgical technique, careful intraoperative monitoring and vigilant perioperative care one will ensure optimal patient outcomes.

Guter Review.
Hummel M, Perez J, Hagen R, Gelbrich G, Ernestus RI, Matthies C.

OBJECTIVE
Some patients suffer postoperative hearing loss even when the intraoperative auditory brainstem response (ABR) is preserved during vestibular schwannomas surgery. This study was conducted to evaluate whether there are dynamic changes of the ABR after surgery.

PATIENTS AND METHODS
In a prospective study from 2010-2012, 46 patients (24 female and 22 male) with vestibular schwannomas were investigated by intraoperative and postoperative ABR monitoring. Development of ABR quality during and after surgery (Class 1 normal, Class 5 complete loss) was correlated to auditory outcome.

RESULTS
At the end of surgery, 17 patients had an ABR Class 1-4 and 29 had Class 5. Four hours after surgery, 9 of 23 (39%) patients showed an ABR quality change, and 24 hours after surgery, 15 of 30 (50%) had undergone ABR quality changes. Four different types of postoperative ABR courses could be distinguished-Course 1: stable with reproducible ABR, Course 2: unstable with reproducible ABR, Course 3: unstable with ABR loss, and Course 4: stable with ABR loss. These courses correlated highly significantly with the intraoperative development (P < 0.001) and with hearing outcome (P = 0.003).

CONCLUSION
The study identifies ongoing changes of ABR quality and hearing function after the end of vestibular schwannoma surgery. Therefore it seems worthwhile to continue ABR monitoring in the postoperative phase in order to identify patients who are at risk of a secondary hearing deterioration and start therapeutic interventions in a timely manner.

Bedenkenswert.
OBJECTIVE

To characterize the risk and predictors of growth during observation of vestibular schwannomas (VS).

STUDY DESIGN

Retrospective case series.

SETTING

Single academic, tertiary care center.

PATIENTS

Five hundred sixty-four consecutive VS patients who underwent at least two magnetic resonance imaging (MRI) studies before intervention.

INTERVENTION(S)

Serial MRI studies.

MAIN OUTCOME MEASURE(S)

Tumor growth, defined as a $\geq 2$ mm increase in the maximum tumor diameter between consecutive MRI studies, or between the first and last study.

RESULTS

A total of 1296 patients (1995-2015) with VS were identified. Of those, 564 patients (median age 59.2 years; 53.5% female) were initially observed and underwent multiple MRI studies (median follow-up 22.9 months, interquartile range [IQR] 11.7-42.7). The median maximum tumor diameter at presentation was 1.00 cm (IQR 0.6-1.51 cm). In all, 40.8% of tumors demonstrated growth and 32.1% underwent intervention (21.5% microsurgery, 10.5% radiation) during the surveillance period. Multivariable Cox regression analysis showed that for each tumor, the risk of growth or intervention was significantly increased for larger initial VS diameters (HR=2.22; 95% CI: 1.90-2.61) and when disequilibrium was a presenting symptom (HR=1.70; 95% CI: 1.30-2.23). Patient age, sex, aspirin use, and presenting symptoms of asymmetric hearing loss, tinnitus, and vertigo were not associated with tumor growth.
CONCLUSION

To date, this is the largest series of observed VS reported in the literature. Risk of VS growth is significantly increased among patients who present with larger tumors and who have concomitant disequilibrium.

DEFINE PROFESSIONAL PRACTICE GAP AND EDUCATIONAL NEED

No cohort with this sample size has assessed vestibular schwannoma growth rates in conjunction with this number of variables.

LEARNING OBJECTIVE

To characterize vestibular schwannoma growth rates and predictors of growth.

*Wait & see löst eben oft nicht das Problem sondern verschiebt nur die Lösung.*