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**Literature search results**

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**Search details**

Pseudoprogression in grade IV gliomas after chemotherapy or radiotherapy following surgery.

**Resources searched**

NICE Evidence; TRIP Database; Cochrane Library; EMBASE; MEDLINE; Google Scholar;

**Database search terms:** "grade IV glioma*"; GLIOBLASTOMA; ASTROCYTOMA; GLIOMA; glioblastoma*; astrocytoma*; "grade IV" adj2 (glioma* OR astrocytoma* OR glioblastoma*); "grade 4" adj2 (glioma* OR astrocytoma* OR glioblastoma*); chemo*; radiotherap*; exp RADIOTHERAPY; exp ANTINEOPLASTIC AGENTS; postoperative; postsurgical; postsurgery; post-operative; post-surgical; post-surgery; "after surgery"; pseudoprogression; pseudo-progression; psPD

**Evidence search string(s):** (glioblastoma OR "grade IV glioma" OR "grade 4 glioma") (chemotherapy OR radiotherapy) (postoperative OR "after surgery" OR post-operative) pseudoprogression

**Google search string(s):** (glioblastoma OR "grade IV glioma" OR "grade 4 glioma") (chemotherapy OR radiotherapy) (postoperative OR "after surgery" OR post-operative) intitle:pseudoprogression

**Summary**

There seems to be some research on pseudoprogression in grade IV gliomas following
Guidelines and Policy

European Society for Medical Oncology
High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2014

Evidence Reviews

None found.

Published Research – Databases

1. Defining pseudoprogression in glioblastoma multiforme.
   Citation: European Journal of Neurology, October 2013, vol./is. 20/10(1335-41), 1351-5101;1468-1331 (2013 Oct)
   Publication Date: October 2013
   Abstract: BACKGROUND AND PURPOSE: Pseudoprogression is a frequent phenomenon observed since the introduction of postoperative therapy with radiotherapy and temozolomide (RT/TMZ) in glioblastoma multiforme (GBM) patients. However, the criteria defining pseudoprogression, its incidence, the time of occurrence and its impact on therapy and outcome remain poorly defined.METHODS: The objective of this study is to compare two sets of criteria (liberal and stringent), defining pseudoprogression, in a cohort of patients treated before and after the introduction of RT/TMZ in the standard postoperative treatment. This retrospective review includes 136 unselected and consecutively treated patients with pathologically diagnosed GBM.RESULTS: Pseudoprogression was observed in 10 (12%) cases applying the stringent criteria, and in 18 (23%) patients when using the liberal criteria, in the cohort treated with RT/TMZ. Pseudoprogression was observed in only one patient treated with RT alone. The median time to pseudoprogression was 4 weeks after the end of RT. Patients with pseudoprogression had a median survival time of 28 months, compared with 12 months for patients without pseudoprogression.CONCLUSIONS: The incidence of pseudoprogression after RT/TMZ strongly depends on the applied criteria. However, regardless of the stringency of the criteria, the impact on survival remains the same. 2013 The Author(s) European Journal of Neurology 2013 EFNS.
   Source: Medline
   Available in fulltext from European Journal of Neurology at EBSCOhost

2. Hypofractionated chemoradiotherapy with temozolomide as an appropriate treatment option for glioblastoma patients with poor prognostic features
   Author(s) Lim Y., Kim I.H., Han T.J.
   Citation: European Journal of Cancer, September 2013, vol./is. 49/(S786), 0959-8049 (September 2013)
   Publication Date: September 2013
   Abstract: Background: Since high-risk GBM patients showed median OS of less than 1
year, clinical benefit of the 6-week postoperative treatment for the high-risk patients has been questioned. This study evaluated the feasibility and safety of hypofractionated radiotherapy (RT) with concomitant temozolomide (TMZ) for glioblastoma (GBM) patients with poor prognostic features. Material and Methods: From Feb 2007 to Dec 2011, 33 patients with pathologically confirmed GBM received hypofractionated concurrent chemoradiotherapy (CRT) with TMZ, with or without adjuvant TMZ. The patients were either >70 years or <70 years with one or more risk factors (pre-RT ECOG score >3, stereotactic biopsy only, or immediate disease progression after surgical procedure). The median radiation dose was 45 Gy (range, 30 to 45 Gy) with a fraction size of 3 Gy. Results: With the median age of 66.0 years, 18 patients (54.5%) showed poor performance status (ECOG >3) before starting CRT and 16 patients (48.5%) received stereotactic biopsy only. The median overall survival (OS) and progression-free survival (PFS) were 10.6 months and 4.4 months, respectively. Pre- and post-RT poor performance status (ECOG >3) (HR 3.12, 95% CI 1.21-8.07 and HR 4.51, 95% CI 1.44-14.12, respectively) and no early pseudoprogession (PsPD) (HR 5.43, 95% CI 1.58-18.61) were associated with poor OS. In PFS, post-RT performance status (ECOG >3) (HR 2.97, 95% CI 1.15-7.62) and extent of tumor (HR 2.50, 95% CI 1.05- 5.96) were statistically significant. While acute neurologic symptoms during the CRT were reported in 5 patients (15.2%), there was no treatment-related aggravation in performance status with acceptable toxicity profiles. Conclusion: We suggest a reasonable and well-tolerated therapeutic approach of hypofractionated concurrent CRT with TMZ in high-risk GBM patients. Despite the presence of one or more poor prognostic features in the patient cohort, the median OS comparable to previous studies was remarkable. Maintenance of good performance status before and after concurrent CRT will be beneficial for better prognosis.

Source: EMBASE


Citation: Radiation Oncology, 2013, vol./is. 8/(38), 1748-717X;1748-717X (2013)

Publication Date: 2013

Abstract: PURPOSE: To determine the safety and efficacy of hypofractionated intensity modulated radiation therapy (Hypo-IMRT) using helical tomotherapy (HT) with concurrent low dose temozolomide (TMZ) followed by adjuvant TMZ in patients with glioblastoma multiforme (GBM).METHODS AND MATERIALS: Adult patients with GBM and KPS > 70 were prospectively enrolled between 2005 and 2007 in this phase I study. The Fibonacci dose escalation protocol was implemented to establish a safe radiation fractionation regimen. The protocol defined radiation therapy (RT) dose level I as 54.4 Gy in 20 fractions over 4 weeks and dose level II according to the dose escalation protocol. Grade 3 hematological toxicity was limited to two patients and one patient developed Grade 4 Pneumocystis jiroveci pneumonia.CONCLUSION: Hypo-IMRT using HT given with
concurrent TMZ is feasible and safe. The median OS and PFS are comparable to those observed with conventional fractionation. Hypofractionated radiation therapy offers the advantage of a shorter treatment period which is imperative in this group of patients with limited life expectancy.

Source: Medline

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4. Is pseudoprogression (PSP) impacted by a very early progression (VEP)? a retrospective cohort study

Author(s) Wertz M., Padovani L., Bequet-Boucard C., Barrie M., Matta M., Muracciole X., Chinot O.

Citation: Neuro-Oncology, September 2012, vol./is. 14/(iii57), 1522-8517 (September 2012)

Publication Date: September 2012

Abstract: BACKGROUND: After the concomitant chemoradiotherapy, the evaluation of the tumor control in glioblastoma (GBM) is impacted by the pseudoprogression (psP). The psP is a widely accepted concept with an uncertain incidence (7 to 31%) and involves the use of subsequent imagery. Taking into account tumor assessment from surgery to progression, this study aims to refine the definition of the psP in a homogenous group of GBM. Moreover we attempt to discern how the tumor evolution before radiotherapy (RT) could help to identify the psP. METHODS: A retrospective cohort of patients with newly diagnosed GBM, treated from 2008 to 2010 by RT and concomitant temozolomide (TMZ) followed by adjuvant TMZ was studied. MRI were evaluated at multiple times: preoperative, postoperative, prior to RT when available, 1 month after RT and every 2 month until progression. Early progression (EP) was defined by a progression on the RT + 1 MRI. Pseudoprogression (psP) was defined as an EP that is followed either by a stable status on the RT + 3 and RT + 5, either by a response status on the RT + 3 or the RT + 5. True early progression (TEP) was defined by an EP that is followed by a progression status on the RT + 3 or RT + 5 when assessable. Very early progression (VEP) was defined by a progression during the interval between surgery and RT. RANO criteria were applied. Progression free (PFS) and overall survival (OS) were measured by Kaplan-Meier curves and Log-rank test was used to detect significant differences. RESULTS: Analysis of the first 75 patients was achieved. Based on postoperative MRI, macroscopically total resection, partial resection and biopsy were realized for respectively 19 (25.3%), 49 (65.3%) and 7 (10.3%) patients. There was no available MRI between surgery and RT in 17 cases. On the 58 analyzable patients, 29 were in EP (50%) including 10 psP (17.2%) and 19 TEP (32.7%). The PFS in the TEP group was significantly lower compared to the no EP (p < 0.001) and the psP (p = 0.002) group. No statistically different was found for the OS. Between no EP and psP groups, no distinct outcome was found for PFS and OS. In 12 patients, two MRI were available between surgery and RT. VEP was observed in 10/12 cases. 1 VEP was lost to follow-up. On the 9 analyzable patients, subsequent imagery revealed 2 psP, 2 TEP and 5 no EP. Taking into account the VEP, 2 patients were not in
progression on the RT + 1 MRI and changed their status from psP to no EP.

CONCLUSION: The incidence of the psP tends to be lower in this cohort than in previous studies. PFS doesn't significantly differ by comparing the no EP and psP group. Taking into account the pre-RT period, a subset of psP status could rather be considered as no EP, decreasing the incidence of psP. This preliminary analysis support the role of the tumor assessment between surgery and RT. Full analysis of the cohort will be presented.

Source: EMBASE
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5. Decreased incidence of the measurable enhancing lesion after chemoradiation therapy with temozolomide in glioblastoma patients receiving 5-aminolevulinic acid-assisted tumorectomy

Author(s) Yeom J.A., Choi S.H., Shin H.S., Kim S.C., Jung S.C., Ryoo I.

Citation: Neuroradiology, August 2012, vol./is. 54/1 SUPPL. 1(S121), 0028-3940 (August 2012)

Publication Date: August 2012

Abstract: PURPOSE The purpose of our study was to evaluate the incidence of measurable enhancing lesions, suggestive of pseudoprogression or true-progression after 5-aminolevulinic acid(ALA)- assisted tumorectomy, which was compared with that after conventional surgery followed by chemoradiation(CCRT) therapy with temozolomide(TMZ) in glioblastoma patients. MATERIALS AND METHODS A total number of 95 patients who received brain tumor surgery for glioblastoma and CCRT with TMZ between July 2000 and January 2012 were included for study(mean age 52.1 years; male=57, female=38). In all patients, conventional magnetic resonance imaging(MRI) was performed after surgery and after CCRT with TMZ. We reviewed the MRI images, and confirmed whether measurable enhancing lesions were demonstrable on post-CCRT MRI. In the patients with measurable enhancing lesion, pseudoprogression or trueprogression was determined by follow-up images or pathology. For the statistical analysis, we used Fisher's exact test. RESULTS Eight of 31 patients who underwent 5-ALA-assisted tumorectomy showed measurable enhancing lesions on post- CCRT MRI, while in 35 of 64 patients treated with conventional surgery, we found measurable enhancing lesions on post- CCRT MRI, which resulted in significant difference (P=.009). Among the measurable enhancing lesions, pseudoprogression was determined in three of eight patients with 5-ALA-assisted tumorectomy and in 12 of 35 patients treated with conventional surgery(P=1.00). CONCLUSION We found that the patients receiving 5-ALA-assisted tumorectomy showed lower incidence of the measurable enhancing lesion after CCRT with TMZ than those with conventional tumorectomy, and the incidence of pseudoprogression was not significantly different between two groups. Thus, we believe that 5-ALA-assisted operation enabled more resection of high grade foci than conventional tumorectomy in glioblastoma.

Source: EMBASE
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6. Quantitative T2* perfusion evaluation in the differential diagnosis between recurrence and pseudo-progression in patients affected by glioblastoma multiforme treated with radiotherapy and temozolomide

**Author(s)**: Pugliese S., Romano A., Minniti G., Bozzao A.

**Citation**: Neuroradiology, August 2012, vol./is. 54/1 SUPPL. 1(S118), 0028-3940 (August 2012)

**Publication Date**: August 2012

**Abstract**: PURPOSE: Evaluation of T2*-weighted dynamic susceptibility-weighted contrast-enhanced (DSC) imaging, and the derived rCBV and Ktrans, in the differential diagnosis between recurrent GBM and early radiation necrosis (the so-called pseudoprogression) in patient affected by glioblastoma multiforme treated with surgery followed by radiotherapy and temozolomide chemotherapy. METHODS AND MATERIALS: A retrospective study was performed in 115 patients, affected by GBM, enrolled after surgery and radiotherapy associated to temozolomide. They all underwent DSC-MRI follow-up. In 24 of them, early follow-up MRI (within 4 months) revealed a new nodular area of contrast enhancement within the radiation field. The diagnosis of recurrence vs pseudoprogression was established with clinical-radiological follow-up or surgical resection. ROIs were drawn semiautomatically on the enhancing areas, avoiding cortical vessels; then they were copied on the CBV and K trans maps. The values obtained were normalized to the contralateral white matter. T test was used to compare the groups. RESULTS: Mean rCBV (2.7 vs 1.7 P<0.05), maximum rCBV (4 vs 2.6 P<0.05) and minimum rCBV (1.2 vs 0.7 P<0.06) were higher in patients with a recurrence than in patients with pseudoprogression. Mean Ktrans (68.7 vs 112.7 P<0.05) maximum Ktrans (287 vs 312.8 P<0.05) minimum Ktrans (1 vs 14.5 P<0.05) were lower in patients with a recurrence than in patients with pseudoprogression. We propose a mean rCBV cut-off>2.3 (sensibility: 64%; specificity: 75%; positive predictive value: 70%; negative predictive value: 70%). CONCLUSIONS: DSC perfusion MRI can help to differentiate pseudoprogression from tumor recurrence thus impacting further treatment.

**Source**: EMBASE

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7. Pseudoprogression in patients with glioblastoma multiforme after concurrent radiotherapy and temozolomide

**Author(s)**: Topkan E., Topuk S., Oymak E., Parlak C., Pehlivan B.

**Citation**: American Journal of Clinical Oncology: Cancer Clinical Trials, June 2012, vol./is. 35/3(284-289), 0277-3732;1537-453X (June 2012)

**Publication Date**: June 2012

**Abstract**: Background: To evaluate pathologically confirmed incidence of pseudoprogression and its impact on survival in glioblastoma multiforme (GBM) patients treated with radiotherapy and concurrent temozolomide (TMZ), followed by 6 months of TMZ maintenance therapy. MATERIALS AND Methods: Sixty-three patients with histologic proof of GBM underwent 60 Gy (2 Gy/fr, 30 fractions) of brain radiotherapy concurrent with continuous 75 mg/m<sup>2</sup>/d TMZ, followed by 6 cycles of maintenance TMZ (200 mg/m<sup>2</sup>/d for 5 d, every 28 d). Response assessment was performed by magnetic resonance imaging every 2 months. All patients with radiologic doubt of early tumor progression (<6 mo) underwent salvage surgery. Results: All patients underwent surgical resection. Gross total, subtotal resection, and biopsy were performed in 17 (27.0%), 32 (51.6%), and 14 (21.4%) patients, respectively. Lesion enlargement on first follow-up magnetic resonance imaging evidenced in 28 (44.4%) patients. Salvage
pathologies revealed pseudoprogression in 12 of 28 (42.8%) patients corresponding to an overall pseudoprogression rate of 19%. Survival analysis revealed that patients with pseudoprogression had superior overall and progression-free survival rates at both 1 and 2 years (P<0.05 for each, respectively). Conclusions: Current results indicates the urgency of need for novel imaging techniques and/or biochemical marker(s) that can better distinguish pseudoprogression from true progression to avoid unnecessary and potentially harmful surgical interventions in almost half of the radiologically progressive GBM patients. Our additional observation which suggests better survival for patients with pseudoprogression warrants to be studied in larger patient cohorts. Copyright 2011 by Lippincott Williams & Wilkins.

Source: EMBASE

8. Pseudoprogression and Treatment Effect

Author(s) Jahangiri A., Aghi M.K.

Citation: Neurosurgery Clinics of North America, April 2012, vol./is. 23/2(277-287), 1042-3680;1558-1349 (April 2012)

Publication Date: April 2012

Abstract: The standard of care for newly diagnosed malignant glioblastoma entails postoperative radiotherapy and adjuvant chemotherapy with temozolomide. There has been an increase in the incidence of enhancing and progressive lesions seen on magnetic resonance imaging (MRI) following treatment. Conventional MRI with gadolinium contrast is unable to distinguish between the effects of treatment and actual tumor recurrence. New modalities have provided additional information for distinguishing treatment effects from tumor progression but are not 100% sensitive or specific in diagnosing progression. Novel radiographic or nonradiographic biomarkers with sensitivity and specificity verified in large randomized clinical trials are needed to detect progression. 2012.

Source: EMBASE

9. The Concepts, Diagnosis and Management of Early Imaging Changes after Therapy for Glioblastomas

Author(s) Sanghera P., Rampling R., Haylock B., Jefferies S., McBain C., Rees J.H., Soh C., Whittle I.R.

Citation: Clinical Oncology, April 2012, vol./is. 24/3(216-227), 0936-6555;1433-2981 (April 2012)

Publication Date: April 2012

Abstract: Since postoperative radiotherapy plus concomitant temozolomide followed by adjuvant temozolomide has become standard treatment for glioblastoma, the phenomenon of early post-treatment enlargement of the imaged tumour volume, usually without clinical deterioration, has become widely recognised. The term pseudoprogression has been used to describe a poorly understood pathophysiological process. In this review, the pathophysiological concepts, relevance, diagnosis and management of patients with ‘pseudoprogression’ and ‘pseudoresponse’ are discussed. Guidelines are given with respect to radiological imaging modality, mode and frequency. Further biological and clinical insights into these phenomena require carefully designed prospective studies. 2011 The Royal College of Radiologists.

Source: EMBASE

10. Integrated boost IMRT with FET-PET-adapted local dose escalation in glioblastomas. Results of a prospective phase II study.


Citation: Strahlentherapie und Onkologie, April 2012, vol./is. 188/4(334-9), 0179-7158;1439-099X (2012 Apr)
Abstract: PURPOSE: Dose escalations above 60 Gy based on MRI have not led to prognostic benefits in glioblastoma patients yet. With positron emission tomography (PET) using [(18)F]fluorethyl-L-tyrosine (FET), tumor coverage can be optimized with the option of regional dose escalation in the area of viable tumor tissue. METHODS AND MATERIALS: In a prospective phase II study (January 2008 to December 2009), 22 patients (median age 55 years) received radiochemotherapy after surgery. The radiotherapy was performed as an MRI and FET-PET-based integrated-boost intensity-modulated radiotherapy (IMRT). The prescribed dose was 72 and 60 Gy (single dose 2.4 and 2.0 Gy, respectively) for the FET-PET- and MR-based PTV-FET((72 Gy)) and PTV-MR((60 Gy)). FET-PET and MRI were performed routinely for follow-up. Quality of life and cognitive aspects were recorded by the EORTC-QLQ-C30/QLQ Brain20 and Mini-Mental Status Examination (MMSE), while the therapy-related toxicity was recorded using the CTC3.0 and RTOG scores. RESULTS: Median overall survival (OS) and disease-free survival (DFS) were 14.8 and 7.8 months, respectively. All local relapses were detected at least partly within the 95% dose volume of PTV-MR((60 Gy)). No relevant radiotherapy-related side effects were observed (excepted alopecia). In 2 patients, a pseudoprogression was observed in the MRI. Tumor progression could be excluded by FET-PET and was confirmed in further MRI and FET-PET imaging. No significant changes were observed in MMSE scores and in the EORTC QLQ-C30/QLQ-BRAIN20 questionnaires. CONCLUSION: Our dose escalation concept with a total dose of 72 Gy, based on FET-PET, did not lead to a survival benefit. Acute and late toxicity were not increased, compared with historical controls and published dose-escalation studies.

Source: Medline

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11. Addition of paclitaxel poliglumex (ppx) to IMRT plus concurrent temozolomide in the treatment of high-grade gliomas

Author(s) DiPetrillo T.A., O'Connor B.M., Jeyapalan S., Boxerman J., Goldman M., Kahn J., Blitstein M., Cielo D., Oyelese A., Doberstein C.

Citation: International Journal of Radiation Oncology Biology Physics, November 2010, vol./is. 78/3 SUPPL. 1(S262), 0360-3016 (01 Nov 2010)

Publication Date: November 2010

Abstract: Purpose/Objective(s): PPX is a macromolecule drug conjugate of paclitaxel and polyglutamic acid. The latter allows the drug to preferentially enter the more porous blood vessels of tumor cells. PPX has demonstrated radiation enhancement factors in xenograft models that exceed 4.0. We report the early clinical response in a Phase II study assessing the efficacy of PPX, added to the standard treatment of radiation and temozolomide (TMZ), for newly diagnosed high-grade brain gliomas (WHO grade III and IV). Materials/Methods: Patients were histopathologically confirmed to have newly diagnosed glioblastoma multiforme (GBM) or anaplastic gliomas (AG) with an ECOG <2. Adjuvant treatment started three weeks after surgery and consisted of daily TMZ (75 mg/m2) and weekly intravenous PPX (40 mg/m2) during the 6 weeks of IMRT (46 Gy in 2 Gy fractions followed by a 14 Gy boost for a total dose of 60 Gy). Thereafter, the patients received TMZ (150-200 mg/m2/sup>2</sup>) every 28 days for 5 days. For each patient, volumes of enhancement and FLAIR hyperintensity were calculated on all post-PPX MRI exams obtained during follow-up (1 month after IMRT and subsequently every 2-3 months). These were compared with the post-op baseline images. We applied the current response criteria (response assessment in neuro-oncology (RANO); Wen PY et al: J Clin Oncol 28:1963,2010) in order to classify patient outcome as complete or partial response and stable or progressive disease. Results: Since December 2008, 17 patients (9 males; 8 females) have been enrolled, including 10 GBMs, 1 gliosarcoma, and 6 AGs. The median age was 56 (range, 36-78). KPS was >70 for ten patients, = 70 for two patients and <70 for five patients. Five patients underwent gross total resection (GTR), four underwent near GTR, three underwent...
subtotal resection (STR) and five had biopsies only. Three patients developed grade IV thrombocytopenia during treatment and had to be taken off study. No sub-acute or late toxicities have been reported during follow-up (maximum 14 months). Follow-up imaging features were consistent with a complete response in six patients, a partial response in three patients, stable disease in one patient and progressive disease in six patients (enhancement in two of these patients later resolved without treatment, consistent with pseudoprogression). One patient has yet to have post-treatment imaging. Fourteen patients are alive. Three died from progressive disease. Conclusions: PPX concurrent with TMZ and IMRT yielded a complete response in 6 out of 17 patients, including 2 patients with AG who had a surgical biopsy only. Furthermore, only four patients had true progression. We plan on enrolling more patients based on these encouraging clinical results.

Source: EMBASE

12. Pattern of recurrence and pseudo-progression in glioblastoma patients treated with postoperative radiotherapy with concurrent temozolomide

Author(s) Van Mieghem E., Wozniak A., Geussens Y., Menten J., De Vleeschouwer S., Van Calenbergh F., Sciot R., Lobelle J., Clement P.

Citation: Neuro-Oncology, September 2010, vol./is. 12/(iii38), 1522-8517 (September 2010)

Publication Date: September 2010

Abstract: BACKGROUND: Combined postoperative therapy with temozolomide (TMZ) and radiation has become standard first-line treatment in glioblastome multiforme (GBM). Pseudo-progression is often observed since the introduction of this concurrent regimen. The objective of this study is to compare the incidence of pseudo-progression, pattern of recurrence, and overall survival (OS) in patients treated before and after introduction of concurrent TMZ in this indication. METHODS: A retrospective review was conducted of all pathologically proven GBM cases treated postoperatively in our center between 2004 and 2008. OS was calculated from the time of diagnosis. Pseudo-progression was examined by two different criteria. The first strict criteria define pseudo-progression as >25% increase in tumor size or the occurrence of a new contrast-enhancing lesion, with, in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis by second resection. The second more liberal criteria also included cases with stable disease for at least 6 months after first progression. Recurrence was judged unusual occurring contralaterally or extracerebrally. Tumor status was assessed before and after surgery, 1 month after completion of radiotherapy, and every 3 months thereafter. RESULTS: A total of 136 patients were analyzed, 80 males and 56 females, median age 62 years (17-81), median Karnofsky performance index at diagnosis 70 (20-90). In total, 123 cases were primary GBMs, 13 were secondary, 13 patients had multifocal disease, 69 patients underwent macroscopically complete resection, 40 partial resection, 24 biopsy. 3 had no primary surgery, but were diagnosed by biopsy later. Seventy-three patients were intent to treat with concurrent chemo-radiation followed by 6 cycles adjuvant TMZ, of which 37 completed the full treatment as planned (50%). Median OS in the combined group was 16 months compared with 8 months in the other group (P = .00003). Pseudo-progression was observed in 10 cases in the combined group (16%) vs none in the other group using the strict criteria (P = .003). Applying more liberal criteria, pseudo-progression was found in 17 cases (27%) in the combined group vs one in the other group (P = .0003). The median time to pseudoprogression was 4 weeks after radiation. Only pseudo-progression assessed by the liberal criteria is associated with a significantly better OS. An unusual pattern of relapse was observed in 15 (21%) patients who were treated with the combination compared with 6 (10%) in the others (P = .05).

CONCLUSIONS: The median OS in the group who received combined therapy was 16 months. Combined treatment is associated with higher incidence of unusual sites of relapse. Contralateral or extracerebral relapses were observed in more than twice as many patients. Pseudo-progression after combined treatment strongly depends on the criteria being used.

Source: EMBASE

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13. 18f-FET-PET hypermetabolic brain lesions: A correlation study to MRI and histopathologic findings

**Author(s)** Muigg A., Nowosielski M., Schwetz J., Gotwald T., Putzer D., Maier H., Stockhammer G., Hutterer M.

**Citation:** Journal of Clinical Oncology, May 2010, vol./is. 28/15 SUPPL. 1, 0732-183X (20 May 2010)

**Publication Date:** May 2010

**Abstract:** Background: Due to the specific incorporation of $^{18}$f-fluoroethyl-L-tyrosine ($^{18}$f-FET) into glioma cells, a number of studies have proven the clinical value of $^{18}$f-FET-PET to identify brain lesions as gliomas and to determine the extent of the brain tumor for treatment planning and biopsy guidance. However, the specificity of $^{18}$f-FET-PET in brain tumor diagnosis is still unknown. Therefore, the aim of this study was to correlate $^{18}$f-FET-PET hypermetabolic brain lesions to histopathologic diagnosis and MRI findings. Methods: We retrospectively analysed pre- and post-operative $^{18}$f-FET-PET scans of 200 patients with suspected neoplastic brain lesions and compared the results to MRI and histopathologic findings. Results: Comparison of preoperative $^{18}$f-FET-PET metabolic active brain lesions with histopathologic findings revealed that not only glial tumors, but also other primary brain tumors, including anaplastic ependymoma, primitive neuroectodermal tumors, medulloblastoma, primary CNS lymphoma, pinealoblastoma, acoustic neuroma, anaplastic meningioma, inflammatory multiple sclerosis and ADEM lesions were $^{18}$f-FET hypermetabolic. $^{18}$f-FET activity in inflammatory lesions was remarkably lower than in tumor lesions. In some cases after macroscopic total resection of a malignant glioma and no residual tumor on MRI, $^{18}$f-FET-PET clearly identified residual tumor burden. FET-PET was helpful to discriminate between post-radiation necrosis/pseudoprogression and tumor recurrence. Conclusions: $^{18}$f-FET-PET hypermetabolism is detectable in various neoplastic and inflammatory brain lesions limiting the specificity for glial tumors. After histopathologic diagnosis of a glial tumor $^{18}$f-FET-PET scans are sensitive to identify residual tumor after neurosurgical intervention, which should be implemented in radiotherapy planning. Pre- and postoperative $^{18}$f-FET-PET scans may also be helpful to guide stereotactic biopsy or surgery and to discriminate necrosis/pseudoprogression from tumor recurrence.

**Source:** EMBASE

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14. The growth pattern of recurrent glioblastoma after Gliadel wafer implantation in first recurrences

**Author(s)** Krex D., Weigel P., Podlesek D., Schackert G.
Purpose: Although in recent years several approaches for local therapies in the treatment of glioblastoma multiforme have been tested in clinical trials, carmustine polymers (Gliadel wafer) is the only evaluated local therapy to date. Because of the predominance of temozolomide, Gliadel is frequently used in recurrent gliomas only. However, data about effectiveness and the pattern of rerecurrences are rare. Therefore, we initiated the present MRI-based retrospective study.

Methods: 37 patients had surgery for first recurrence of glioblastoma, where Gliadel wafers (n=1-8) were implanted. Early postoperative MRI was performed documenting the extent of resection, tumor remnants and wafer placements. Follow-up MRI was performed every 2 months looking particularly for tumor growth in relation to the wafer placements. Progression-free and overall survival was recorded. Results: 27 patients were available for evaluation, while 10 patients had incomplete data. In 24 (88%) patients an early tumor growth was recorded in the first MRI follow-up, 2 months postoperative in areas where the wafers were not implanted. If the wafers had been placed in areas with suspicious tumor according to the early postoperative MRI, tumor progression was recorded in the follow-up in 10 (67%) of 15 patients. If the wafers were placed in areas without suspicious tumor remnants (12 patients), regrowth in those areas was recorded only in four (33%) patients, meaning 67% of the patients had no early tumor progression when Gliadel was placed in tumor-free areas. However, tumor pseudoprogression has to be taken into account for all cases. Survival data will be determined.

Conclusions: The use of Gliadel wafer in recurrent glioblastoma is most effective in areas with no tumor remnants, underlining the meaning of surgical resection of recurrent tumors, also.

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Author(s) Yang I, Aghi MK

Citation: Nature Reviews Clinical Oncology, November 2009, vol./is. 6/11(648-57), 1759-4774;1759-4782 (2009 Nov)

Publication Date: November 2009

Abstract: Postoperative adjuvant radiation therapy and temozolomide chemotherapy have become the standard care for newly diagnosed malignant gliomas. The efficacy of these therapies has led to an increase in pseudoprogression and radiation necrosis, both of which are treatment-related effects whose appearance on standard MRI with gadolinium-based contrast agents resembles that of tumor progression or recurrence. Accurate diagnosis of these post-treatment lesions as either tumor recurrence or treatment effects (pseudoprogression or radiation necrosis) is important to determine the patient's prognosis. Modern advancements with magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI), and PET scans have shown promise for distinguishing tumor recurrence from treatment effects. Advances in radiographic techniques will become critically important with the emergence of new antiangiogenic therapies. Consequently, MRS, DWI, and PET need to be incorporated into routine post-treatment investigations to improve the specificity.
and sensitivity of distinguishing tumor recurrence from treatment effects. Further research will also be needed to develop improved algorithms that use these modalities, and to develop new modalities with even greater accuracy than those currently available.

**Source:** Medline

Available in fulltext at *Nature Reviews. Clinical Oncology*; Collection notes: On first login to a ProQuest journal you will need to select 'Athens (OpenAthens Federation)' from Select Region, and then 'NHS England' from Choose your Library.

16. Pseudoprogression after radiotherapy with concurrent temozolomide for high-grade glioma: clinical observations and working recommendations

**Author(s)** Chaskis C., Neyns B., Michotte A., De Ridder M., Everaert H.

**Citation:** Surgical Neurology, October 2009, vol./is. 72/4(423-428), 0090-3019 (October 2009)

**Publication Date:** October 2009

**Abstract:** Background: Treatment of newly diagnosed GBM with postoperative RT and concomitant TMZ followed by 6 months of TMZ maintenance therapy has been shown to significantly improve overall survival compared with RT alone. Standard clinical assessments of these patients include Gd-MRI as well as neurologic evaluation. Frequently, patients exhibit immediate post-RT changes in enhancement on Gd-MRI that mimic tumor progression (ie, pseudoprogression or radiation-induced imaging changes). With the introduction of concomitant RT plus TMZ for treatment of malignant glioma, there appears to be an increasing incidence of pseudoprogression. Case Description: In our experience, pseudoprogression after concomitant RT plus TMZ is typically not observed at first imaging immediately after completion of the therapy; but delayed focal enhancement mimicking tumor progression frequently occurs during the 6 months of maintenance therapy with TMZ. Pseudoprogression may reflect the radiosensitizing effect of TMZ during concomitant therapy, and retaining patients on treatment allows them to have enhanced survival and preserved quality of life. We observed 3 cases of pseudoprogression among 54 consecutive patients who were treated with this regimen. These patients developed pseudoprogression within 2 to 6 months after completion of concomitant RT plus TMZ, but all 3 patients completed maintenance chemotherapy and remained progression free for at least 15 months after diagnosis. Conclusion: Functional imaging may improve the noninvasive diagnosis of pseudoprogression, but randomized prospective studies are needed to evaluate the real impact of pseudoprogression and validate neuroradiological techniques able to make a reliable distinction between tumor recurrence and pseudoprogression. 2009 Elsevier Inc. All rights reserved.

**Source:** EMBASE

17. Reversible nodular enhancement following resection with biodegradable carmustine (BCNU) wafer placement followed by vaccination with dendritic cells pulsed with tumor lysate for patients with newly diagnosed glioma

**Author(s)** Rudnick J.D., Phuphanich S., Naor R., Luptrawan A., Nuno M., Moser F.G., Chu R.M., Black K.L., Yu J.S.

**Citation:** Neuro-Oncology, October 2009, vol./is. 11/5(631-632), 1522-8517 (October 2009)

**Publication Date:** October 2009

**Abstract:** INTRODUCTION: Our prior immunotherapy trials demonstrated efficacy in generating a tumor-specific immune response in malignant glioma and potential for high tumor-specific toxicity and sustained tumoricidal activity. Immunotherapy may synergize with chemotherapy, and biodegradable carmustine (BCNU) wafers extend overall survival from 11.6 to 13.9 months. This is a subset analysis of imaging findings from our vaccine trial. Postsurgical nodular enhancement is well defined after BCNU wafer placement, but the natural history of this enhancement is yet to be elucidated. This relationship has not been correlated with O<sup>6</sup>-methylguanine methyltransferase (MGMT), a predictor of pseudoprogression, or studied in the absence of cytotoxic chemotherapy.
METHODS: Patients with high-grade glioma histology were studied after resection (no residual enhancement) and biodegradable BCNU wafer placement. Screening leukapheresis was used to isolate mononuclear cells, which were differentiated into dendritic cells, pulsed with tumor lysate, and then three intradermal vaccines were administered at 2-week intervals. Magnetic resonance imaging (MRI) was obtained preoperatively, < 24 h postoperatively, following concurrent chemoirradiation, and postvaccination, per standard protocol. Immunohistochemistry was performed with MGMT analysis.

RESULTS: Six patients underwent surgery between May 2007 and September 2008; mean age was 58 (range, 26-74 years). Notably, 66% (4/6) developed nodular enhancement within 1 month after completion of chemoirradiation. The mean duration for the resolution of enhancement was 11 weeks (range, 4-18 weeks). MGMT expression was elevated (>20%) in one of four of the nodular enhancing patients and one of two patients without enhancement.

CONCLUSION: Although not powered for statistical significance, nodular enhancement is common after BCNU wafer placement and chemoirradiation. This may be a distinct phenomenon from pseudoprogression with specific imaging characteristics and may be mistaken for tumor progression. There is no correlate with MGMT status. Resolution of enhancement occurs within 3 months and prior to the initiation of chemotherapy. The natural history and radiographic features will be presented.

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... with temozolomide as the new standard of care for patients with glioblastoma, there has related necrosis occurs more frequently and earlier after temozolomide chemotherapy than after ... a survival benefit for postoperative 60-Gy whole-brain radiotherapy (WBRT), radiotherapy ... Cited by 433 Related articles All 16 versions Cite Save

... as a potential novel biomarker for distinguishing pseudoprogression from true progression in patients with glioblastoma treated with temozolomide and radiotherapy
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KM Knudsen-Baas, G Moen, Ø Fluge... - Acta Neurologica ..., 2013 - Wiley Online Library ... Standard therapy for glioblastoma multiforme (GBM, WHO grade IV) is concurrent chemotherapy with temozolomide (TMZ) and radiotherapy to 60 Gy ... 1A). The glioma was resected and found to be an astrocytoma with partial dedifferentiation to glioblastoma. ... Cited by 6 Related articles All 4 versions Cite Save

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JL Clarke, S Chang - Current neurology and neuroscience reports, 2009 - Springer ... as can postsur-gical changes [4]. In particular, regions that demonstrate restricted diffusion on an immediately postoperative MRI will ... 5. Chamberlain M, Glantz M, Chalmers L, et al.: Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. ... Cited by 55 Related articles All 9 versions Cite Save

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T Popolizio, MT Cascavilla, N Sforza, A Casillo... - Imaging Gliomas After ..., 2012 - Springer ... 73-year-old patient with right temporal glioblastoma treated with partial surgical excision and combined radiation therapy-chemotherapy. 3T MR follow-up performed at 1, 3, 9 and 12 months after surgery and combined radiation therapy-chemotherapy. ... All 6 versions Cite Save

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I Caroline, MA Rosenthal - Journal of Clinical Neuroscience, 2012 - Elsevier

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AA Brandes, A Tosoni, F Spagnolli... - Neuro- ..., 2008 - neuro-oncology.oxfordjournals.org

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... five of sixty-two patients with high-grade glioma who received radiotherapy (RT) with ... are shown in Table 1. Forty (73%) patients were diagnosed with glioblastoma multiforme. ... Surgical resection, gamma knife surgery, ACNU/CDDP, PCV chemotherapy, or metronomic TMZ were ... Cited by 1 Related articles All 11 versions Cite Save More

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... Glioblastoma multiforme (GBM) is the most common primary malignant type of brain ... MR imaging lesions immediately after the end of concurrent chemotherapy and radiation therapy ... material–enhanced MR imaging performed within 24–48 hours after surgery before subsequent ...
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