Malignant transformation of low grade gliomas into glioblastoma a series of 10 cases and review of the literature

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Abstract

Background: Diffuse infiltrative low-grade gliomas (LGG) of the cerebral hemispheres in the adult are tumors with distinct clinical, histological and molecular characteristics. WHO (World Health Organization) classification recognizes grade II astrocytomas, oligodendrogliomas and oligoastrocytomas. Conventional MRI is used for differential diagnosis, guiding surgery, planning radiotherapy and monitoring treatment response.

Advanced imaging techniques are increasing the diagnostic accuracy. Low-grade gliomas have been documented to undergo transformation into high-grade gliomas, and the time interval of this transformation has been reported to generally occur within 5 years in about 50% of patients diagnosed with low-grade gliomas.

Methods: We have reviewed all adult patients operated on for hemispheric glioblastoma at N Oblu Hospital in Iasi between 2006 and 2009 and in particular those patients with secondary glioblastoma.

Results: from the total 110 cases of glioblastoma, ten of them were secondary to malignant transformation of an previously operated low grade glioma. Of the 10 patients with secondary glioblastoma, the initial histology was: gr II astocytoma in 6 cases, oligoastocytoma in 2 cases and in oligodendroglioma in 2 cases. The mean patient age was 46.1± 0.9 years and the most frequent symptom was represented by seizures 70%, the mean time from the first symptom to diagnosis was 11,2 months. 40% of the cases had subtotal resection and 60% had total resection (defined by the surgeon at the time of operation). 5 patients received radiotherapy postoperatively, 2 received both radio and chemotherapy and 3 had no adjuvant treatment. In our series the median time to malignant transformation was 32,5 months.

Conclusions: Younger age, normal neurological examination and oligodendroglial histology are favorable prognostic factors, total/near total resection can improve seizure control, progression-free and overall survival, mean while reducing the risk of malignant transformation. Early post-operative radiotherapy improves progression free but not overall survival. Chemotherapy can be useful both at recurrence after radiotherapy and as initial treatment after surgery to delay the risk of late neurotoxicity from large-field radiotherapy.

Keywords: astrocytoma, low-grade glioma, glioblastoma, oligodendroglioma, malignant transformation

Low-grade gliomas are primary brain tumors classified as Grade I and II by the WHO grading system (14, 27) and occur primarily in children and young adults. The most common LGGs are the WHO Grade I pilocytic astrocytomas and the WHO Grade II diffuse astrocytomas (include fibrillary, gemistocytic and protoplasmic variants), oligodendrogliomas, and mixed oligoastrocytomas. It is important to separate gemistocytic astrocytoma, because it is more prone to malignant progression

Patients with low-grade gliomas have a more favorable prognosis than patients with high grade glioma The median survival for patients with low-grade gliomas is between 5 and 10 years (6, 9, 10, 13, 19) compared with a survival of only 14 months in patients with malignant glioma (GBM) (28). Despite this more favorable prognosis, patients with LGGs may survive for up to 20 years, in 50–75% of patients with low-grade gliomas the tumors grow continuously and tend to progress to a higher grade, leading to neurological disability and ultimately to death (8, 24) In adults there are numerous prognostic factors reported in various prospective studies that have been shown to affect survival in patients with LGG, the most consistent are histological type, patient age, extent of resection (using postoperatively MRI imaging), and tumor size. Pilocytic astrocytomas, regardless of site (cerebral hemispheres, cerebellum, or spinal cord), are associated with a 10-year patient survival rate of ~ 80%, (6, 11, 14) but the rate is 100% in the subset of patients with brain tumors who undergo GTR. (3, 22) Within the diffuse LGG group there is a significant difference in patient outcome based on histological tumor type.

The factors consistently shown to be associated with improved survival8 for patients with gliomas are younger age, (13, 23) higher KPS scores, (18) oligodendroglioma pathology, (17) postoperative radiation therapy, (25) and GTR. (1, 15, 26)

The only factors that have been consistently shown to be associated with tumor recurrence (8) or malignant degeneration are preoperative contrast enhancement, (11, 12) tumor size, (1, 11) and STR. (1, 3)

Methods

We have analised all the patients operated on at 3rd Neurosurgical Department in N Oblu Hospital for malignant glioma between 2006 and 2009 and from the total of 110 cases ten percent of the malignant glioma were secondary to a malignant transformation of a low grade glioma. Our point of interest was represented by the patients with initial diagnostic of low grade gliomas.. Patients ≥ 18 years old with tissue-proven diagnosis of a hemispheric WHO Grade I or II glioma (FA, oligodendroglioma, or mixed glioma) (14) at the initial diagnosis, supratentorial tumor location and adequate (> 6 months) clinical follow-up and imaging reports were included in the study.

Patients with, WHO Grade III or IV glioma including anaplastic astrocytoma, glioblastoma multiforme, anaplastic oligodendroglioma, or anaplastic mixed oligoastrocytoma at the initial operation; nonsupratentorial tumor location including optic chiasm, optic nerve(s), pons, medulla, cerebellum, or spinal cord; prior malignancy unless disease free ≥ 5 years were excluded.

The clinical, operative, and hospital course records were reviewed. Information collected from clinical notes included patient demographics, age, presenting symptoms and signs, the interval between the first symptom and diagnostic, pre- and postoperative neuroimaging, extent of resection, postoperative neurological function, adjuvant therapy (radiotherapy and chemotherapy)medication history such as steroids and anticonvulsants. Preoperative MR images, including T1-weighted images with and without contrast enhancement as well as T2-weighted images (and FLAIR images when available), were required. The preoperative tumor presence or absence of contrast enhancement was recorded. Perioperative death was defined as death within 30 days of surgery.

Tumor recurrence was defined as any definitive evidence of tumor recurrence or progressive growth on MR imaging as per the neuroradiology reports. Malignant degeneration was defined as either a notable increase in tumor contrast enhancement and/or a histopathologically proven malignant degeneration in tissue acquired during biopsy or resection (WHO Grade III or IV).

Results

From all of low grade gliomas operated on between 2006 – 2009 ten of them have suffered malignant transformation. All the patients have underwent primary and secondary resection, 60 percent of the cases were secondary to grade II astrocytomas (diffuse astrocytoma), 20 percent were secondary to oligodendroglioma and another 20 percent were secondary to oligoastrocytoma. The mean patient age was 46.1± 0.9 years, and 8 (80%) patients were male. The initial symptom was represented by seizures in 7 cases followed by motor impairment in 2 cases and rise intracranial hypertension in 1 case. The mean time from the initial symptom to diagnosis was 11.2±1.6 months. In our series 80% of the tumors were limited to a single cerebral lobe and in 20% there were involved 2 lobes, the most frequent affected lobe was the frontal lobe (6 cases) followed by the parietal lobe (5 cases). All of our cases had involvement of functional structures , in 6 cases there were functional areas involved, 2 cases involved the bazal ganglia and another 2 cases involved vascular structures (cavernous sinus, carotid artery). As treatment 4 patients had subtotal surgical resection and 6 total resection (as defined by the neurosurgeon at the time of surgery) . The main complication was represented by hematoma in the tumoral bed wich was observed in 30% of the cases. 50% had radiotherapy postoperatively 20% had both radio and chemotherapy while 30% recived non of them. The median time to malignant transformation in our series was 32.5 months. (Figure 1 and Table 1)

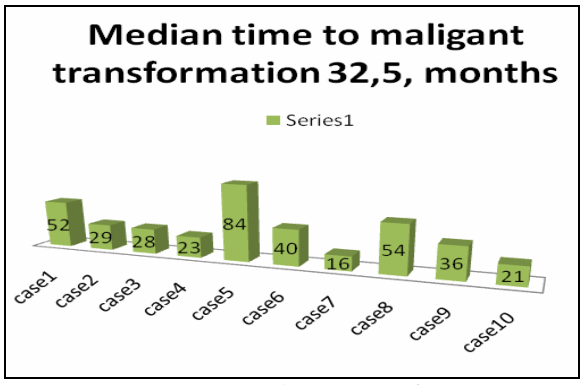

Figure 1 Time to malignant transformation

Table 1

Characteristics of malignant transformed low grade gliomas series

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case9	Case 10
Sex	M	M	M	F	M	M	M	M	M	F
Age	42	41	37	55	59	45	60	39	50	33
1st Sign	Seizures	Seizures	Seizures	Left Hemiparesis	Seizures	Partial Seizures	Jacksonian Seizures	Olfactive Seizures	Right Hemiplegia	Ricp Sindrome
T To Dg (Months)	2	36	30	1	2	2	10	3	`2	1
Loc	F	FTP	F	P	P	P	F	FTI	P	FTI
Funct Areas	-	1	1	1	1	-	1	-	1	-
Bazal Ganglia	-	1	-	-	-	-	-	1	-	-
Vascular Srtucture	-	-	-	-	-	-	-	1	-	1
Biopsy	-	-	-	-	-	-	-	-	-	-
Str	-	1	-	1	1	-	-	1	-	-
Gtr	1	-	1	-	-	1	1	-	1	1
Dg Ap	Gr II Astro-cytoma	Gr II Astro-cytoma	Gr II Astro-cytoma	Oligodendro-glioma	Oligodendro-glioma	Gr II Astrocytoma	Oligoastro-cytoma	Oligoastro-cytoma	Gr II Astrocytoma	Gr II Astrocytoma
Postop Complic	Menin-gitis	-	-	-	-	-	Local Hematoma	Local Hematoma	-	Local Hematoma
Rxt	1	-	-	-	1	-	1	1	-	1
Rtx+Cht	-	1	-	-	-	-	-	-	1	-
Cht	-	-	-	-	-	-	-	-	-	-
Reintervention (Months)	52	29	28	23	84	40	16	54	36	21
Pfs (Months)	48	23	27	21	84	40	16	42	36	21
Ap At Reinter-vention	GBM	GBM	GBM	GBM	GBM	GBM	GBM	GBM	GBM	GBM

Mo- months, F-frontal, P-parietal, T-temporal, I-insular, GBM-glioblastoma multiforme, PFS- progression free survival, Dg AP- anatomopathological exam, T to DG-time to diagnosis, RXT-radiotherapy, CHT-chemotherapy, STR-subtotal resection, GTR-gross total resection

Next we will present two eloquent cases from our series:

Case I 33 y o female presented for seizures for about 6 months, the MRI scan (Figure 2a) show a hipointense FTP lesion without contrast enhancement, she was operated using a pterional approach with subtotal resection, and the anatomopathological result was gr II astrocytoma. The patient went for

radiotherapy and she had 6 cure of LINAC. At 9 months the patient was asymptomatic and the MRI study show a stabile lesion with no signs of progression or contrast enhancement (Figure 2b), the same aspect is observed at 21 months postoperatively (Figure 2c). At 22 months postop she came for right brachial monoparesis and depression the MRI scan show 2 areas of contrast enhancement (Figure 2d) and programmed for a PET scan wich was performed 1 month later wich show an hipermatabolic are in the right temporal pole (Figure 2e). She went for a second surgery with subtotal resection of the lesion and the anatomopathological result was glioblastoma multiforme. Postop the patient had a difficult evolution and the CT scan 1 month later showed a multicentric localization with involvement of both cerebral hemispheres (Figure 2 g-h).

Case II 42 y old male presented for seizures for over 2 months and rised ICP syndrome, the CT scan with contrast enhancement show the lesion without contrast enhancement in the left frontal pole (Figure 3a), the patient was operated on (GTR) and the histology was gr II astrocytoma, he went for radiation therapy (6 cure of LINAC), at 4 months the patient was asymptomatic and the MRI exam show no signs of recurrence (Figure 3b), at 12 months the patient had no neurological impairment and the MRI show a stable aspect with a hyperintense lesion in T2 in the left frontal pole (Figure 3c) (scar secondary to surgery and radiotherapy) and we decided to go for surveillance and the MRI at 30 months postoperatively show no signs of progression or recurrence, same aspect as previous MRI exam) (Figure 3d).

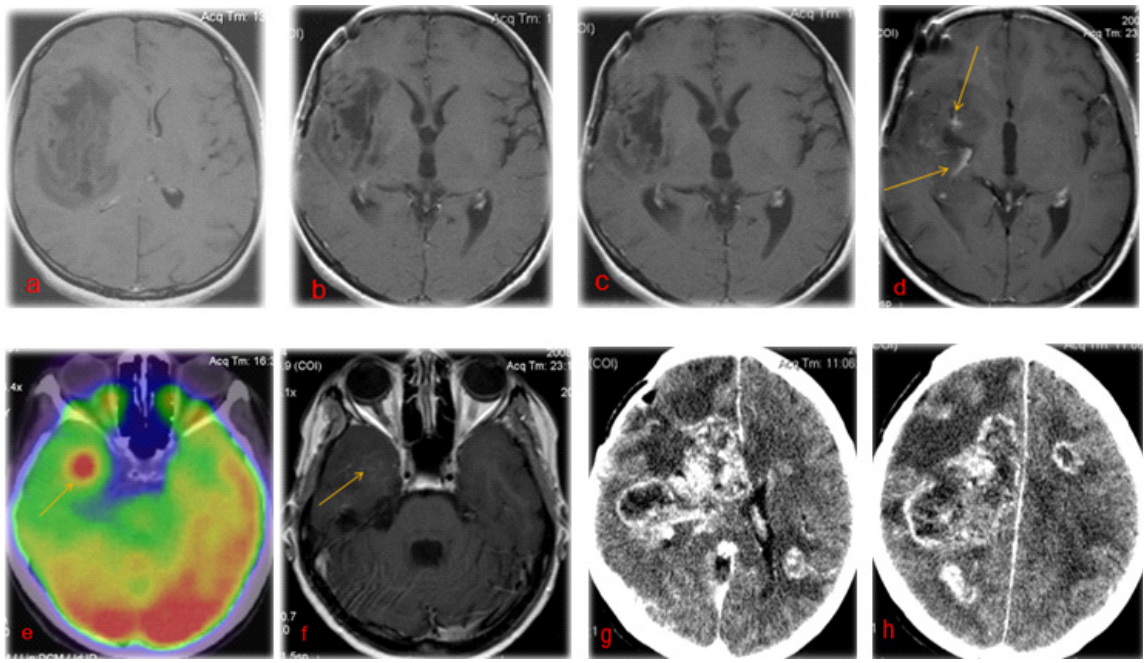

Figure 2 **A.** Axial T1- weighted contrast enhanced MRI image show FTP area of hiposignal without contrast enhancement, **B.** and **C.** Images obtained 9 and 21 months later at the same patient after surgery and 6 cure of LINAC stable images, **D.** axial MRI images at 22 months are sowing 2 areas of contrast enhancement which weren't present on the previous exam, **E.** PET scan is showing an area of hipermetabolism in the right temporal lobe and **F.** the correspondent images on T1-weighted with contrast enhanced MRI image **G.** and **H.** at 23 months after second surgery CT images obtained 1 month later show involvement of both cerebral hemispheres

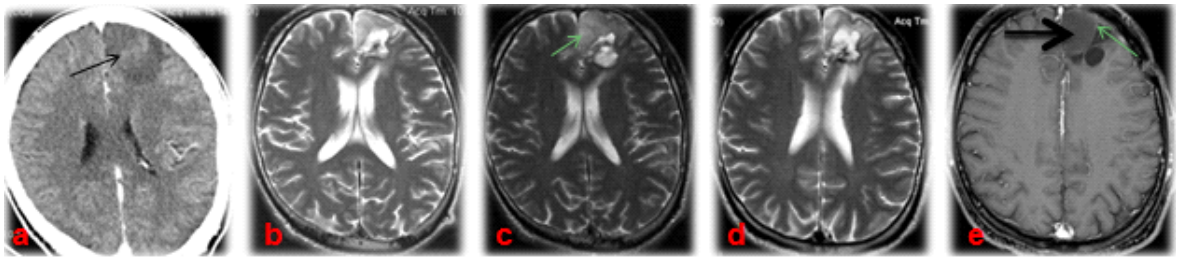

Figure 3 A. Computer tomography with contrast enhancement show a izointense lesion without contrast enhancement without mass effect and surrounded by edema, **B.** MRI T2 axial image hyperintense area in the left frontal lobe at 4 months postoperatively and after radiotherapy, **C.** MRI exam at 12 months T2 axial shows a stable hyperintense lesion in the left frontal pole surrounded by minimum edema (arrow), **D.** T2 axial at 30 months the lesion is stable with disappearance of edema, **E.** MRI exam at 52 months T1 with contrast enhancement show a hypointense lesion (thick arrow) in the left frontal pole and a thin rim of contrast enhancement (thin arrow)

But at 56 months the patient presented for memory impairment, the MRI exam with contrast enhancement (Figure 3e) showed in T1 a hypointense lesion located within 2 cm from the previous tumoral bed with a thin rim of contrast enhancement without perilesional edema, we decided for reintervention and the patient was operated on using the old approach with gross total removal appreciated by the surgeon at the time, the histology this time was glioblastoma multiforme and he was sent to the oncology clinic for chemotherapy (temozolamide) and further surveillance.

Discussion

The annual incidence of low grade glioma is about 4700 cases per year (27), which makes them onethird as common as their higher grade counterparts.4 This relatively low incidence has prevented the development of standardized treatment protocols. (2, 22) Treatment may include surveillance, biopsy, surgery, radiotherapy, or chemotherapy, and varies among different centers, location, and clinical presentation. (22) The majority of these tumors undergo recurrence or malignant transformation over time. The results vary among different studies with a 5 - year progression from 50 to 70% - and malignancy-free survival rates from 30 to 70%. (6, 13, 17, 18, 25)

Some patients have tumors that remain indolent for a couple of years, in our study only one patient had a PFS of 84 months, whereas others rapidly recur and progress leading to neurological deterioration and subsequent death. This heterogeneity in patient evolution has led to the necessity of identification of certain factors associated with survival, recurrence, and malignant development for patients undergoing resection of a low-grade glioma.

The factors consistently known to be associated with improved survival include:

1. younger age (patients < 40 years) (13, 23). In our series 3 patients were younger than 40 years but they didn't had a better prognostic than the group of patients older than 40 years this is due the fact that we had a small and non-homogenous series.
2. higher KPS score, (18)
3. oligodendroglioma pathology, patients with FAs and oligodendrogliomas have similar rates of recurrence and/or progression although patients with FAs had a greater propensity to develop into higher

grade tumors than patients with oligodendrogliomas, this may be due to the fact that FAs are primarily composed of aberrant astrocytes, which have a greater tendency to undergo malignant degeneration (17, 27)

4. postoperative radiation therapy, (25) Although improved PFS was demonstrated for patients treated with immediate RT, this did not translate into improved OS. Besides prolonging the time to tumor progression, RT has several other potential benefits, such as symptom control, particularly epileptic seizures (27). In our series 5 patient received radiotherapy and another 2 received both radio and chemotherapy but with no impact among PFS and

5. GTR (< 1 cm residual tumor), The first report of outcome based on an MR imaging based assessment of surgical resection for LGG was reported by Berger et al. (1) in a series of 53 patients from the University of Washington. The extent of resection (based on the volume of residual disease) and tumor size were inversely correlated with the likelihood of tumor recurrence, time to recurrence, and tumor grade at the time of recurrence, recent studies have shown that gross total resection independently decrease the risk of malignant transformation, that suggest that GTR should be pursued when these tumors are amenable to radical resection. (1, 8, 15, 26) A critical point is a precise definition of total resection that for LGGs that do not enhance implies removal of all the hyperintense regions on T2 or FLAIR images and thus can only be determined by comparing preoperative and post-operative tumor volumes on MRI, respecting this standard even with intraoperative MRI-guided surgery, total resection is achieved in no more than 36% of patients (24). GTR was achieved in 6 cases of our series but it was appreciated by the surgeon, without an immediate postoperatively MRI to confirm the extent of resection and these may also explain the short period until malignant transformation, comparatively with the data existing in the literature.

The only factors that have been consistently shown to be associated with tumor recurrence or malignant degeneration are:

1. preoperative contrast enhancement, (8, 11, 12, 27) which occurs where the blood-brain barrier is disturbed primarily in tumor areas, (2, 3) Contrast enhancement imaging often suggests a high-grade glioma, but it can also be present in 15–40% of patients with low grade gliomas. (7, 11, 23) The prognostic implications of contrast enhancement have been controversial and primarily limited to survival studies. (11, 14, 16, 17, 20) Studies on contrast enhancement and recurrence remain relatively unknown and understudied. (17, 29) contrast-enhancing low-grade gliomas may behave more like their higher grade, contrast-enhancing counterparts, which means that they are more likely to recur following resection. These tumors may therefore benefit from more aggressive and/or earlier use of adjuvant therapies.

2. tumor size, the risk of recurrence increases 1.3 times for each centimeter increase in size and is independent of the extent of resection, tumor sizes ≥ 3 cm have the greatest statistical significance, with a 3.5 - fold increased risk of tumor recurrence. Larger low-grade gliomas, like malignant gliomas, (21) may have more microsatellite lesions and individual cell invasion, as well as more residual cells following resection, as a consequence of having a larger tumor mass. (21) These

factors may not only predispose to tumor recurrence, but suggest that earlier treatment while the tumor is smaller will delay recurrence, presumably by decreasing the number of invading and/or residual cells that escape the tumor mass, which may eventually transform to a malignant phenotype,

3. STR. (1, 3) and

4. molecular abnormalities (27) James L. Frazier reported in 2009 2 cases of rapid malignant transformation (12 weeks) in patients operated on for low grade astrocytomas , which didn't enhance on the initial MRI and confirmed by anatomopathological exam and imunohistochemestry low value of ki 76, but both cases had, overexpresion of EDGF and absence of p53 mutation, molecular abnormalities seen in primary glioblastomas which may suggest possible risk factors for rapid malignant transformation.

Current recommendations according to guidelines on management of low-grade gliomas elaborated by EFNS: European Federation of Neurological Societies and EANO: European Association for Neuro-Oncology and published in European Journal of Neurology June 2010 27 are:

"• Astrocytomas, oligodendrogliomas and oligoastrocytomas are diagnosed using morphological criteria according to WHO classification (Level A).

• Combined loss of 1p/19q is a marker in favor of the diagnosis of oligodendroglioma or oligoastrocytoma (Level B).

• MRI with contrast enhancement is the gold standard to monitor LGG after surgery: an MRI examination every 6 months might be enough, unless the physicians think otherwise (good practice point).

• MRS is useful for the differentiation of LGG from non-tumoral lesions, pre-operative definition of extent and guiding stereotactic biopsies (Level C).

• DSC-MRI can be employed in the follow-up to predict malignant transformation (Level C).

• PET with FDG is useful for detecting malignant transformation in astrocytomas (Level C) and for differentiation between radiation necrosis and tumor recurrence (Level B)

• PET with MET is useful for differentiation of LGG from non-tumoral lesions (Level B), guiding stereotactic biopsies (Level B), pre-treatment evaluation (Level B) and monitoring treatment (Level C).

• Prophylactic AEDs must not be used before any epileptic seizures have occurred (Level A).

• AEDs should be started after the first seizure (Level A). AEDs should be individualized according to seizure type, comedication, comorbidity and patient preferences (good practice point).

• In patients who need a treatment with chemotherapeutics, non-EIAEDs are to be preferred (Level B).

• Surgical resection represents the first treatment option, with the goal to maximally resect the tumor mass whenever possible, whilst minimizing the postoperative morbidity (Level B).

• The identification of the eloquent cerebral areas, which have to be preserved during surgery, is performed through pre-operative neuroimaging modalities (functional MRI, fiber tracking) and intraoperative brain mapping techniques (Level B), and awake surgery could improve the results (Level C).

• When surgery is not feasible (because of tumor location, extension or comorbidities), a biopsy (either stereotactic or open) should be performed to obtain a histological diagnosis (good practice point).

• For patients with unfavorable prognostic factors (older age, incomplete or no resection, existing neurological symptoms), an adjuvant treatment is indicated at any time (Level B), and this is more commonly RT (good practice point).

• A total RT dose of 50.4–54 Gy in fractions of 1.8 Gy represents the current standard of care (Level A).

Modern RT techniques (conformal dose delivery or intensity modulated techniques) should preferably be used (Level B).

• Younger patients (<40 years of age) with (nearly) complete resection and tumors with an oligodendroglial component have a more favorable prognosis and can be observed after surgery (Level B), but close follow-up is needed (good practice point).

• Chemotherapy is an option for patients with recurrence after surgery and radiation therapy (Level B).

• Chemotherapy is an option as initial treatment for patients with large residual tumors after surgery or unresectable tumors to delay the risk of late neurotoxicity from large-field RT, especially when 1p/19q loss is present (Level B).

• Neuropsychological tests, at diagnosis and during the follow-up, can be useful, being selected according to the needs of the clinical setting (good practice point). The neuropsychological tests must have standardized materials and administration procedures, published normative data, moderate to high test–retest reliability, brief administration time (30 – 40 min) and be suitable to monitor changes over time (good practice point).

• Cognitive rehabilitation can be helpful (Level B)"

Conclusions

Patients with low-grade gliomas have a more favorable prognosis than patients with high grade glioma. Despite this, the majority of patients with low-grade gliomas suffer either tumor progression or degeneration into to a more malignant lession (8) in our series the median to malignant transformation was 32,5 months which is comparable with the data existing in the literature (32 months (8)).

Younger age, normal neurological examination, oligodendroglial histology and 1p loss (we don't have the possibility to evaluate molecular markers) are favorable prognostic factors.

Early post-operative radiotherapy improves progression free survival but not overall survival. Chemotherapy can be useful as initial treatment after surgery or at recurrence after radiotherapy.

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