CASE STUDY

ACTA Vol. 16, No. 3, 2018, 307-319
NEUROPSYCHOLOGICA

Received: 12.05.2018
Accepted: 09.10.2018

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

HEALTH-RELATED QUALITY OF LIFE OF A PATIENT FOLLOWING NEUROSURGERY ON GLIOBLASTOMA MULTIFORME (GBM)

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SUMMARY

Background: Health-related quality of life (HRQoL) plays a role as a patient-centered meaningful endpoint, assessing the direct clinical benefit for a patient. The inclusion of HRQoL measurements in a glioma patient may provide important data to inform clinicians on treatment decision-making. The aim of the study was to evaluate cognitive decline and HRQoL in the clinical care of a patient following neurosurgery on of glioblastoma multiforme (GBM).

Case Study: A 69-year-old female developed malignant brain glioma in the right temporal-occipital area; this being confirmed by CT and MR study and neuropathological findings. She had complained of headaches, dizziness, nausea, vomiting as well as attention and memory loss, and anxiety, sadness and a slowing down in the performance of daily activities. The symptoms rapidly became worse and she was referred to a neurosurgery department for consultation. She was successfully neurosurgically operated on. She was examined with the use of neuropsychological tests three times: the first examination was conducted before the neurosurgical operation, the second two weeks after, and the third half year after the neurosurgical operation. In the first examination by the standard Polish version of the *Mindstreams*™ Interactive Computer Tests disturbances for all the tested cognitive functions occurred. The greatest changes were to occur however in the areas of visual-spatial functions. attention, executive functions and memory. In the second test, a return to the norm was achieved for the disturbed cognitive and executive functions. In the third examination (half a year after the neurosurgical operation), the cognitive and executive functions were still not bad, but had slightly decreased. Similar trend was observed in HRQoL. A significant difference in the health profile between the 1st and 2nd as well as between 1st and 3rd examination was detected for the eight SF-36 domains - HRQoL was improved. While only slight but no significant changes occurred between 2nd and 3rd examination. HRQoL was still not bad, but had slightly decreased.

Conclusions: The patient after the neurosurgical operation of glioblastoma multiforme (GBM) is capable of carrying out daily activities, but shows some level of reduced complains for functional capacity, pain, general health and vitality, emotional and social functioning for mental health which has led to the impaired HRQoL.

Key words: tumorectomy, cognitive functions, HRQoL

BACKGROUND

The diagnosis of a malignant brain tumor is devastating to patients and their families. The patients' inevitable loss of independence, which can occur suddenly or gradually, is tragic, while the eventual total dependence can be overwhelming to the family and caregivers (Davis and Stoiber 2011).

Each year, about 5–6 cases out of a 100,000 are diagnosed with primary malignant brain tumors, of which about 80% are malignant gliomas (MGs), with glioblastoma multiforme (GBM) accounting for more than a half of MG cases (Alifieris & Trafalis 2015; Ostrom, Gittleman, Fulop et al. 2012; Siegel, Naishadham & Jemal 2013). Glioblastoma multiforme (GBM) is the most aggressive tumor that begins within the brain, it grows rapidly and has a tendency to recur throughout treatment (Zarnett, Sahgal, Gosio et al. 2015). It is associated with a disproportionately high mortality rate (Alifieris & Trafalis 2015).

Initially, the signs and symptoms of GBM are non-specific. They may include headaches, personality changes, nausea and vomiting (Dirven, Taphoorn, Reijneveld et al. 2014). The patient may also develop localized neurological symptoms, seizures, memory loss, mood swings or lapsed in concentration (Henriksson, Asklund & Poulsen 2011; Pąchalska, Kaczmarek & Kropotov 2014). The kind of symptoms produced depends more on the location and size of the tumor than on its pathological properties and it impact. A worsening of symptoms is often rapid and may have a negative impact on the patient's quality of life (Alifieris & Trafalis 2015).

In the world subject literature there is no description of a clear way to prevent the disease (Ho, Reijneveld, Enting, et al. 2014; Gallego 2015). **Neurosurgery** and/or radiotherapy are still fundamental elements of standard therapy for patients, after which chemotherapy and radiation therapy are used (Chinot, Wick, Mas et al. 2014). The medication temozolomide is used frequently as part of chemotherapy (Hart, Garside, Rogers et al. 2013; Alifieris & Trafalis 2015; Khosla 2016). High dose steroids may be used to help reduce swelling and decrease symptoms (Young, Jamshidi, Davis et al. 2015). It is unclear whether trying to remove all or simply most of the tumor is better for a patient's conditions (Van Meir; Hadjipanayis, Norden et al. 2010), and his quality of life.

Despite maximum treatment, the GBM usually recurs (Chinot, Wick, Mason et al. 2014; Alifieris & Trafalis 2015). The most common length of survival following diagnosis is 12 to 15 months, with fewer than 3% to 5% of people surviving longer than five years (van den Bent MJ, Brandes AA, Taphoorn MJ, et al. 2013; Alifieris & Trafalis 2015). However, even multimodal treatment including neurosurgery, radiotherapy and chemotherapy does not result in a cure, with only the prolongation of (progression-free) survival achievable (Chinot, Wick, Mason, et al. 2014). Without treatment, survival is typically three months (Schapira 2007).

Because of the incurable nature of GBM, treatment is not only directed at prolonging survival, but also at maintaining or improving the health-related quality of life (HR-QoL) during the entire disease trajectory (Henriksson, Asklund &

Poulsen 2011). HR-QoL is a multidimensional concept with domains covering physical, cognitive, role emotional and social functioning, as well as symptoms induced by the disease and its treatment (Aaronson 1988; Pąchalska, Kaczmarek & Kropotov 2014). Consequently, HRQoL plays a role as a patient-centered meaningful endpoint, assessing the direct clinical benefit for the patient (Dirven, Taphoorn, Reijneveld et al. 2014). The inclusion of HRQoL measurements may provide important data to inform clinicians on treatment decision-making (Aaronson 1988; Henriksson, Asklund & Poulsen 2011; Pąchalska, Kaczmarek & Kropotov 2014; Dirven, Johan, Koekkoek et al. 2016).

Neurocognitive functions are an important determinant of HR-QoL (Giovagnoli, Silvani, Colombo et al, 2004). Not surprisingly, neurocognitive function assessments have been incorporated as major components within patient assessments, along with common and widely used questionnaires to assess health-related QoL (HR-QoL). Recently, an increasing number of studies and clinical trials have incorporated neurocognitive function measures over the course of the entire disease trajectory (Correa 2010; Khuntia, Brown, Li et al. 2006). Especially in patients with high-grade glioma this is an important endpoint during treatment, particularly in those with glioblastoma multiforme (GBM) given its dismal prognosis despite the limited advances in standard therapy (Li, Bentzen, Li et al, 2008).

It is well recognized on the one hand that impairment of neurocognitive functioning, resulting in behavioral, emotional, and intellectual difficulties, occurs in nearly all patients with GBM and eventually compromises their independence (Taphoorn & Klein 2004). On the other, the evaluation of neurocognitive functions may serve as an index of the effectiveness of a particular method of treatment. A potentially positive impact of neurosurgery on the neurocognitive function, performance status and/or QoL has also started to emerge from reports of clinical studies among GBM patients, and relevant information about therapy-related neurotoxicity or the pathophysiologic mechanisms that may underlie RT and chemotherapy injury to the brain (Alifieris & Trafalis 2015).

A meta-analysis focused on the evaluation of various methods of therapy in the field of improving neurocognitive functions, and thus the quality of life in people with GBM, did not give conclusive results enabling unambiguous conclusions to be drawn (Li, Bentzen, Li et al, 2008; Correa 2010; Henriksson, R., Asklund, T., & Poulsen, H. S. 2011). However, the authors see an urgent need for QoL (Byrne, Waller, Piercy et al 2017). Attention should also be paid to non-aggravating and effective HR-QoL research.

The aim of these studies was to evaluate cognitive decline and HRQoL in a clinical care of a patient folowing the neurosurgery on glioblastoma multiforme (GBM).

Ethics statement

According to the guidelines of the Helsinki Declaration (2008), the subjects participating in the experiment were informed in detail about the test procedure and they provided written consent for their participation in the project. The study

protocols received ethical approval from the Ethical Committee of the Regional Medical Chamber (KB6/16).

CASE REPORT

A 69-year-old female developed malignant brain glioma in the right temporal-occipital area; this being confirmed by CT and MR study (see Fig. 1A-E, 2, 3 A-B; 4 A-C) and neuropathological findings (see: fig. 5). She had complained of headaches, dizziness, nausea, vomiting as well as attention and memory loss, and anxiety, sadness and a slowing down in the performance of daily activities. The symptoms rapidly became worse and she was referred to a neurosurgery department for consultation. She was successfully neurosurgically operated on.

Under general anesthesia, intravenous-intrathecal replacement, replacement breathing, the patient's position on the left side, the skull was opened with the free temporal – occipital area through craniotomy. A dura mater was opened in a circular form with a centrifugal extension. It was found that the *cancer* tumor infiltrates the dura mater in the occipital region - this part of the dura was excised.

There were large, pathological venous vessels on the cortex of the brain. The cerebral cortex was incised in the posterior temporal region. At a depth of about

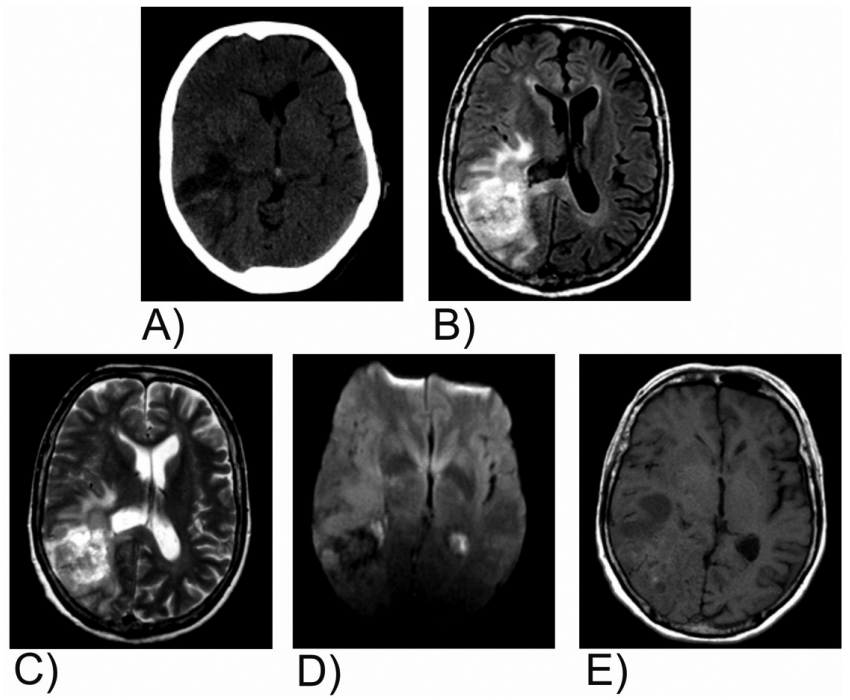

Fig. 1A. Presurgical brain CT, axial plane; Inhomogenous expansive lesion in the right temporooccipital region; B) FLAIRT2 and C) frFSET2 sequences: inhomogenous hiperintense lesion in the right temporooccipital region with mass effect – finger-like surrounding edema and midline shift; D) DWI sequence: no evident restricted diffusion within the lesion; E) GRET1 sequence: small hiperintense foci of hemorrhage inside the tumor

2 cm there was a cyst. The tumor was carefully dissected from the healthy-looking nervous tissue. The tumor was brownish and discolored, harder than healthy tissue, and propagated backwards from the cyst in the direction of the occipital pole. The tumor was completely removed macroscopically, however the neurosurgeons were aware of the maximal safe resection of the eloquent area during the excision of this tumor. Persistent parenchymal and venous bleeding was blocked with bipolar coagulation and oxycel. The dural defect was supplemented with Tachosil. The bone flap was removed due to the swelling of the brain and the insertion of the brain into the craniektomy hole. Three days after the operation, the swelling subsided.

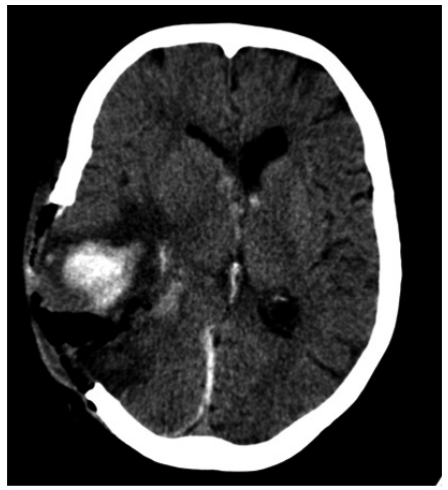

Fig. 2. Postsurgical brain CT, axial plane: Area of bleeding and edema in the postoperative field

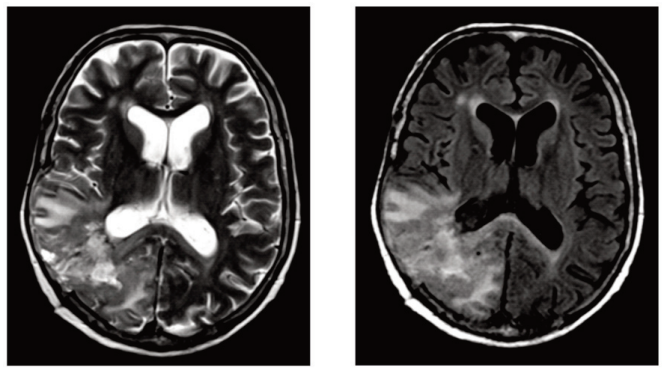

Fig. 3AB. Brain MR, three months after surgery and XRT, axial plane: A) frFSET2 and B) FLAIRT2 sequences: inhomogenous hiperintense lesion in the right temporooccipital region, „soap bubble" appearance of some parts of lesion, smaller finger-like edema around and only discrete lateral ventricle compression, no signs of the midline shift – signs of XRT necrosis regression of the postoperative changes

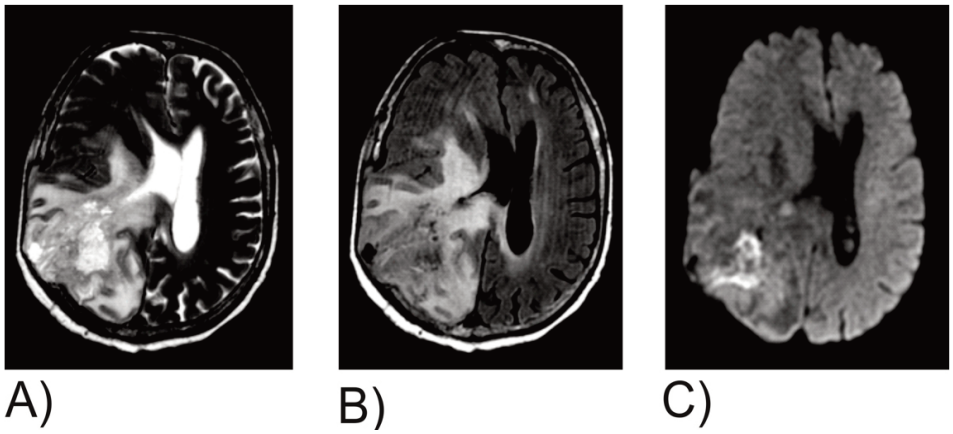

Fig. 4 ABC. Control brain MR, one month later, axial plane: A) frFSET2 and B) FLAIRT2 sequences: inhomogenous hiperintense mass in the right temporooccipital region, enlargement of the finger-like edema, „soap bubble" appearance of some parts of lesion and mass effect – pronounced lateral ventricle compression again with signs of midline shift; C) DWI sequence: area of restricted diffusion inside the lesion – suspicion of the recurrent tumor together with XRT necrosis

MRI examination

MRI of the brain performed after the CT examination and before surgery confirmed the suspicion of glioblastoma (Fig. 1A-E). A control brain CT examination performed after surgery (Fig. 2) showed typical postoperative changes (edema and bleeding) in the place of the detached tumor. Control brain MR after radiotherapy (three month after surgery) demonstrated a small area of XRT necrosis and partial regression of the postoperative changes (Fig. 3A,B). One month later the control brain MRI showed intensified signs of XRT necrosis and suspicion of the recurrent tumor (Fig. 4A-C).

Neuropathological findings

The tumor had the typical features of glioblastoma with high cellular and nuclear polymorphism, numerous necrotic areas, high mitotic and a Ki67-labelling index, and endothelial proliferations. The tumor diffusely invaded subarachnoid space (Fig.5A-E).

Neuropsychological examination

She was examined three times: the first examination was conducted before the neurosurgical operation, the second two weeks after, and the third half year after the neurosurgical operation.

Cognitive measures

The standard Polish version of the *Mindstreams*™ Interactive Computer Tests was employed (Pąchalska, Kaczmarek & Kropotov 2014). The effect of the neurosurgical operation on the neuropsychological functioning of the patient is presented in Fig. 6.

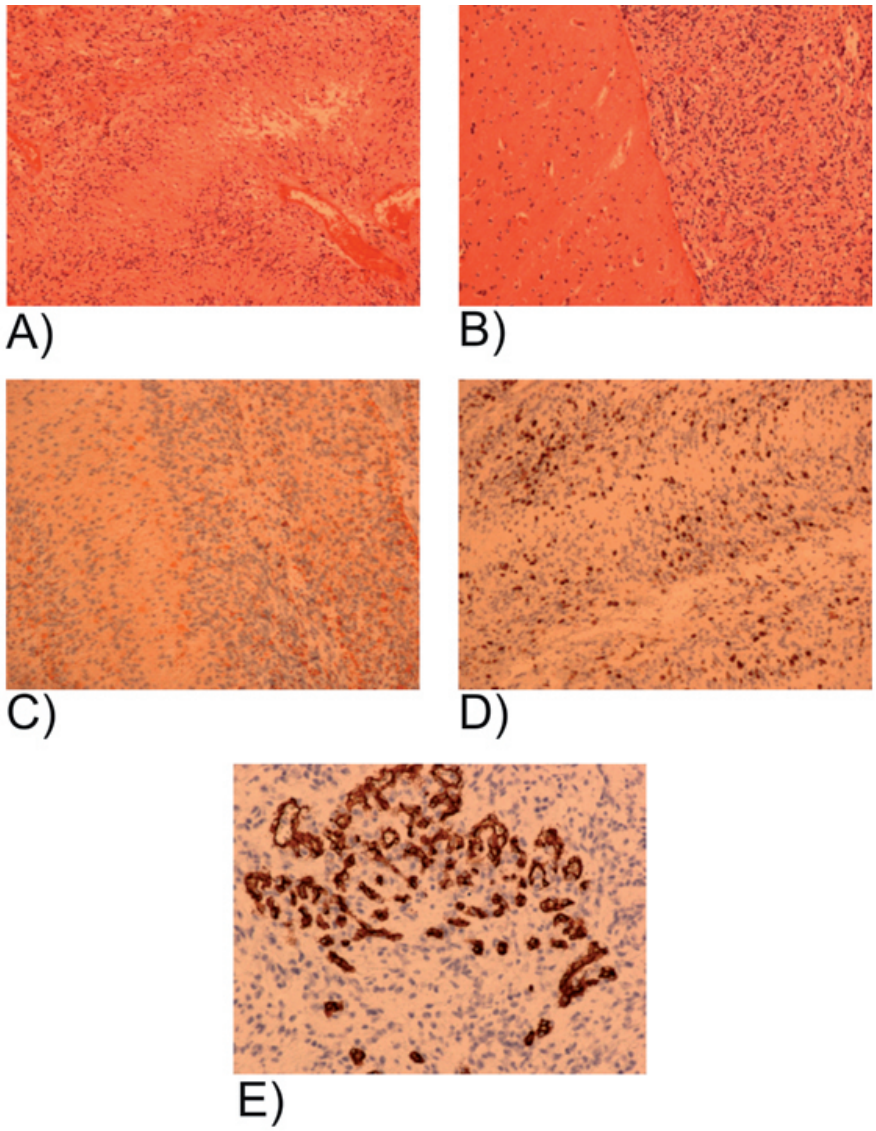

Fig. 5. Glioblastoma; A) Dense but in this region relatively mild polymorphic infiltrate with focus of the necrosis in the center surrounded by palisade formation. (B) Invasion of subarachnoid deal space; C) GFAP immunopositivity; D) High labelling index of Ki67, E) Endothelial hyperplasia CD34 immunohistochemistry

In the first examination by the standard Polish version of the *Mindstreams*™ Interactive Computer Tests disturbances for all the tested cognitive functions occurred. The greatest changes were to occur however in the areas of visual-spatial functions. attention, executive functions and memory. In the second test, a return to the norm was achieved for the disturbed cognitive and executive functions. In the third examination (half a year after the neurosurgical operation), the cognitive and executive functions were still not bad, but had slightly decreased.

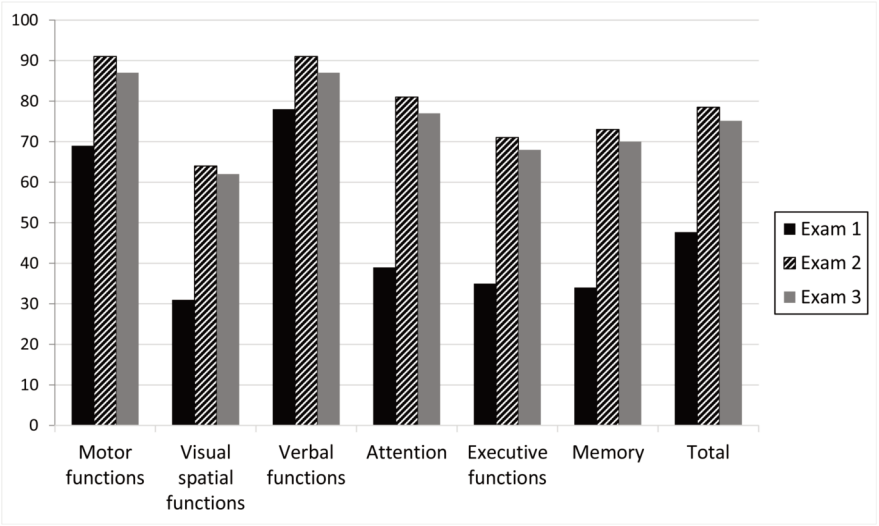

Fig. 6. The effect of neurosurgery on the neuropsychological functioning as measured by the standard Polish version of the Mindstreams™ Interactive Computer Tests

HRQol measures

The Short Form 36 (SF-36) was used to assess HR-QoL. It includes a 36-item, patient-reported survey of patient health, and their measure of health status. The original SF-36 is available and accessible under the public domain license. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The higher the score, the more the disability (more complaints for limitations). The lower the score, the lower the disability of the patient (less complaints for limitations).

RESULTS

A significant difference in the health profile between the 1st and 2nd as well as between 1st and 3rd examination was detected for the eight SF-36 domains. While only slight but no significant changes occurred between 2nd and 3rd examination.

The result of the SF-36 domains in the first examination was 60 points for physical functioning (PF); 69 points for the role physical (RP); 71 points for bodily pain (BP); 66 points for general health perception (GH); 69 points for vitality (VT); 73 points for the social functioning (SF); 78 points for the role emotional (RE) and 62 points for mental health (MH).

In the second examination we observe a much better HR-QoL, which was expressed in the decrease in her complaints with this being: 31 points for physical functioning (PF); 23 points for the role physical (RP); 38 points, for bodily pain (BP); 34 points for general health perception (GH); 39 points for vitality (VT); 42 points for the social functioning (SF); 37 points for the role emotional (RE) and 38 points for mental health (MH).

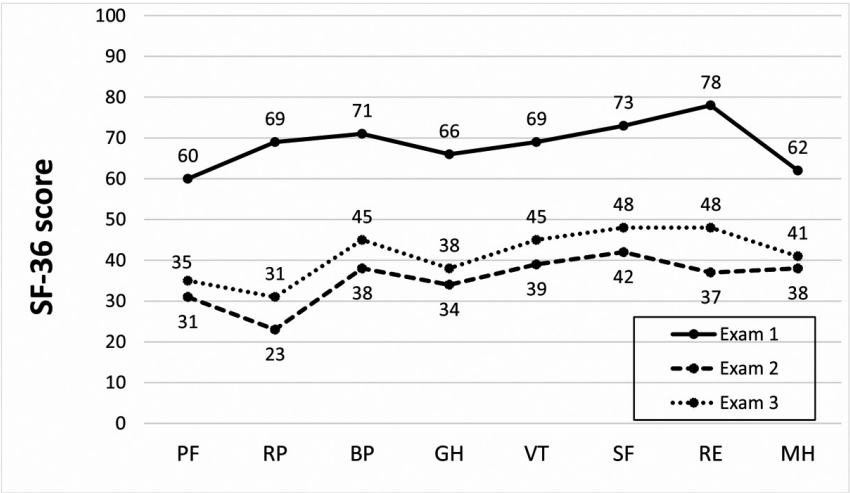

Fig. 7. Graph showing the profiles of SF-36 in the 1st and the 2nd examination of the patient: PF – physical functioning; RP – role physical; BP – bodily pain; GH – general health perceptions; VT – vitality. SF– social functioning; RE – role emotional; MH – mental health

In the third examination (half a year after the neurosurgical operation), the quality of life was still not bad, but the number of complaints had slightly decreased, these being: 35 points for physical functioning (PF); 31 points for the role physical (RP); 45 points, for bodily pain (BP); 38 points for general health perception (GH); 45 points for vitality (VT); 48 points for social functioning (SF); 48 points for role emotional (RE) and 41 points for mental health (MH).

DISCUSSION

The longitudinal studies of our patient showed that neurocognitive disorders (attention, memory, executive functions, and graphomotor speed) before the neurosurgical operation, and these decreased her quality of life occured. There were also disorders in the general physical and psychological and social functioning of the SF-36. After the neurosurgical operation, these disorders underwent a significant and statistically significant decrease, which means an improvement in beurocognitive functioning and HR-QoL. This improvement lasted for half a year after surgery, although the patient's condition began to deteriorate slightly. However the patient did not decide on radiotherapy.

This might be related to the fact that during the operation it was possible to remove the whole tumor, which in pressing on other tissues had disrupted the proper functioning of the brain. Under these conditions, it was possible to regain a number of functions again. Such an improvement in functions has also been observed by other authors, which led them to the conclusion that neurosurgical resection is the standard in care for gliomas, and the extent of resection (EOR), both high- and low-grade gliomas (Yordanova Y, Moritz-Gasser S, Duffau 2011;

Almeida, Chaichana, Rincon-Torroella et al. 2015; Almeida JP, Chaichana KL, Rincon-Torroella 2015; Ius, Isola, Budai et al. 2012).

How can one interpret such an improvement?

Two major mechanism underlie this improvement: the first is associated with the technical nuances of the neurosurgical operation in which neurosurgeons pay attention to a maximal safe resection during brain tumor removal (see also: Dziedzic & Bernstein 2014; Hervey-Jumper & Berger 2015; Hervey-Jumper SL, Li J, Lau 2015). In other words, individualized surgery in neuro-oncological treatment of GBM is based on the goal of achieving a maximal tumor resection without inducing new neurological deficits (Ghinda, & Duffau 2017; Sanai, Berger 2008; Ahmadi, Dictus, Hartmann et al. 2009; McGirt, Chaichana, Attenello et al. 2008). The benefits are: a shorter hospital stay, less blood loss, reduced pain and anxiety, cost effectiveness, as well as lower complications and morbidity (Chacko, Thomas, Babu et al. 2013; Brown, Shah & Bregy 2013).

The second mechanism is connected with the neuroplasticity allowing the formation of new neuronal connections in the brain (Ghinda, & Duffau 2017). Neuroplasticity is the ability of the brain to reorganize itself during normal development and in response to illness (Kong, Gibb & Tate 2016). Neuroplasticity has been documented in glioma patients, for example, it has been reported that lesions that occur in “eloquent” areas, such as Broca’s or Wernicke’s area, may not result in detectable language deficits (Duffau, Capelle, Denvil 2003; Desmurget, Bonnetblanc, Duffau 2007; Kim, Amankulor, Peck et al. 2014; Kośla, Bryszewski, Jaskólski et al. 2015). In the case of our patient the tumor was completely removed macroscopically, however the neurosurgeons were aware of maximal safe resection of the eloquent area during tumor removal. Therefore, there was the possibility of neuroplasticity and this fact could be strongly associated with the neurocognitive functioning and quality of life of this patient after the neurosurgical operation.

It should be added that good results in terms of quality of life and cognitive functions and quality of life, which were still observed in study II, six months after surgery, can also be associated with the fact that the patient did not decide on radiotherapy. It is known from the subject literature that radiotherapy undoubtedly involve a lot of complications, which were also observed by other authors (Chinot, Wick, Mason et al 2014), and thus with the deterioration of neurocognitive functions and with the deterioration of HR-QoL.

HRQoL could possibly be considered as a co-primary endpoint in future trial designs, together with a surrogate endpoint such as progression-free survival, to ensure that both a direct treatment effect and a direct clinical benefit for the patient will be assessed. Routine assessment of HRQoL has proven to be feasible in clinical practice and was found to facilitate the communication between patients and physicians. However, despite the discussion of HRQoL issues, so far this has not had an impact on patient management and clinical decisions. Standard multidimensional HR-QoL questionnaires might therefore contain too many items and consequently lack the sensitivity necessary to detect QoL changes in patients with high-grade glioma (Henriksson, Asklund, & Poulsen 2011).

Currently, neurocognitive dysfunction is considered the most frequent complication among long-term survivors. A good proposition is the evaluation of neurocognitive functions, which proved to be sensitive to changes induced by neurosurgical surgery, which we proved in our patient and which other authors have presented. In the case of the examined patient, simple neuropsychological tests proved to be more practical, which allowed one to assess the degree of neuro-cognitive deterioration before surgery and the improvement obtained after the operation both in the direct examination and half a year after surgery.

Further studies are needed to confirm these findings and to better understand the natural history of the H-RQoL of GBL patients.

CONCLUSIONS

The patient after the neurosurgical operation of glioblastoma multiforme (GBM) is capable of carrying out daily activities, but shows some level of reduced complains for functional capacity, pain, general health and vitality, emotional and social functioning for mental health which has led to the impaired HRQoL.

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