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Original article

The course of quality of life and neurocognition in newly diagnosed patients with glioblastoma

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ABSTRACT

Background: The importance of QoL and neurocognitive functions in patients with glioblastoma (GB) is above controversy by now. We followed newly diagnosed GB patients treated with radio-chemotherapy during their course of disease by continuously evaluating their quality of life (QoL) and cognitive functions.

Methods: We included consecutive patients with newly diagnosed GB from 2010 to 2013 at the Medical University of Vienna. To assess QoL the EORTC QLQ C30 and BN20 questionnaire were used. Neurocognition was measured with the NeuroCog FX. The evaluations were done 6 times every three months, beginning at the beginning of radio-chemotherapy.

Results: 42 patients participated in this study. We also recorded QoL and neurocognition in 23 patients after the first disease progression. Patients maintained their cognitive summary score until relapse. Patients with left-sided tumors showed significant lower scores in the subscale verbal fluency than patients with right-sided tumors. The global health score of QoL decreased after the fifth evaluation (13 months after diagnosis) whereas a peak of fatigue symptoms was obtained at the third evaluation. Furthermore, fatigue symptoms increased strongly 7 months after diagnosis and patients' financial difficulties were mentioned more frequently by younger patients and in patients with lower education levels.

Conclusions: QoL and cognitive long-term assessments are feasible also in some patients with GB after a symptomatic progression. Our study demonstrates maintenance of QoL and cognitive summary scales before tumor progression. Moreover, it highlights subgroups according to tumor location and socioeconomic factors.

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Patients diagnosed with glioblastoma (GB) are confronted with the outlook of a limited survival span [1,2], combined with an increasing burden of symptoms [3,4]. Standard of care for GB is surgery followed by radiotherapy (RT) and concomitant and adjuvant temozolomide (TMZ) [2]. Due to this tri-modal therapy, the disease-free survival rate for these patients improved over the last decade and the interest in quality of life (QoL) and cognitive outcomes emerged.

However, evaluation of QoL in brain tumor patients is not consistently measured outside of trials, as it is time consuming and burdensome for patients, proxies and for health care personnel involved [5]. Nevertheless, some studies recorded lower QoL levels in patients with brain tumors compared to other solid tumors and of course to healthy controls [6,7].

For brain tumor patients, cognitive decline is regarded to have a significant impact on QoL [8,9] and (subjective) cognitive deficits are frequently already present before tumor surgery [10–12]. The prevalence of neurocognitive dysfunctions may also be relevant for the decision-making capacity and thus for providing informed consent to the treatment options proposed by the treating physicians. Moreover, there is evidence that cognitive deficits related to gliomas can be improved through training and cognitive rehabilitation [9,13,14]. Therefore, consequently measured outcomes from GB patients are necessary to form a basis for adequate follow-up care.

In this prospective longitudinal study, we followed 42 patients with newly diagnosed GB during their therapy and analyzed their molecular tumor data. We aimed at evaluating the development of

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the patients' neurocognitive function and QoL every three months. The endpoint of the study was reached after the 6th evaluation, sixteen months after initial diagnosis.

Patients and methods

The patients' inclusion criteria were newly diagnosed primary GB histologically confirmed, age ≥18 years, WHO Performance score ≤2, sufficient skills of the German language and absence of previous cancers or psychiatric disorders. We informed all eligible patients referred to the Medical University of Vienna from March 2010 to January 2013 about the study and asked for their consent.

The first assessment was done as soon as possible after referral but at the latest at the start of concomitant therapy and further 5 assessments every three months were scheduled to cover up to sixteen months after diagnosis.

To assess QoL, we used the EORTC QLQ-C30 and BN20 questionnaire. These instruments are widely used for self-reported assessment of QOL including questions for symptoms especially brain tumor patients suffer from. All analyses were done according to the EORTC recommendations [15]. We transformed the scores to a linear scale ranging from 0 to 100; the higher the score the higher the level of functioning or symptoms.

Neurocognition was measured with the computer program NeuroCog FX. The program has been already used in patients with brain tumors [16–18] and is also useful for repeated testing [16,17]. It addresses four domains (working memory, attention, verbal/figural memory and verbal fluency/language) with eight tasks. Also for this test, we transformed the scores to a linear scale ranging from 0 to 140 whereas 100 points display the obtained median score of the normal population.

All evaluations were done in an undisturbed room and took about 30 min each. QoL and cognition analysis were done with regard to differences in age, educational levels, and tumor data.

The time to progression was defined as the period between the date of GB diagnosis (resection/biopsy) and the date of tumor progression, as verified by 3-Tesla Magnet resonance imaging (3 T-MRI) scans. The RANO criteria were applied for the definition of progressive disease [19].

Pyrosequencing-based assessment was applied to analyze the O6-Methylguanin-DNA-Methyltransferase (MGMT) promoter methylation status [20].

The local ethics committee has approved the study.

Statistical considerations

All data were analyzed with SPSS-statistics-v.20. We used descriptive methods to describe the patients' characteristics. For group comparisons, analysis of variance (ANOVA) considering multiple testing with Bonferroni correction and the chi-square test with continuity correction were used. For analysis of survival functions, Kaplan–Meyer method (log-rank test) was applied. To compare patients' data before and after progression of disease we used the *T*-test with dependent samples. We set the significance level with 0.05.

Results

Patients

Out of 59 patients, 42 patients were eligible for participation in this study. Two patients declined participation, six were not fluent in the German language, two had a history of psychiatric disorders and seven patients scored >2 in WHO performance score. In total, 147 assessments evaluating QoL and neurocognitive functions were done. All 42 patients included in the study completed the test battery at first assessment. The median time from diagnosis to baseline assessment was 36 days (11–57 days). From the first to the sixth evaluation, 84% of patients dropped out of the study protocol. Of note, 31 follow-up evaluations were done in 23 patients with progressive disease. The main reason for drop-out was deterioration of clinical condition (24 patients) followed by patient refusal (3 patients) and loss to follow up with 2 patients (Fig. 1).

Patient's characteristics are given in Table 1. The median age of the 15 female and 27 male patients was 54 years (20–75 years). The educational levels varied whereas six patients had achieved higher academic degrees. Thirty patients were employed at the time of diagnosis and twelve were already retired. Ten patients remained in their profession for some time after the GB diagnosis, among them three with a university degree (Fig. 2).

Treatment

All patients were treated according to the current standard treatment of the EORTC-NCIC regiment [2]. The time from surgery/biopsy to start of radiochemotherapy was three weeks in median (15–37 days).

A tumor resection was performed in 35 patients, neurosurgical biopsy in the remaining 7 patients. According to the *RANO* criteria [21], a complete tumor resection was achieved in 27, a partial resection in 8 cases.

All patients underwent 3D-conformal RT with 2 Gy per fraction given 5 days per week for 6 weeks up to 60 Gy with concomitant daily TMZ (75 mg per square meter of body-surface area per day, from the first to the last day of radiotherapy), followed by six cycles of adjuvant TMZ (150–200 mg per square meter for 5 days during each 28-day cycle) [1,2]. Image acquisition, treatment planning and RT were performed according to routinely used protocols for brain tumor patients at our department of RT. EFFICAST® was used as immobilization device for the planning computer tomography (CT) and during treatment. Post-operative treatment planning CT and MR were obtained with intravenous contrast medium using a multislice CT scanner and a 3-Tesla-MR with slice thickness of 2 mm. The T1-weighted and flair MR study sets were chosen for co-registration with the planning CT scan for structure delineation using BrainLab IPlan 4.1.1. The RT target was defined as postoperative residual tumor and cavity plus an isotropic margin of 2 cm [22]. The treatment planning was performed on Oncentra Masterplan 4.3.

The median planning target volume (PTV) was 357.75cm^3 (see Table 1). Depending on the localization of the PTV, between three and five fields were applied to guarantee the required target coverage. The RT treatment planning was performed following the ICRU 50/62 recommendations for 3 D-conformal RT [23,24]. Electronic portal imaging devices and on-board cone beam CTs were used during the first week of RT daily and followed by once weekly in order to verify the patients' position.

Survival duration/MGMT-status

The median progression free survival (PFS) of the participating patients was 9.5 months (2.2–30.9 months). At the time of final data analysis, one patient was still alive at 50 months after diagnosis. The median survival time was 18.5 months (2.3–50 months) using the Kaplan–Meyer method. The MGMT methylation status was determined in 32/42 available tumor tissues. Kaplan–Meyer analysis showed significantly different PFS and survival times (OS) in favor of patients with methylated MGMT status ($p = 0.027$ for PFS 13.2 versus 8.2 months; $p = 0.001$ for OS 26.0 versus 12.2 months).

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