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# Postoperative hypofractionated radiotherapy of patients with glioblastoma: three courses of irradiation separated by 2 or 4 week intervals. A preliminary report on a randomized trial

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*Aim. To asses the efficacy of two postoperative hypofractionated regimens of radiotherapy and to define the prognostic factors in adult patients with glioblastoma multiforme.*
*Material and methods. Between 1994 and 2004, 118 patients with glioblastoma multiforme were randomized to one of two treatment arms: ITW (interval of two weeks) or IFW (interval of four weeks). The three irradiation courses were separated by intervals of 2 weeks (ITW) or 4 weeks (IFW). In each of them a dose of 20 Gy in five fractions in five days was delivered to the tumor bed.*
*Results. Treatment tolerance was found to bee good in both arms. Actuarial 2- and 3-year overall survival was 16.4%, 3.3% in arm ITW and 10.5%, 1.8% in arm IFW. This difference is not statistically significant (at the 0.05 level). Multivariate analysis revealed that only age and neurological performance status (NPS) correlated with survival. Patients under 40 years of age and patients with very good NPS (i.e. 1 according to the EORTC/MRC score) had the best prognosis.*
*Conclusions. The two different hypofractionated radiotherapy regimens administered to our patients provided, approximately, the same survival rates. Both regimens were well tolerated and their results were comparable with those of standard therapy.*
*Patient age and their neurological performance status were the most important prognostic factors.*

**Key words:** glioblastoma, radiation therapy, hypofractionation

## Introduction

Glioblastoma, which is the most common and most malignant primary brain tumor in adults, presents a supreme challenge to the local modes of therapy. There is abundant evidence that it cannot be eradicated by the presently available surgical and radiotherapeutical techniques. Thus, we believe that treatment of this tumor should be as simple, short and devoid of side effects as possible.

Gliński reported a randomized study of 108 patients comparing 50 Gy in 25 fractions to the whole brain to a hypofractionated regimen consisting of three courses of irradiation separated by 1-month intervals. The first two courses of hypofractionated radiation consisted of 20 Gy in 5 fractions to the whole brain, while the third course was a 10 Gy boost to the tumor in 5 fractions. An analysis of all 108 randomized patients demonstrated no significant difference in survival between the treatment arms, but there was a significant survival benefit favoring hypofractionated radiation, as compared with conventional radiation in the subgroup of 44 patients with glioblastoma (23% vs. 10% at 2 years at p level = 0.05) [1].

In an attempt to increase the effective biolologic dose to the tumor and to improve local control, twice-a-day accelerated irradiation has been used in our institution. Patients were treated with 2.65 Gy per fraction, twice daily with 6 hour interval between fractions up to the total dose of 53 Gy over 12 days. Survival rate at 2 years was 15% [2, 3].

The objective of this study is to evaluate and compare the efficacy of postoperative hypofractionated schedules of irradiation in two randomized groups of adult patients with glioblastoma.

## Material and methods

The studied population was derived from neurosurgical centers which referred patients to the Maria Sklodowska-Curie Memorial Cancer Center in Kraków for radiation therapy. The study began in January 1994. Through December 2002, 118 patients were accrued. The eligibility criteria for the trial were as follows:

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**Table I. Clinical characteristics of patients by treatment option**

| Clinical characteristics | Treatment schedule IFW | ITW |
|---|---|---|
| No of patients | 57 | 61 |
| Male/female | 32/25 | 33/28 |
| Median age (years) | 49 | 47 |
| Karnofsky's performance status (KPS) | | |
| 60% | 32 (56%) | 30 (49%) |
| more then 60% | 25 (44%) | 31 (51%) |
| Neurological performance status (NPS) | | |
| 1 | 24 (39%) | 16 (28%) |
| 2 | 28 (46%) | 33 (58%) |
| 3 | 9 (15%) | 8 (14%) |
| Tumor location | | |
| frontal | 20 (35%) | 23 (38%) |
| temporal | 19 (33%) | 23 (38%) |
| parietal | 18 (32%) | 14 (23%) |
| occipital | – | 1 (1%) |

– Pathologically confirmed supratentorial glioblastoma (surgery consisted of as complete a excision as was deemed feasible; all surgical specimens were evaluated by the same pathologist)
– Patient age between 18 and 65
– No previous definitive treatment of brain tumor
– Neurological performance status (NPS) good enough to render radiotherapy possible (1-3 pts acc. to the EORTC/MRC scale) [4].
– Karnofsky's performance status (KPS) of 60 and more [5].

Informed consent was obtained before enrollment, acc. to the rules of the Hospital Ethics Committee. Eligible patients were randomized without stratification, using a table of random numbers, to one of the two treatment arms: ITW (interval of two weeks) or IFW (interval of four weeks).

Radiotherapy was started 3-7 weeks after surgery (median time: 38 days). External beam radiotherapy was used with a Cobalt-60 unit or linear accelerator with 6-8 MeV photons, in the supine position. All patients were immobilized with thermoplastic masks. Computerized planning of dose distribution was performed with CT based planning. The dose was specified and normalized at the treatment isocenter with the 95% isodose encompassing the target volume. The PTV (planning target volume) encompassed the tumor bed and oedema with a margin of 2 cm. There were three irradiation courses separated by 2 week (ITW) or 4 week intervals (IFW). In both arms, the patients received 20 Gy in five fractions in five days (from Monday to Friday). If the patients' general or neurological condition deteriorated in-between the courses, supportive care only was given, but these patients were considered evaluable and were not excluded from the statistical analysis.

NPS and Karnofsky's performance status of each patient were carefully recorded before the onset of radiotherapy, immediately after the termination of treatment and at each follow-up examination.

The distribution of patient characteristics by treatment schedule (ITW vs. IFW) has been presented in Tables I and II.

**Table II. Therapeutic characteristics by treatment option**

| Characteristics | Treatment schedule IFW | ITW |
|---|---|---|
| Surgery | | |
| total resection | 11 (19%) | 16 (26%) |
| partial resection | 46 (81%) | 45 (74%) |
| TSI | | |
| 3-4 weeks | 28 (49%) | 29 (47%) |
| more then 4 weeks | 29 (51%) | 32 (53%) |
| Irradiation technique | | |
| two fields | 16 (28%) | 22 (36%) |
| three fields | 41 (72%) | 39 (64%) |

TSI- time between surgery and first course of irradiation

### Supportive treatment

Systemic anticonvulsants were administered to all patients during irradiation. Dexamethasone was given in a dose of 12-24 mg/day, only as symptomatic medication required for the control of cerebral edema.

### Follow-up

Patients were followed-up every 4 months after treatment completion. Physical and neurological examinations were performed at each follow-up visit. A CT scan of the brain was obtained when clinically indicated.

### Statistical methods

At the time of this analysis, 116 of 118 patients were known to be dead. Overall survival (OS) analysis was performed using the Kaplan-Meier method for uinivariate variable testing with log-rank statistics, while Cox's proportional hazard modeling was used for multivariate testing [6, 7]. In all statistical procedures, p values below 0.05 were considered significant. Survival was measured from the date of first irradiation until death or date of last follow-up. The following factors were studied for the prognostic significance for OS: sex, age, KPS and NPS status, tumor location, extent of tumor resection, time between surgery and the first course of irradiation, and technique of irradiation (number of fields).

## Results

### Tolerance to the treatment

Irradiation was generally well tolerated in both groups. Skin reactions in the ITW group were not reported to be more severe than those of IFW regimen. Signs and symptoms of increased intracranial pressure occurred in three patients (5%) from the ITW group and in four patients (7%) from the IFW group.

Three patients from the ITW arm and five patients in IFW arm did not complete planned treatment because of disease progression.

### Survival

The Kaplan-Meier survival curves calculated according to the treatment option are presented in Figure 1.

No significant difference was observed between the IFW and ITW regimens, with a two year OS of 10.5% and 16.4% respectively (p=0. 5375)

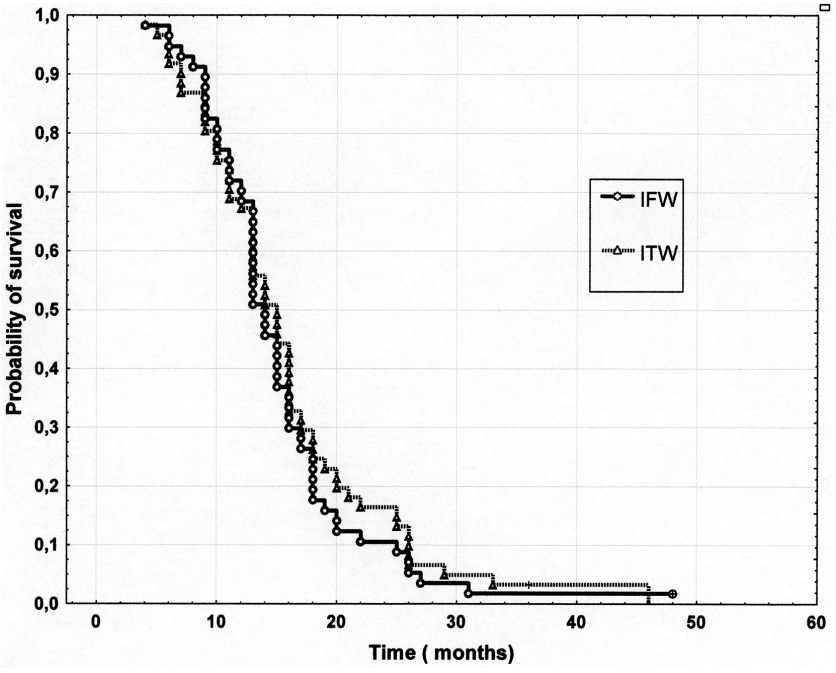


**Figure 1.** Actuarial survival of 57 patients treated with IFW (solid line) and 61 patients treated with ITW (dashed line)

Table III presents the univariate analysis of prognostic factors.

**Table III. Univariate analysis of prognostic factors**

| Factor | No of patients OS | Two-year (%) | Log-rank test p-value |
|---|---|---|---|
| Age (years) | | | |
| 40 and under | 35 | 27 | |
| over 40 | 83 | 2.6 | 0.0000 |
| Gender | | | |
| male | 65 | 12.9 | |
| female | 53 | 14.2 | 0.2933 |
| KPS | | | |
| 60% | 62 | 8.1 | |
| more then 60% | 56 | 19.6 | 0.0032 |
| NPS | | | |
| 1 | 40 | 22.7 | |
| 2 | 61 | 10.5 | |
| 3 | 17 | - | 0.0002 |
| Tumor location | | | |
| frontal | 43 | 16.1 | |
| temporal | 42 | 14.5 | |
| parietal | 32 | 6.2 | 0.6223 |
| occipital | 1 | - | |
| Surgery | | | |
| total resection | 27 | 16.8 | |
| partial resection | 91 | 12.7 | 0.2389 |
| TSI | | | |
| 3-4 weeks | 57 | 13.1 | |
| more then 4 weeks | 61 | 14.2 | 0.9264 |
| Irradiation technique | | | |
| two fields | 38 | 18.4 | |
| three fields | 80 | 11.2 | 0.7931 |

Multivariate analysis showed that only age and NPS correlated with survival. Patients under 40 years of age and patients with NPS score 1 had the best prognosis (Table IV).

**Table IV. Definitive Cox's model**

| Factor | Relative | risk p-value |
|---|---|---|
| Age (years | | |
| 40 and less | 1.00 | |
| more then 40 | 2.85 | 0.0000 |
| NPS | | |
| 1 | 1.00 | |
| 2 | 1.28 | |
| 3 | 2.55 | 0.0045 |

The probability of survival according to patient age and NPS has been presented on Figures 2 and 3.

## Discussion

Hypofractionation refers to the use of a fewer number of large size radiation fractions. As radiotherapy is not curative and survival is short, a hypofractionated schedule that would provide the same survival as a conventionally fractionated one, and with equivalent toxicity, would be useful in the management of patients with glioblastoma [8]. Hypofractionated regimens have been proposed in many centers, and the following radiation schedules were used: 30 Gy in 6 fractions, 30 Gy in 10 fractions, 36 Gy in 12 fractions, 37.5 Gy in 15 fractions, and 42 Gy in 14

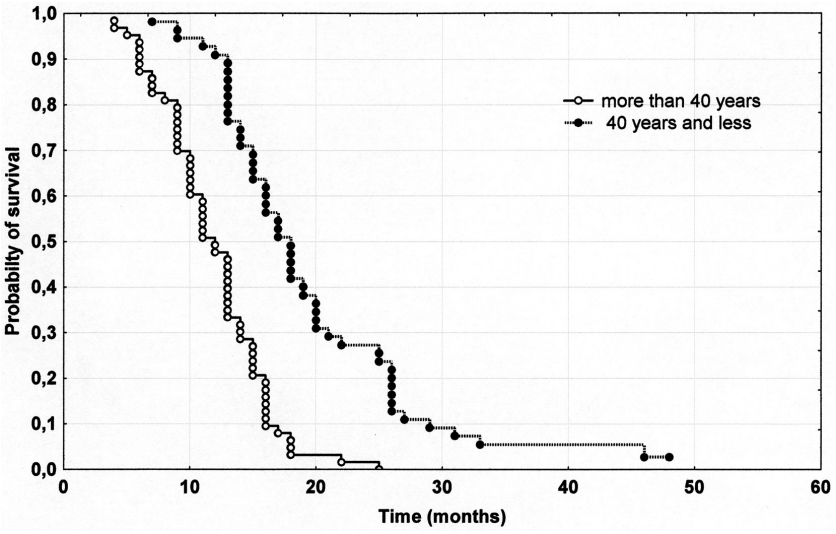


**Figure 2.** Actuarial survival according to patient age

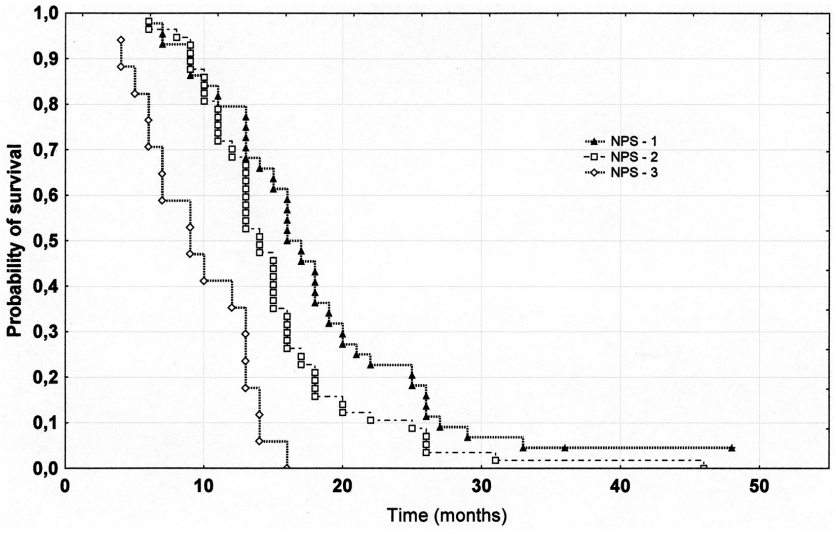


**Figure 3.** Actuarial survival according to the NPS

fractions. The number of patients treated in these series ranged from 21 to 219. Age criteria varied from 38 to 70 years, KPS was generally 50 and less, median survival ranged from 4 to 8 months [9, 10-14]. Slotman et al. presented a prospective, non-randomized study of 30 patients treated with a hypofractionated radiation schedule (42 Gy in 14 fractions). Median survival time (MST) was 36 weeks and age, KPS, and extent of surgery correlated strongly with survival. Patients with three favorable prognostic factors (age less then 50 yrs., KPS 80-100, and 75% or more of the tumor mass excised had the best prognosis (MST: 50 weeks) [11]. Bauman et al. cautioned, that elderly patients with a higher pretreatment KPS (above 50) may benefit from a higher dose radiotherapy regimen [9].

In our material the patient characteristics did not differ from those published recently by other Polish oncological institutions [15, 16]. Glioblastomas were more frequent in men, the median age of patients was over 55 years, frontal and temporal lobe localization was observed in 35% of cases, and less than 25% of patients underwent total tumor resection.

In our series of 118 adult patients with glioblastoma we found that, in uinivariate analysis, patient age, KPS and NPS correlated with survival. To establish the relative value of the known prognostic factors we performed a multivariate analysis. If all variables (age, gender, KPS, NPS of patients, tumor location, surgery, TSI, irradiation techniques) were entered into the model with a stepwise forward multiple regression, only age and NPS were found to influence the prognosis of survival. We have proven, that the youngest quartile, up to 40 years of age, achieved a 2-year OS of 27%, while older patients had markedly poorer survival, with a 2-year OS of 2.6%. Patient age is widely recognized as a patient-related prognostic factor. Several other studies had demonstrated better results in younger patients. The cut-off point seems to lie somewhere between 40 and 45 years of age [1, 2, 8,

9, 11, 17]. An interesting observation was made by Kępka et al. In their study age did not achieve statistical significance when the cut-off point value of age was set at 50 years. Using this approach to data assessment, there was no difference in one year-survival, but at two years, patients below 50 years of age had a more favorable treatment outcome [15]. In study from the Świętokrzyskie Cancer Center in Kielce, patient age was assessed to be statistically significant for both overall and progression-free survival [16]. Lutterbach et al. have selected an age-range of 60-65 years to define the two different prognostic subgroups for survival, with a significant worsening in the case of older patients [18].

In our material there was no statistically significant difference in survival between patients who underwent total resection as compared to partial resection. 2-year OS for the former group was 16.7%, as compared to 12.8% in the latter group. In a study from the Maria Sklodowska-Curie Memorial Cancer Center in Warsaw, the extent of resection was the best predictor of survival. The MST after total tumor removal was twice a long as that after biopsies and partial or subtotal resections, i.e. 12 vs. 6 months, respectively [15]. The role of surgical resection in the management of patients with malignant gliomas remains controversial, despite the prospective randomized studies of BTSG and other trials, demonstrating a significant impact of the extent of surgery on median survival, even when adjusted for age, histology and performance status [19]. Simpson et al. have shown a positive correlation of survival time and extent of resection, and conclude that a maximal surgical resection consistent with acceptable preservation of neurological function should be an integral part of multimodal management of patients with malignant gliomas [20]. Wood et al. have confirmed a negative correlation between the size of the residual tumor and survival [21]. Some reports did not find any correlation between the extent of surgery and survival [1, 2, 16]. Basing upon our own experience we think that the impact of the extent of surgery is difficult to ascertain due to the inadequate terminology used in surgical reports, which vary from surgeon to surgeon.

Tumor location had no influence on survival time. In patients with frontal, temporal and parietal sites the 2-year OS was 16%, 14.6% and 6.2% respectively. The relevance of tumor location is unclear, some authors have observed better outcomes in patients with frontal lobe tumors, whereas others did not [2, 17, 22]. One could speculate, that complete tumor resection is easier to achieve in case of frontal localisation [20].

Gender did not significantly affect survival, as has been also reported by other authors [1, 2, 17].

We have not proven the prognostic value of KPS on patient outcome, which contradicts the data of Ducci, i.e. that the KPS is one of the most significant prognostic factors [23]. Sachsenheimer et al. evaluated the KPS as regarding survival and found that 75% of patients maintained a KPS of 70 for approximately 1 year; and then presented with a rapid decline in function immediately before death. Consequently, KPS used alone may not adequately reflect the effects of both tumor presence and treatment on OS [24].

The most direct measurement of the effect of the tumor on the brain is neurological impairment. Thus, to evaluate neurological function we applied the EORTC/MRC neurological deficit score and we have observed a significant difference between the prognosis of patients with grade 1, 2, and 3 NPS. The corresponding 2-year OS was 22.7, 10.1, and 0%, respectively. Our findings are consistent with the observations of Florek et al. who noted a 2-year OS of 10% and 21%, respectively, for 1-2 and 3-4 NPS values [16].

While designing this study we believed that a hypofractionated course of irradiation will not confer any true survival advantage for glioblastoma patients; our main aim was to achieve equivalent survival with a shorter radiation scheme (ITW). The efficacy of the two different hypofractionated regimens administered to our patients provided, approximately, the same and, unfortunately, poorly results. We, therefore, conclude that patients with glioblastoma treated with hypofractionated regimens do not have a worse outcome than patients irradiated with a conventional regimen. From the social and financial standpoint, this can be an interesting finding.

Concomitant chemoradiotherapy (the addition of temozolomide to conventional irradiation) is associated with some new successes in the treatment of glioblastoma [25, 26]. Maybe non-conventional fractionated radiotherapy will be considered as a part of forthcoming trials in which temozolomide or other alkylating agents will be used.

## Conclusions

Both our hypofractionated regimens were well tolerated and provided similar results.

Patient age and their neurological performance status were the most important prognostic factors.

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