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Postoperative radiotherapy in 131 patients with glioblastoma multiforme: the single institution experience

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Aim. To evaluate the results and to define the prognostic factors in postoperative radiotherapy of cerebral glioblastomas.
Material and Method. Between 1984 and 1996, 131 patients with glioblastoma multiforme (GBM) were treated in the II Radiation Oncology Department of the M. Curie-Sklodowska Memorial Cancer Centre in Warsaw. Median age of the patients was 57 years, median duration of neurologic symptoms – 5 weeks, 30% of the patients had undergone complete surgical excision of the tumour. Patients received hypofractionated irradiation 20–40 Gy in 3–4 Gy per fraction in 50.5%, 42 Gy in 2.8 Gy per fractions in 14.5%, and conventional irradiation of 56–62 in 2 Gy per fraction in 34%. Actuarial overall survival was calculated using the Kaplan-Meier method and the log-rank test was used for the comparison of variants.
Results. Actuarial overall survival rates at 1 and 2 years were 30- and 7% respectively. Median survival time for all the studied patients was 9 months. Based upon univariate analysis pre-treatment performance status (PPS) and extent of surgery were significant prognostic factors (p=0.02). Actuarial survival rates at 1 and 2 years for patients in WHO PPS 0-1 were 39- and 14%, and for patients in WHO PPS 2–3 they were 16- and 2.5% respectively. Median survival time was 12 months for patients after complete surgical resections and 6 months for patients after biopsies, partial and subtotal excisions. There was a tendency towards a longer survival time of younger patients (60 years and less) (p=0.05). Neurological performance status, the size of the tumour before surgery, and the tumour location were not significantly related to survival.
Conclusions. Survival after postoperative radiotherapy in GBM patients remains poor. The extent of surgery and WHO PPS were prognostic factors for overall survival. Information gained in a retrospective study, such as this, provides a basis for the choice of treatment policy in glioblastomas.

Wyniki pooperacyjnej radioterapii u 131 chorych na gąbczaka wielopostaciowego mózgu

Cel pracy. Podsumowanie wyników radioterapii pooperacyjnej chorych na gąbczaka wielopostaciowego mózgu, leczonych w latach 1984–1996 w naszym ośrodku i określenie czynników rokowniczych związanych z przeżyciem.
Materiał i metoda. Analizie poddano 131 chorych napromienianych w II Zakładzie Teleradioterapii Centrum Onkologii w Warszawie w latach 1984–1996. Mediana wieku analizowanej grupy wynosiła 57 lat, mediana trwania dolegliwości neurologicznych – 5 tygodni, 30% chorych napromieniano po zabiegach radykalnych, a 70% po zabiegach subtotalnych, częściowych i biopsjach. Dawki radioterapii wahały się od 20 Gy w 5 frakcjach przez 30-36 Gy w 10–12 frakcjach do 60 Gy w 30 frakcjach. Prawdopodobieństwo przeżycia oceniono metodą Kaplana-Meiera. Przy zastosowaniu testu logrank oceniono wpływ na przeżycie następujących czynników rokowniczych: wieku, stanu ogólnego, stanu sprawności neurologicznej, lokalizacji nowotworu, rozmiarów guza przed zabiegiem neurochirurgicznym, doszczętności zabiegu neurochirurgicznego.
Wyniki. W badanej grupie oszacowane jednoroczne przeżycie wyniosło 30%, a przeżycie dwuletnie – 7%. Mediana przeżycia wynosiła 9 miesięcy. Statystycznie znamienny wpływ na przeżycie w analizie jednowymiarowej miały: stan ogólny (p=0,02) i doszczętność zabiegu neurochirurgicznego (p=0,02). Przeżycie jedno-, i dwuletnie dla chorych w stanie ogólnym 0–1 według WHO wynosiło odpowiednio 39% i 14%, podczas gdy chorzy w stanie ogólnym 2–3 wg WHO przeżywali 1 i 2 lata odpowiednio w 16% i w 2,5%. Chorzy po zabiegach makroskopowo radykalnych przeżywali 1 i 2 lata w 52% i 10%, podczas gdy jedno- i dwuletnie przeżycie chorych poddanych zabiegom subtotalnym, częściowym i biopsjom wyniosło 16% i 4%. Mediana przeżycia dla chorych po zabiegach radykalnych wynosiła 12 miesięcy, a dla chorych po zabiegach nieradykalnych 6 miesięcy. Zarysowała się tendencja do poprawy przeżycia w grupie chorych poniżej 60 r. ż. (p=0,05). Pozostałe czynniki, jak stan

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sprawności neurologicznej, rozmiary guza przed zabiegiem neurochirurgicznym, lokalizacja nowotworu pozostały bez wpływu na przeżycie.
Wnioski. Wyniki napromieniania pooperacyjnego u chorych na gąbczaka wielopostaciowego są złe. Zakres operacji i stan ogólny chorych okazały się w naszym materiale najsilniejszymi prognostycznymi czynnikami. Obecność określonych czynników rokowniczych winna determinować wybór techniki radioterapii.

Słowa kluczowe: gąbczak wielopostaciowy, radioterapia, czynniki rokownicze
Key words: glioblastoma, radiotherapy, prognostic factors

Introduction

Despite aggressive treatment prognosis in case of glioblastoma (GBM) patients remains poor. Postoperative radiotherapy has been found to be efficient in prolonging the median survival time from 6 months for patients undergoing sole surgery to 8-10 months [1, 2]. Many retrospective studies identified a number of prognostic factors, which included age at the time of diagnosis, overall performance status, neurological deficits, tumour size, tumour location and extent of resection [1, 3, 4, 5]. The partitioning analysis of the outcome of 1578 patients treated according to RTOG randomised trials identified 6 prognostic groups based on tumour histology, age, extent of resection, performance status, neurological deficits and mental status [6, 7]. We review our experience with cerebral glioblastomas treated between 1984 and 1996 at the II Radiation Oncology Department of the M. Sklodowska-Curie Memorial, Cancer Centre of Oncology in Warsaw. This analysis focuses on the overall survival time and on the prognostic factors.

Material and method

Between 1984 and 1996, 161 patients with histologically confirmed diagnosis of GBM were referred to our Department. Thirty patients were excluded from analysis, because 14 had diagnosis of a distinct variant of GBM – gliosarcoma, 7 were younger than 16 years, 7 had prior radiotherapy to the brain because of lower-grade gliomas, 2 discontinued treatment and were lost from follow-up. Eventually 131 patients were included in the analysis. Pre-radiotherapy patient characteristics are presented in Table I. Neurological deficit status was assessed from each patient's medical record according to the EORTC/MRC score (appendix 1) [8]. The extent of tumour resection was defined by the surgeon. Only 57 (44%) patients underwent CT examination after resection in order to assess the extent of surgery.

Radiotherapy was started 3–6 weeks after surgical treatment (median time: 33 days). Different doses, fractionation schedules, treatment volumes and possible chemotherapy associations were employed. The distribution of patients into the various treatment groups is summarised in Table II. Schedules of 5 x 4 Gy and 10 x 4 Gy were designed for the patients with the poorest prognosis (advanced age and low WHO performance status). Schedules of 10-12 x 3 Gy was designed for younger patients (usually 50 years and less) with a low WHO

Tab. I. Patient characteristics

Variable	Category	No of patients (percentage) or * Value for continuous parameters
Sex	Male: Female	90 (69%): 41(31.0%)
Age	Median (range)	* 57 years (19–76)
WHO performance status before the onset of radiotherapy	0–1	73 (56.0%)
	2	38 (29.0%)
	3	20 (15.0%)
Neurological deficit status according to EORTC/MRC score before start of radiotherapy	1	36 (27.5%)
	2	34 (26.0%)
	3	35 (26.5%)
	4	26 (20.0%)
Duration of symptoms before diagnosis	Median (range)	* 5 weeks (1–50)
Size of tumour on the greatest dimension before surgery	≤5 cm	68 (52.0%)
	>5 cm	53 (41.0%)
	unknown	9 (7.0%)
Tumour location	– frontal	24 (18.3%)
	– temporal	26 (20.0%)
	– parietal	14 (11.0%)
	– occipital	4 (3.0%)
	– more than one lobe	62 (47.0%)
	– cerebellum	1 (0.7%)
Extent of resection	total	35 (26.7%)
	partial and subtotal	90 (68.7%)
	biopsy	6 (4.6%)

Tab. II. Radiotherapy techniques, doses and associations with chemotherapy in the analysed group of 131 GBM patients irradiated after surgery

Total dose and fractionation schedule	20 Gy in 5 fractions and 5 days of treatment	7 (5.5%) patients
	40 Gy in 10 fractions with a gap of 1 month after 5 fractions	12 (9.0%)
	30–39 Gy in 10–13 fractions and 12–16 days	48 (36.5%)
	42 Gy in 15 fractions and 19 days	19 (14.5%)
	56–62 Gy in 28 –31 fractions and 6 weeks	45 (34.5%)
Treated volume	whole brain	55 (42.0%) patients
	whole brain to 40–50 Gy with a boost to tumour	43 (33.0%)
	limited to tumour volume with 2–3 cm margins	33 (25.0%)
Energy of radiation	photons X of 200 keV	12 (9.0%) patients
	photons of Co60	85 (65.0%)
	photons X of 4 MV, 9MV or 15 MV	20 (15.0%)
	Co60 and photons X or electrons	14 (11.0%)
Chemotherapy (CCNU)	without chemotherapy	53 (40.5%) patients
	before and after radiotherapy	13 (10.0%)
	immediately after end of radiotherapy	36 (27.5%)
	at relapse	29 (22,0%)

pre-treatment performance status (PPS). Conventional fractionation up to 56–60 Gy was a treatment policy for patients with a 0–1 WHO PPS. Hypofractionated schedule of 15 x 2.8 Gy was applied during the last 3 years of the analysed period in a majority of patients with malignant gliomas and corresponded to changes in treatment policies related to poorly prognosing cancer in our institution. Changes in treatment volume from encompassing the entire brain to the tumour only (with a 2–3 cm margin all around) had also corresponded to the evolution of treatment policy according to publications which report data supporting the use of partial brain irradiation in this issue [9]. We have also recommended the use of Lomustine (CCNU) at the relapse of treatment after radiotherapy. Many patients with a poor performance status were not fit for this approach. Some irradiated patients received chemotherapy in other centres before and/or after radiotherapy. Follow-up information was available from charts, all patients had visits scheduled at 4–6 weeks after treatment completion and subsequently every 3 months.

Survival characteristics were calculated according to the Kaplan-Meier method. The prognostic significance of patient's age (≤50 years vs. >50 years and in 3 groups: ≤35 y., 36–60 y., and >60 y.), WHO PPS (pre-treatment performance status) (0–1 vs. 2–3), status of neurological deficits (EORTC/MRC 1–2 vs. EORTC/MRC 3-4), tumour size before surgery (≤5 cm vs. >5 cm), tumour location (frontal, temporal, parietal and/or occipital), extent of tumour resection (total resections vs. subtotal, partial resections or biopsies) were assessed using the log-rank test [10]. Survival was measured from the date of the onset of radiotherapy.

Results

There were 128 deaths among analysed patients, 1 patient is alive (163 months from date of radiotherapy onset), 2 were lost from follow-up.

Sixty-six patients (50%) underwent computerrised tomography examination (CT) of the brain after radiotherapy, but the assessment of the radiotherapy effect was possible only in 53 (40%) patients of this group with post-surgical, pre-irradiation CT scan. In the group of 53 patients, 22% had complete radiological response, 28% partial response, 28% no change, and 22% progressive disease. The neurological status improved in 34%, in 44% it was stable and 34% patients deteriorated.

The 1- and 2-year survivals were 30% and 7%, respectively (Fig. 1), with a median survival of 9 months. Table III shows the association of all 6 examined possible prognostic variables with survival. Of these 6 variables only the extent of resection (p=0.02) (Fig.2) and WHO

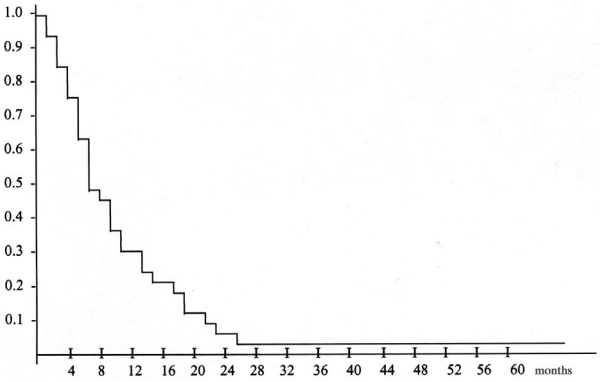


Fig.1. Survival of 131 GBM patients irradiated after surgery in The II Radation Oncology Department the Maria Sklodowska-Curie Memorial Cancer Centre-Institute of Oncology in Warsaw between 1984 and 1996

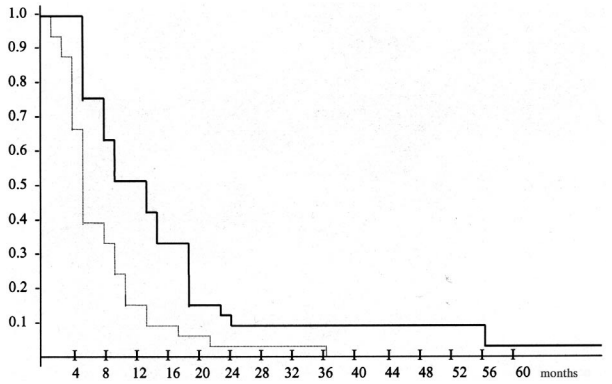


Fig. 2. Survival in the group of 131 GBM patients irradiated after surgery according to the extent of tumour resection: —— total resections, ------- less than total resections

PPS (p=0.02) (Fig.3) were significantly associated with survival in the univariate analysis. Age (≤50 y. vs. >50 y.), neurological deficit status, tumour size before surgery and tumour location did not influence survival. However, there was a tendency towards longer survival times in younger patients. When three subgroups differing as to age were identified – (1) to 35 years, (2) 36–60 years, (3) >60 years, the one-year survival time was 46-, 39-, and 17% respectively. These differences did not reach statistical significance (p=0.054), mainly because of the small size of subgroups. Nevertheless, the trend is apparent.

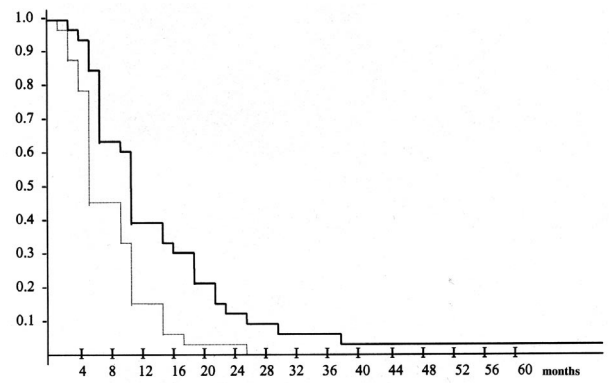


Fig. 3. Survival in 131 GBM patients irradiated after surgery according to the WHO performance status: —— WHO 0–1, ------- WHO 2–3

A separate analysis revealed a dose-effect relationship in survival of GBM patients. Median survivals for patients with fractionation schedules 5 x 4 Gy, 10–12 x 3 Gy, 2 series of 5 x 4 Gy, 15 x 2.8 Gy, 28–31 x 2 Gy were respectively – 3, 7, 9, 9 and 11,5 months. As could be anticipated, the groups of patients receiving lower doses had a lower performance status. The group of patients receiving 5 x 4 Gy frequently succumbed to their disease prior to achieving all planned course of radiotherapy (2 series of 5 x 4 Gy). There was an increase in median survival time in the group of patients receiving chemotherapy (11 months) in comparison to the one without chemotherapy (6 months). There were 68% patients with WHO PPS 0--1 in the chemotherapy group, whilst only 37% in the group without chemotherapy. The poorer initial performance status of patients who received lower doses of radiotherapy and who had never received chemotherapy did alter the conclusion concerning the possible relationship between the increase of survival and the dose of radiotherapy or addition of chemotherapy to the treatment. For this reason radiotherapy dose and use of chemotherapy are not shown in Table III.

We did not observe any significant acute toxicity of radiotherapy, however 90% of patients received steroids during treatment. It is difficult to gather from a retrospective study such as this, how often was the increase in steroid use required, and to distinguish treatment related oedema symptoms from treatment failures. Late radiological effects of radiotherapy such as cortical atrophy, ventricular dilatation and calcifications were discernible in 12 patients (24% of these who had a CT scan after 6 months and more counting from the onset of radiotherapy). One patient not only presented radiological changes but also experienced memory and attention problems leading to considerable social handicap.

Discussion

Patient characteristics in the presented study did not differ from that published by other authors. In our experience, as is the case in literature, GBM occurred more frequently in men than in women and median age of patients was 57 years [1, 4, 11]. The median time from symptom onset to diagnosis, known to be one of the shortest among brain tumours, was 5 weeks [11]. Beyond the short natural history of the tumour, a large mass with extensive oedema at presentation is proof of the particular aggressiveness of this disease. Only 35% of the tumours are, at the moment of diagnosis, limited to one lobe [12]. In our study nearly half of the tumours were multilobed. On diagnosis the size of the tumour exceeded 5 cm in more than 50% of the cases and less than 30% of all patients underwent total resection, which remains in unison with data reported by other authors [1, 4].

The survival figures for the entire group are similar to other reports: one-year survivals range from 20 to 40%, and from 4 to 20% of patients are still alive after 2 years. Five-year survivals are extremely rare [1, 4, 13]. Despite intense investigations aiming at the improvement of the therapeutic ratio of radiotherapy by adding chemotherapy, radiosensitizers and/or alternating fractionation schedules, the prognosis for GBM patients remains poor [1, 2, 4, 15]. Radioresistance of GBM and the proven relationship between radiation dose in the range of 40–60 Gy and survival lead to many trials of dose escalations using different methods [16]. Results of dose escalation studies using brachytherapy or stereotactic techniques are not sufficiently convincing [17, 18]. In our study, the observed improved survival time of patients receiving higher radiation doses was brought on by pre-treatment patient selection. As was already mentioned, larger dose per fraction and lower total doses were prescribed to patients with discernible poor prognostic factors. Improved survival of patients treated with chemotherapy in our stu-

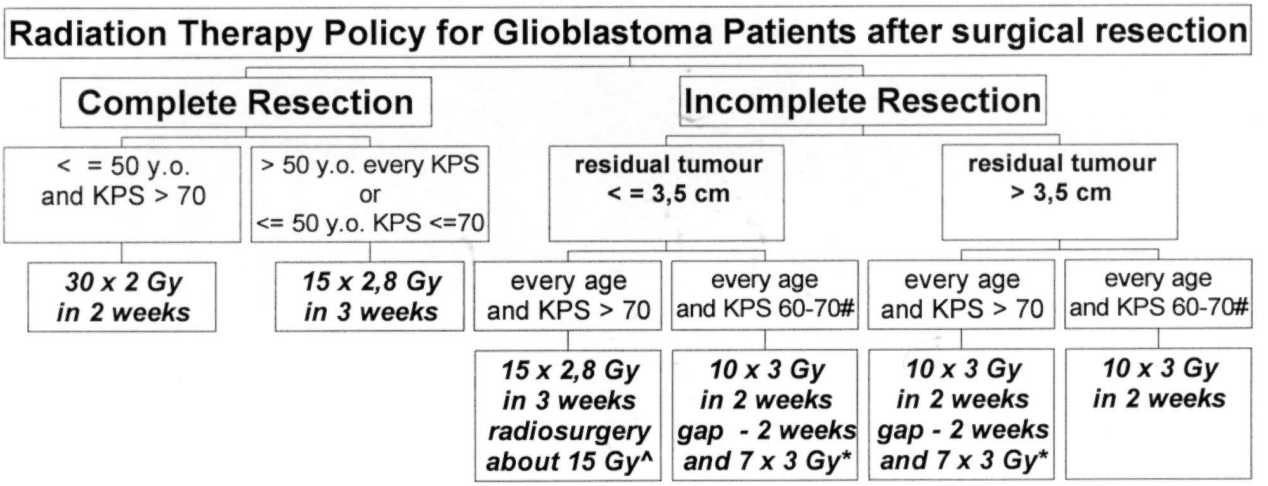
Tab. III. Influence of selected factors on the survival of 131 GBM patients irradiated after surgery

Variable	No of patients	One-years survival	Two-years survival	P value	Median survival
EXTENT OF RESECTION					
– total	35	52.0%,	10.0%	0.02	12.0 months
– biopsies, partial, subtotal	96	16.0%,	4.0%		6.0 months
WHO PERFORMANCE STATUS					
0–1	73	39.0%,	14.0%	0.02	10.5 months
2–3	58	16.0%,	2.5%		7.0 months
AGE					
≤50 years	43	30.0%,	16.0%	NS	9.0 months
>50 years	88	28.0%,	3.0%		8.5 months
≤35 years	13	46.0%,	15.0%	0.054	9.5 months
36–60 years	76	39.0%,	12.0%		9.0 months
>60 years	42	17.0%,	0.0%		7.0 months
NEUROLOGIC DEFICIT STATUS – EORTC/MRC					
1–2 Grade	70	33.0%,	10.0%	NS	10.0 months
– EORTC/MRC					
3–4 Grade	61	25.0%,	3.0%		7.0 months
SIZE OF TUMOUR BEFORE SURGERY					
≤5 cm	68	24.0%,	7.5%	NS	8.5 months
>5 cm	53	28.0%,	10.0%		7.0 months
TUMOUR LOCATION					
Frontal	24	23.0%,	11.0%	NS	8.0 months
Temporal	26	22.0%,	11.0%		6.0 months
Parietal and/or Occipital	25	35.0%,	4.0%		10.5 months

dy is probably also related to unbalanced performance status distribution, as explained above. Chemotherapy did not follow strict treatment protocols. In our institution chemotherapy was offered at relapse to patients with a better performance status, while the remaining patients, with a poor performance status were only offered supportive treatment. About 30% of the patients referred to our Department for radiotherapy received chemotherapy outside the Institute according to unknown prescription criteria. Nevertheless the final analysis has shown that patients receiving chemotherapy had a slightly superior performance status than those treated with postoperative radiotherapy only.

Age, performance status and neurological deficits are widely recognised as patient related prognostic factors in the case of brain tumours [3]. Depending on the size of the presented groups and the manner of data collection these variables reach different value of statistical significance in retrospective series [1, 3, 4]. In our study age did not reach a statistical significance, while basing upon RTOG partitioning analysis of randomised trials on malignant gliomas, a cutpoint value for age was chosen at 50 years [6]. Using this approach to data assessment there was no difference in one-year survivals, but at two years patients younger than 50 years had a more favourable treatment outcome (Table III). It proves that long survivals occur mainly among younger patients. The choice of the optimal cutpoint value for age in the statistical analysis of brain tumours remains an unsolved problem. Gliński, following numerous reports, suggests 40 years of age as the cutpoint used to define the low-risk and high-risk groups for the prediction of treatment outcome in cerebral gliomas [1]. Some authors have selected a range of age from 60 to 65 years to define the two different prognostic subgroups for survival, with significant worsening in case of older patients [15, 4]. Our data is similar, because patients more than 60 years of age revealed a 2--year survival time less by twofold as compared to the two other younger analysed subgroups. We attribute the lack of statistical significance to the low number of all three *a priori* distinguished subgroups. Our study, like other reports, has shown that the performance status is a powerful predictor of overall survival. As reported by Bauman *et al.* the performance status may be applied to select a subset of elderly patients who may benefit from a more intense course of radiation, because in their study pre-treatment KPS (Karnofsky Performance Status) was a more valuable predictor of survival than patients' age [19]. Neurological deficit status did not appear to compromise survival in our study. However, we do agree that retrospective evaluation of the neurological status using the medical record of each patient may be too subjective and deficient, which could be brought on by the lack of information.

Simpson *et al.* in an analysis of 645 patients identified a frontal location of GBM as a positive survival predictor [4]. Others did not report this feature to be an important prognostic factor [1]. We did not detect the benefits of



KPS: Karnofsky Performance Status (appendix 2) [20], y.o.: years old,
for patients with KPS ≤50 if fit for radiotherapy schedule 5 x 4 Gy is proposed, with eventual second course of 5 x 4 Gy, if improvement of KPS,
* total dose 51Gy in 17 fractions and 5.5 weeks, ^ minimum dose, depending of tumour location

Fig. 4. Treatment policy concerning GBM patients referred to postoperative radiotherapy in the II Radiation Oncology of the Maria Sklodowska-Curie Memorial Cancer Centre-Institute of Oncology in Warsaw since April 2000

any tumour location for survival. Additionally, large volume of tumours associated with frequent involvement of 2--3 lobes compromises the use of tumour location for predictive purposes in GBM. In unison with other reports a preoperative tumour size was unrelated to survival [4, 5].

In our study the extent of resection was the best predictor of survival. For irradiated patients the median survival time after a total resection was twice as long to that after biopsies and partial and subtotal resections (12 vs. 6 months). Other authors report similar results. Simpson *et al.*, mentioned already above, basing upon a large experience of RTOG trials had shown a positive correlation of the survival time with the extent of resection. Survival improved from 6.6 to 10.5 months with increased extent of resection [4]. An analysis of 510 GBM patients irradiated after surgery by J.R.Wood *et al.* revealed a negative correlation of the size of residual tumour with survival ($p<0.0001$) [5]. These data support the surgical removal of the greatest possible volume of tumour as safety allows. Some reports did not find any correlation of extent of surgery with survival. Gliński, basing upon own experience and a review of published data, explains this controversy by the inadequate surgical reports of the extent of resection [1].

It may be concluded that in view of the poor results with radical radiotherapy in GBM patients with unfavourable prognostic features an abbreviated, palliative treatment may be more appropriate. Patients with favourable prognostic factors may benefit from carefully designed clinical trials in view of dose escalation using modern methods which allow for maximum sparing of healthy tissues. Since April 2000, basing on our-own experience and published data, mainly the outcome of 1578 malignant glioma patients treated on consecutive RTOG protocols and encouraging results of short-course radiotherapy for poor prognosis GBM patients [6, 7] we have altered our treatment protocols. Our new treatment policy in cases of GBM is schematically summarised in Fig.4. The shortened regimen seems an appropriate treatment option for GBM patients with the poorest prognosis. New technologies, such as stereotactic irradiation devices, have brought on the construction of protocols of dose escalation for selected GBM patients in view of the improvement of the irradiation therapeutic ratio.

Conclusions

- The results of postoperative radiotherapy for GBM patients remain poor.
- The extent of resection, and the WHO performance status were associated significantly with the survival of GBM patients irradiated after surgery.

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Appendix No 1.
EORTC/MRC Neurological Deficits Score [8].
1. absence of any neurological deficit detectable
2. minor neurological deficits; without any impairment of normal activity
3. neurological deficits leading to some impairment of normal activity (paresis, minor mental changes)
4. serious neurological deficits leading to disability to care for the self: paralysis, aphasia, serious mental (emotional and/or cognitive) changes.
5. any communication with patient impossible

Appendix 2. Karnofsky performance status: 100 point scale [20]
100. Normal, no complaints, no evidence of disease
90. Able to carry on normal activity, minor signs or symptoms of disease
80. Normal activity with effort, some signs or symptoms of disease
70. Cares for self, unable to carry on normal activity, or do active work
60. Requires occasional assistance, but is able to care for most needs
50. Requires considerable assistance and frequent medical care
40. Disabled, requires special care and assistance
30. Severely disabled, hospitalisation necessary, although death is not imminent
20. Very sick, hospitalisation necessary, active supportive treatment necessary
10. Moribund, fatal processes progressing rapidly

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