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Clinical Article

Debulking or biopsy of malignant glioma in elderly people – a randomised study

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Summary

Background. Patients with radiologically (MRI and/or CT images) suspected malignant glioma is referred to radiotherapy after craniotomy and resection of the tumour or after diagnostic biopsy. Patients with poor preoperative status and elderly patients are diagnosed more often by biopsy and treated by radiotherapy rather than by craniotomy and tumour resection. However, based on previous retrospective studies it is not possible to conclude which procedure is better for elderly patients. Thus a prospective study comparing these two procedures with elderly patients was planned.

Methods. 30 patients older than 65 years with radiologically (CT and/or MRI) obvious malignant glioma were randomised into two groups: I) stereotactic biopsy and II) open craniotomy and resection of the tumour. Nineteen patients were diagnosed to have grade IV glioma and four patients grade III glioma. Seven out of 30 (23%) were followed in the ''intention-to-treat'' group with diagnosis of stroke (n = 3), metastasis (n = 2), malignant lymphoma (n = 1) and one with out histological diagnosis. Patients with histologically verified malignant glioma (grade III–IV) were diagnosed by stereotactic biopsy (n = 13) or by open craniotomy and resection (n = 10) and all the patients were referred to radiotherapy. Survival and time of deterioration were followed.

Findings. The overall median survival time was 146 (95% CI 89–175) days after the procedure. The estimated median survival time was 171 (95% CI 146–278) days after the craniotomy versus 85 (95% CI 55–157) days after the biopsy ($p = 0.035$). The estimated survival time was 2.757 times longer (95% CI 1.004–7.568, $p = 0.049$) after craniotomy. However, there was no significant difference in the time of deterioration between these two treatments ($p = 0.057$). Amount of radiotherapy given had a significant effect on survival ($p = 0.001$).

Interpretation. Longer survival time is achieved after open craniotomy and resection of tumour. However, overall benefit of open surgery to patient seems to be modest, while time of deterioration did not differ between two treatment groups. Our results support previous studies on the benefit of radiotherapy in the treatment of malignant glioma.

Keywords: Malignant glioma; resection; biopsy; radiotherapy.

Introduction

So far there is no curative treatment for patients with malignant glioma and the expected survival after diagnosis is less than one year [10, 16]. Patients over 65 have an even shorter survival, from 4 months to 9 months [2, 11, 17]. Diagnosis is verified by biopsy taken during surgery (craniotomy and resection of tumour or biopsy only) and patients are referred to postoperative radiotherapy. In addition to conventional radiotherapy some patients may get interstitial chemotherapy [7, 23], gene-therapy [20], postoperative radiosurgery [13], targeted toxin therapy [9] or neutron capture therapy [3, 14] to improve outcome. However, new treatment methods are not curative treatment.

There is no previous prospective study comparing craniotomy (i.e. resection of tumour) and diagnostic biopsy before radiotherapy. Neither does there exist a general consensus concerning the effect of cytoreductive surgery on survival [6, 15]. Based on some retrospective studies [1, 5, 12, 18] open surgery does not increase survival or the time of independence significantly. However, based on retrospective studies conclusions cannot be drawn about the benefit of cyto-

reductive surgery for malignant gliomas because of "selection bias"; patients in the two treatment groups are not randomised. The most important predictive factors for longer survival of patients with malignant glioma are age [12, 15, 19] and preoperative status [12, 19].

We found it important to compare craniotomy and resection of tumour versus diagnostic biopsy for elderly patients. Elderly patients have often associated diseases and retrospective studies suggest short survival time with malignant glioma.

Materials and methods

Study protocol

This study was carried out at the department of neurosurgery, at Helsinki University Hospital in Finland during 1993–1996. It was accepted by the ethics committee of Helsinki University Central Hospital (21.10.1992). Inclusion criteria were as follows; 1) radiologically malignant supratentorial glioma, 2) Karnofsky performance status more than 60 at the time of randomisation, 3) patient older than 65 years at the time of radiological diagnosis, and 4) informed consent to participate in the study.

Patients who did not fullfill the inclusion criteria or were unwilling to participate, were excluded.

An up-date preoperative scan (CT and/or MRI) was performed prior to randomisation. The preoperative status was evaluated, and if needed a preoperative NYHA was evaluated by an internist or by anaesthesiologist. Patients were randomised to stereotactic biopsy- or open craniotomy-group. Procedures were performed by an experienced neurosurgeon. A histological specimen from the tumour was analysed by the neuropathologist. In order to evaluate the extent of tumour resection a postoperative CT or MRI with contrast enhancement was performed for all patients in the craniotomy group within 1–3 days after the procedure. The patients in the biopsy group were controlled by CT or by MRI only in the case of neurological deterioration. Clinical evaluation of postoperative status was done one, and in most cases two weeks after the procedure and Karnofsky performance status was evaluated. All patients were referred to radiotherapy, which was started as soon as it was technically possible.

Patients included in the study were followed-up by regular contacts (out patient clinic or telephone) until deterioration (not able to live at home; time after which patient stayed permanently in hospital or in a nursing home, i.e. Glasgow outcome scale {GOS} over 3) and/or until death.

Patient profile

Altogether 30 patients were included in the study. Sixteen of them were randomised into diagnostic stereotactic biopsy and 14 of them were randomised into open surgery and resection of tumour (craniotomy). Three patients randomised into biopsy group had other diagnoses than malignant glioma (2 metastasis of adenocarcinoma and 1 haematoma) and they were followed as 'intention-to-treat' patients. Four patients were randomised into craniotomy group but followed as 'intention-to-treat' patients; one patient refused operation after being randomised into open surgery and three patients had additional diagnosis other than malignant glioma (malignant lymphoma, haematoma, and one infarct).

The age and karnofsky performance status (KPS) of the patients did not differ statistically between the craniotomy and biopsy group (see Table 1).

Overall median age of the patients was 70 years (range 66–80 years). In the craniotomy group the median age was 70 years with a range of 66–80 years. Patients treated by biopsy had median age of 72 years rangeing from 67 years to 79 years. The mean preoperative Karnofsky performance status (KPS) was 73. The median preoperative KPS was 80 (range 60–90) in the craniotomy group and 70 (range 60–90) in the biopsy treated group. The mean preoperative KPS was 78 with craniotomy treated patients and 70 with the patients treated by biopsy.

Preoperative NYHA was evaluated in the case of associated disease, which might have had effect on the postoperative course. There was no difference between the craniotomy and the biopsy groups.

Statistical methods

Survival time and time of deterioration (not able to live at home; time after which patient stayed permanently in hospital or in nursing home) was collected from 23 patients. The follow-up times were calculated from the date of randomisation to the date of death or hospitalisation, correspondingly. Survival curves for both therapies, biopsy and craniotomy, for both outcome variables were estimated as functions of time with the non-parametric Kaplan-Meier method and compared with the non-parametric log-rank chi-square test. Grade (tumour grade III or IV) adjusted hazard ratios with 95% confidence intervals were also estimated with Cox proportional hazards regression. To test for the comparability of the two therapy groups, the amount of given radiotherapy (Gy) was tested with the two-sample t-test assuming equal variances, and the time in days elapsed to start of the radiotherapy with the non-parametric exact Wilcoxon's test. In analyses, a two-sided p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted with SAS statistical software (Version 8.01, SAS Institute Inc., Cary, NC).

Results

The procedure-related complication rate was 10% in the craniotomy group and 0% in the biopsy group. There was one postoperative haematoma in the craniotomy group (1/10), which needed a re-operation.

Survival

Overall median survival time for the elderly patients with malignant glioma was 146 days (95% CI 89–175) days. The median survival time after craniotomy and resection of tumour was 171 days (95% CI 146–278) days and 85 (95% CI 55–157) days after the biopsy. The difference in the survival time between craniotomy and biopsy groups was statistically significant ($p = 0.0346$). The grade adjusted hazard ratio (HR) was 2.621 (95% CI 1.035–6.641) with $p = 0.0422$. Controlling for the amount of given radiotherapy (Gy) the Gy adjusted HR was estimated as 2.729 (95% CI 1.035–7.195) with $p = 0.0423$.

Table 1. *Patient profile. Patients treated by craniotomy and resection of malignant glioma or by diagnostic stereotactic biopsy prior to radiotherapy are presented in table 1*

No	Tumour (Gr)	Symptom	Karnofsky	Radiotherapy	Det. time	Exitus
Craniotomy and resection						
1. 80 yrs M	IV	deficit	90/90	–	67	89
2. 70 yrs*) F	IV	deficit	80/50	28 Gy	1	106
3. 66 yrs F	IV	deficit	60/60	56 Gy	86	146
4. 66 yrs M	IV	deficit	60/70	60 Gy	125	153
5. 73 yrs M	IV	deficit	90/90	45 Gy	145	167
6. 66 yrs M	IV	epilepsy	90/90	53 Gy	71	175
7. 74 yrs F	IV	ICP ⇑	70/70	54 Gy	70	198
8. 67 yrs M	IV	ICP ⇑	90/90	60 Gy	135	278
9. 69 yrs M	IV	deficit	80/90	60 Gy	289	433
10. 70 yrs M	IV	deficit	70/70	60 Gy	251	590
Diagnostic stereotactic biopsy						
1. 79 yrs F	III	ICP ⇑	70/70	–	18	32
2. 67 yrs F	IV	deficit	60/60	–	12	46
3. 76 yrs M	IV	deficit	60/60	36 Gy	52	52
4. 72 yrs M	IV	deficit	70/70	–	13	55
5. 74 yrs F	III	deficit	70/70	16 Gy	33	77
6. 71 yrs M	IV	deficit	60/60	54 Gy	60	79
7. 69 yrs F	IV	deficit	70/60	60 Gy	78	85
8. 70 yrs F	IV	deficit/ICP ⇑	60/70	51 Gy	88	106
9. 74 yrs F	III	deficit	70/60	50 Gy	92	113
10. 70 yrs F	IV	deficit	80/80	60 Gy	72	157
11. 73 yrs F	III–IV	deficit	80/80	60 Gy 20	140	239
12. 78 yrs F	IV	ICP ⇑	90/90	40 Gy 41	93	253
13. 70 yrs M	III	deficit	70/70	60 Gy 5	123	254

No Represent patients in chronological series (based on survival time), age at the time of procedure (years) and gender (*F* female, *M* male); *tumour* Grade (Gr) of the tumour based on WHO grading of gliomas; *symptom* presenting symptom, local neurological deficit (deficit), epilepsy (epilepsy) or symptoms related to increased intracranial pressure (ICP ⇑); *karnofsky* preoperative/postoperative karnofsky index, evaluated one day before and seven days after the procedure; *radiotherapy* amount of postoperative radiotherapy in (Gy). – indicates that patient failed to get radiotherapy; *det. time* time (days) elapsed to be dependent of others after the treatment (GOS $\leq$ 3); *exitus* time (days) elapsed to death after the treatment; *) patient No 2. A patient who got a postoperative haematoma (procedure-related complication).

Table 2. *Location and size of the tumour is presented. In the craniotomy group the resection volume as evaluated in the postoperative scan is presented*

No	Site of tumour	Pre-op. size	Resection volume
Craniotomy and resection of malignant glioma			
1	parieto-occipital	++	subtotal
2	frontal	++	subtotal
3	temporal	++	subtotal
4	parieto-occipital	++	resection
5	temporal	++	subtotal
6	frontal	++	subtotal
7	temporal	++	total
8	temporo-occipital	+++	subtotal
9	frontal	+++	subtotal
10	temporal	++	total
Diagnostic stereotactic biopsy			
1	frontal	+++	
2	temporal	+++	
3	parietal	++	
4	frontal	++	
5	temporal	++	
6	fronto-temporal	++	
7	temporo-parietal	++	
8	frontal	+++	
9	occipital	++	
10	temporal	++	
11	occipital	+++	
12	frontal	++	
13	fronto-parietal	++	

No Patient number, which corresponds to the numbers on Table 1; Site of tumour in the frontal, temporal, parietal, occipital or in several adjacent brain lobes is presented; *Pre-op size* the size of the tumour as a largest diameter before resection or biopsy; + (0–3 cm), ++ (3–5 cm), +++ (>5 cm); *Resection volume* total (no enchancemet of tumour in post operative scan), subtotal (some, residual enchacemet, less than 30% from the size of primary tumour), resection (residual enchacing tumour, with size more than 30% from the primary tumour in postoperative scan). Postoperative scan done on 1–3 postoperative day.

Table 3. *Comparison of patient's age and postoperative course between the two different treatment groups*

Treatment and outcome	CRT (10 patients)	Biopsy (13 patients)
Median age (yr) and range	70 (66–80)	72 (67–79)
Procedure-related complication rate	1/10	0/13
Radiotherapy (Gy) median and range	55 (0–60)	50 (0–60)
Median time (days) elapsed to the start of radiotherapy and range	38 (14–92)	22 (5–53)
Independent (GOS > II), more than 2 mos	9/10	8/13
Median survival time (days) and range	171 (89–590)	85 (32–254)
Median deterioration time (days) and range	105 (1–289)	72 (12–140)

Deterioration

The median time of deterioration of all the patients with malignant glioma was 78 days with 95% CI from 67 to 93. After the craniotomy the median time of deterioration was 105 days and after the biopsy 72 days. The time of deterioration did not differ significantly ($p = 0.0566$) between craniotomy and biopsy groups. Grade adjusted hazard ratio for the time being independent was 2.757 (95% CI 1.004–7.568) and it was significant ($p = 0.0491$) in favour of craniotomy.

Radiotherapy

All the operated patients (craniotomy and resection of tumour) except one were referred to radiother-

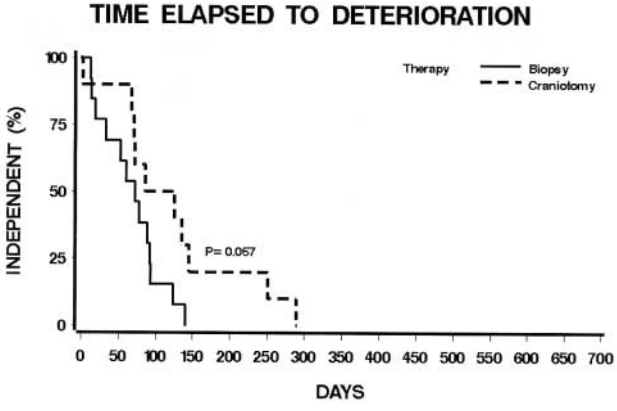

Fig. 1. Survival analysis (Kaplan-Mayer) of elderly patients with a malginant supratentorial glioma. Patients were randomised to craniotomy and debulking or to biopsy. Curves present time elapsed to deterioration. $p = 0.057$ and thus there is not statistically significant difference between two treatment groups

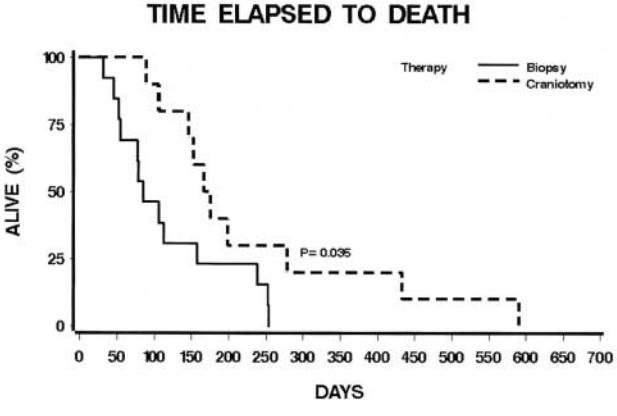

Fig. 2. Survival analysis (Kaplan-Mayer) of elderly patients with a malginant supratentorial glioma. Patients were randomised to craniotomy and debulking or to biopsy. Curves present time elapsed to death. The difference between two curves is statistically significant, $p = 0.035$

apy and were given the median amount of 55 Gy (0–60 Gy). Ten out of 13 biopsy patients were referred to radiotherapy and were given median radiotherapy of 50 Gy (0–60 Gy). The difference with the amount of radiotherapy was not significant ($p = 0.323$). The difference with the time elapsed to start of radiotherapy was not significant (42 ± 24 days after craniotomy and 25 ± 13 days after biopsy). The amount of radiotherapy given (Gy) had significant effect on survival ($p = 0.001$). Reason for no radiotherapy in four patients was that their clinical condition was too bad.

Discussion

Overall median survival time of patients with malignant glioma in this study was 146 days after the diagnostic operation. Median age of the patients was 70 and preoperative median KPS was 70. Survival time was about the same as in the retrospective studies of Kelly and Hunt [11] overall mean survival time of 126 days for 128 elderly patients with average age over 70 years and [2] median survival time 120 days for 23 patients with mean age of 69 years with malignant or anaplastic glioma. However, Piegra *et al.* [17] reported median survival time of 252 days (36 weeks after diagnosis), in 30 consecutive elderly patients with malignant glioma (median age 73 years and mean KPS 66, range 30–100). Our results are in accord with previous studies; malignant glioma is a disease with poor overall outcome and elderly patients have even shorter survival time than on average [10, 16]. Only 2–5% patients with glioblastoma are reported to be long-term survivors i.e. survival more than 5 years after surgical diagnosis [4].

In our study craniotomy and debulking of tumour resulted in longer survival time, with a significantly reduced risk for mortality (HR 0.382; 95% CI 0.0151–0.966; $p = 0.042$). Patients estimated median survival time was 171 days after craniotomy and 85 days after biopsy. The difference between the two treatment groups was statistically significant, despite the small number of patients. The difference in the survival time was significant also if radiotherapy given was taken into account (Gy adjusted HR was significant). For us the result clearly indicates the debulking of malignant glioma with the elderly should be considered as a treatment of choice if longer survival time is the aim. Kelly and Hunt [1] noted some prolongation of survival after resection compared to biopsy in selected over 65 year old patients with malignant gliomas. However, they concluded that the benefit from surgery was modest.

Not only survival but also time of deterioration is an important outcome measure if we discuss fatal disease. Overall median time of deterioration was 78 days. The median time of deterioration after the craniotomy and debulking of tumour was 105 days and 72 days after the biopsy, respectively. The results did not show a statistical difference in the time to hospitalisation ($p = 0.057$). Grade adjusted hazard-ratio (HR) suggested that there was 2.8 times higher risk to deteriorate ($p = 0.049$) after biopsy than after craniotomy. The results suggest that patients may manage at home a little longer if tumour was debulked and thus quality of life may be better after craniotomy. However, the benefit of open surgery is modest if time of independence is taken into account.

Radiological diagnosis of malignant glioma was wrong in 23%. In the case of a single tumour it is not always possible to differentiate glioma from metastasis [21]. Even haematoma or brain abscess can go through radiological changes, which can mimic tumour at some phase [22]. Stroke can be verified by radiological follow up, but in that case you have delay with treatment of some gliomas. In the case of uncertain of radiological diagnosis, modern methods of MRI; i.e. choline magnetic spectroscopy and apparent diffusion coefficient [8] should be used if possible to get a right diagnosis preoperatively.

The results suggest that the amount of radiotherapy given increases the survival time of patients with a malignant glioma. Our result is in accordance with previous studies, which show clearly the benefit of radiotherapy [19, 24]. Radiotherapy failed more often in the biopsy group than in the craniotomy group and median dose of irradiation was 55 Gy in the resection group and 50 Gy in the biopsy group. The difference with the median dose was not significant. The larger amount of radiotherapy given in the craniotomy group was not the only reason for longer survival time in the craniotomy group; Gy adjusted HR showed that the difference in survival time remained significant. Time elapsed to the beginning of the radiotherapy was shorter after biopsy than after resection of the tumour, with mean time to start of radiotherapy 25 days after biopsy and 42 days after craniotomy.

WHO grading scale of gliomas from Gr I–IV is clinically useful and generally accepted. We included Gr III and Gr IV gliomas in this study because both the Gr III and Gr IV gliomas have a poor prognosis

and both the gliomas are usually treated by postoperative radiotherapy [1, 6, 13, 17, 19]. In the present study, the number of patients was too low in order to analyse the impact of grade on operative procedure among these elderly patients with a malignant supratentorial glioma.

Biopsy of intracerebral tumour is a safe procedure and in our study, with a low number of cases no complications were noted. Debulking of tumour resulted in more than 2 months longer survival time if compared with that after biopsy. However, the time of independence in this study, with such a small number of patients, did not show statistical difference. Thus, overall benefit of open surgery is modest in the case of an elderly patient with malignant glioma. During decision making not only chronological but also physiological age should be considered if an operative procedure is planed in an elderly patient with malignant glioma.

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