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Supratentorial Recurrences of Gliomas. Morphological Studies in Relation to Time Intervals With Astrocytomas

By

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With 6 Figures

Summary

We report 137 recurrent supratentorial astrocytomas. The primary tumours diagnosed on the basis of a grading system with three stages were 72 astrocytomas I and 65 astrocytomas II. In the first group 14% of the recurrences were not changed, 55.5% became astrocytomas II, and 30.5% became glioblastomas. In the second group 55.4% were unchanged, and 44.6% became glioblastomas. The postoperative intervals until reintervention or death were statistically examined. It seems that the recurrence time chiefly depends on the nature of the primary tumour. The transformation of an astrocytoma I to a glioblastoma takes longer than the transformation of an astrocytoma II into a glioblastoma. In about two thirds of all astrocytomas an increase of malignancy is to be expected. From the histological picture it is not possible in an individual case to predict the likelihood or speed of malignant change. With regard to the effect of irradiation the authors conclude that radiotherapy most probably does not produce malignancy.

Key words: Supratentorial astrocytomas—Recurrences of astrocytomas—Classification of gliomas—Recurrence intervals—Radiotherapy.

Since the work of Tooth (1912) it has been well known that the gliomatous tumours of the brain are expressions of tumour dynamics. The factors responsible for changes in tumours are still unknown and speculation only is possible. These dynamics above all concern the

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astrocytomas and oligodendrogliomas. In any one tumour we find areas with differing histological appearances. This applies particularly to the recurrences of gliomas.

The most comparable communications in the literature are not sufficient. Either there are described only few cases (*e.g.*, Scheinker 1938, Cornil *et al.* 1951, Vázquez 1966) moreover of different tumour groups, or statistics are concerned in such a manner, that the cases indeed were classified according to arranged uniform principles, at which however subjective criticismes (*e.g.*, the question of the degree of malignity) are not unavoidable (*e.g.*, Gullotta *et al.* 1973, Kuhlendahl *et al.* 1973). Besides the insufficient documentation often suffers not comparable conclusions in individual cases (*e.g.*, Finkemeyer *et al.* 1965). Moreover the cases in question allow us to take position on the malignization of gliomas through the radiation therapy; a problem, again and again discussed and with urgency emphasized (*e.g.*, Stender 1968). Corresponding reports concern almost only individual cases.

Material and Methods

Our observations are based on 137 primary astrocytomas (72 grade 1 and 65 grade 2). Some of the cases have already been reported by Molitor (1966). We were able to examine histological preparations of the primary and of the recurrent tumours. In all cases sufficient material was available for a definite diagnosis to be made. Needle biopsy was not employed. Immediatly after surgery the tissue was fixed in neutral formalin and embedded in paraffin. Sections of 5 µ to 8 µ were stained in different ways and in some cases histochemical methods were applied. Impregnation methods were not used. The primary tumours were located mostly in the frontal and temporal regions. In most cases total or subtotal tumour resection, sometimes with lobe removal, was performed. Postoperative survival for up to two months only was classified as an operative mortality. Irradiation dosage was at least 3,000 rads. In some cases totals of 8,000 to 10,000 rads were given in interrupted courses. The postoperative intervals until recurrence or death were statistically examined. For this the time values were transformed in cumulated frequencies and translated in a Weibull probability net (s. Schröder *et al.* 1968). For the calculation of statistical significance we used the Kolmogoroff-Smirnoff test for independent samples. Besides this the median values with a 95% range of confidence have been calculated.

Results

The grading system (Müller and Schröder 1968) is based on the classification of the astrocytomas, oligodendrogliomas and ependymomas into three stages of histological malignancy. At first we tried to use the four stage system of Kernohan *et al.* (1949). But in our hands it was not possible to demonstrate a convincing differentiation between stages three and four. Therefore we adapted with insignificant modifications the grading system of Ringertz (1950). According to that classification an *astrocytoma of grade 1 (= A 1)* is characterized by a moderate increase in the number of fibrillary or protoplasmic astrocytes with most of the cells showing normal characteristics and few mitotic figures. There is no conspicuous increase in blood vessels. The A 1 tumours may be cystic. In the *astrocytomas of grade 2 (= A 2)* the number of cells is increased, and we find

polymorphic nuclei. The number of mitoses is also increased. Atypical mitoses can be seen. Multinucleated cells are not a common feature. Cystic areas are seldom seen. The distribution of blood vessels is striking. Single areas of necrosis can pass through the tissue in both A 1 and A 2 types of tumour. There is no clear line of demarcation from normal tissue. In contrast to both these groups

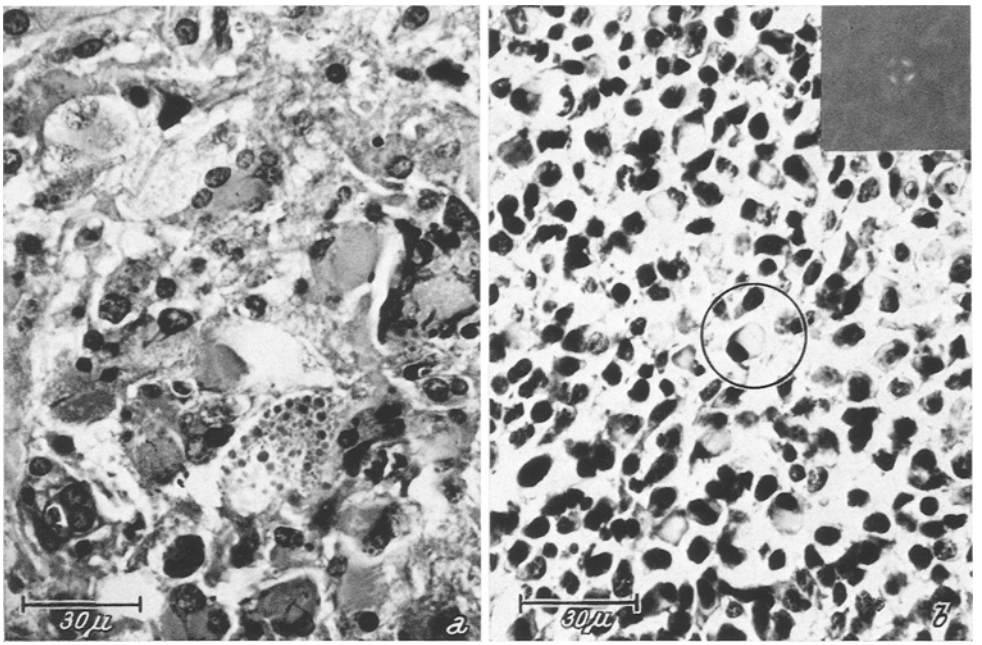

Fig. 1. a) Hyaline droplet degeneration in the cytoplasm. GBl E 22/73 (former A 1 41/68). H.E. b) Gliofibrillary degeneration in tumour cells of a primary A 2 (407/66). H.E. Inset: the birefringent balls of tread-like changes (Gluszcz *et al.* 1971) in the cytoplasm of the encircled cell in polarized light

the *grade 3 astrocytomas (= A 3 or glioblastoma multiforme = Gbl)* are undifferentiated frankly malignant neoplasms. They are pleomorphic, and contain large numbers of giant cells and multinucleated cells. Atypical mitotic features are prominent. Abnormal blood vessels and new capillaries are seen, particularly in the peripheral zones.

Other features are hyaline droplet and gliofibrillary degeneration (Fig. 1) as described by Schlote (1966), Gluszcz (1970), and Gluszcz *et al.* (1971). These occur in astrocytomas of varying malignancy.

The age distribution is represented in Fig. 2. For both groups A 1 and A 2 special diagrams are given. The incidence in both groups is mainly between 31 and 40 years. The middle value for A 1 is 35.5 and for A 2 37.2 years. The sex distribution in group A 1 is 40 males and 32 females, and in group A 2 34 males and 31 females.

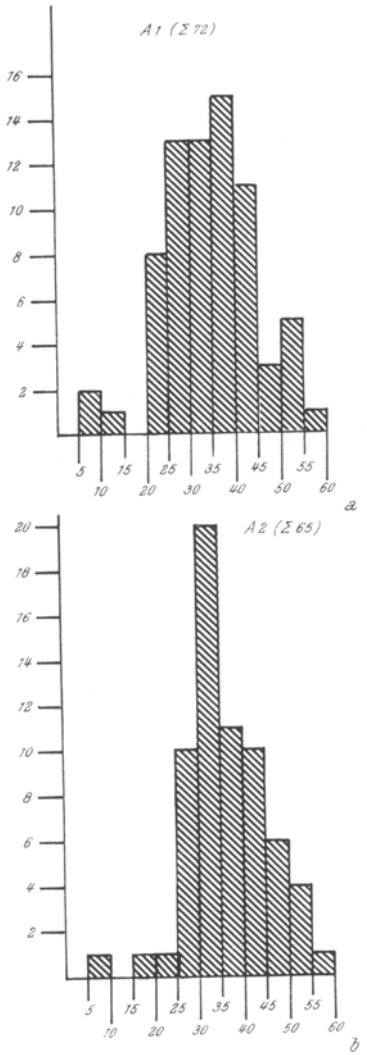

Fig. 2. Age distribution of the starting groups A 1 (a) and A 2 (b). The middle value for A 1 is 35.5 and for A 2 37.2 years

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Legends for the appendix: f = female, m = male; Loc = localisation: f = frontal, t = temporal, p = parietal, l = left, r = right; Rad = irradiation: 0 = not irradiated, + = irradiated; Iv = interval; ? = period of the postoperative interval unknown; → = at the time of inquiry still alive.

Appendix

Starting group A 1

Number	Age	Sex	Loc	Rad	1. Iv	Hist	Rad	2. Iv	Hist	Rad	3. Iv	Hist
114/58	38	f	l—t	0	18	A 1	+	108 →				
9,294	36	m	r—f	0	31	A 1						
415/69	35	m	l—t	0	32	A 1						
444/60	30	f	r—f	+	38	A 1	0	4				
422/65	53	m	l—t	0	40	A 1	+	40				
101/65	34	f	r—t	0	74	A 1	+	13				
384/59	26	m	l—p	+	77	A 1	0	65				
317/65	23	f	l—f	0	79	A 1	0	12 →				
1,222/61	43	m	r—t	+	89	A 1	0	2				
47/58	44	m	r—f	0	136	A 1	0	?				
7,102	28	m	f	+	2	A 2						
322/57	37	f	r—f	0	3	A 2						
10/63	10	m	r—t	0	3	A 2	0	3				
14,409	40	m	r—f	0	4	A 2	0	3				
70/64	25	f	l—t	0	5	A 2	+	9	Gbl			
780/60	58	f	r—f	+	8	A 2						
S 121	25	f	l—t	0	9	A 2	0	?				
443/66	39	f	r—t	0	10	A 2	+	30	Gbl			
289/58	37	f	r—p	0	11	A 2	+	6				
S 105	26	f	l—t	0	13	A 2	0	?				
465/71	37	f	r—f	0	14	A 2	0	9				
1,380/62	15	f	r—p	+	14	A 2	0	4				
418/66	58	m	r—f	0	17	A 2						
206/59	41	m	l—f	+	19	A 2	+	17				
412/63	41	m	r—f	0	19	A 2	+	16				
297/72	27	f	r—t	+	21	A 2	0	?				
46/59	27	f	l—f	0	23	A 2	+	2				
134/58	50	m	r—f	0	23	A 2						
265/72	6	f	r—f	0	23	A 2	+	12 →				
294/59	35	m	l—t	+	24	A 2	0	3				
S 147	34	f	l—t	0	24	A 2	0	?				
226/57	24	m	r—t	+	25	A 2						
424/69	47	m	r—f	0	29	A 2	0	10 →				
458/67	33	m	r—t	0	32	A 2	+	11	Gbl	+	10	
6,166	53	m	r—t	+	33	A 2						
11,373	26	f	l—f	+	34	A 2	0	8				
151/71	21	f	r—t	0	34	A 2	0	?				
283/55	22	m	r—f	0	34	A 2						
580/55	30	m	l—t	+	35	A 2						
170/70	44	f	l—t	0	41	A 2	0	?				
114/69	31	m	l—t	0	42	A 2						
40/57	41	m	l—f	+	43	A 2	+	13				
270/55	25	f	r—f	+	45	A 2	+	20				
62/67	40	m	r—t	0	48	A 2	+	18 →				
9,615	26	f	r—t	0	55	A 02	0	?				

Starting group A 1 (continued)

Number	Age	Sex	Loc	Rad	1. Iv	Hist	Rad	2. Iv	Hist	Rad	3. Iv	Hist
558/55	54	m	l—t	+	58	A 2						
5,257	34	m	r—t	0	60	A 2						
8,261	42	m	l—f	+	60	A 2	0	14				
70/58	43	m	r—p	0	61	A 2	+	48	A 2	0	5	
156/59	36	m	l—t	+	103	A 2	0	11				
0,637	32	f	r—p	0	5	Gbl						
872/56	37	m	r—f	0	12	Gbl	+	12				
2/71	32	f	l—f	+	18	Gbl						
5,537	32	f	l—p	+	20	Gbl	0	?				
507/55	24	f	l—t	0	24	Gbl	+	16	Gbl			
12,687	41	m	l—f	0	24	Gbl	0	?				
487/60	32	m	l—t	+	27	Gbl	0	?				
4/70	47	f	r—f	0	30	Gbl	+	4				
12,550	54	f	r—t	0	31	Gbl	0	9 →				
11,721	38	m	r—f	0	33	Gbl	+	6				
394/65	39	f	l—t	0	36	Gbl	+	?				
801/56	34	m	r—f	0	38	Gbl	+	7	Gbl			
328/58	42	m	l—f	+	39	Gbl						
309/58	39	m	r—t	0	40	Gbl						
672/56	36	f	l—f	+	42	Gbl	0	7	Gbl			
190/69	39	m	r—f	0	43	Gbl						
302/67	41	f	r—t	0	46	Gbl						
7,628	30	m	r—f	0	48	Gbl						
57/57	20	m	l—p	+	57	Gbl	0	10				
41/68	28	m	l—t	0	62	Gbl						
10,689	31	m	r—t	0	75	Gbl	0	?				
1,306/62	35	f	r—f	+	89	Gbl						
						Starting group A 2						
345/71	34	f	r—t	0	4	A 2	0	6				
15/74	40	m	r—t	0	4	A 2	+	→				
1,070/61	20	f	l—p	0	5	A 2	0	?				
47/66	42	f	l—f	0	5	A 2	+	29				
145/74	32	f	l—f	0	5	A 2	+	6 →				
10,886	36	f	l—f	0	6	A 2	0	12				
955/56	34	f	l—f	0	7	A 2						
650/60	35	f	r—f	+	7	A 2	0	3	Gbl			
431/70	38	m	r—f	+	8	A 2						
1,580/62	51	f	l—t	+	9	A 2						
44/66	36	m	l—p	0	14	A 2	+	16	Gbl			
68/70	34	m	r—t	0	14	A 2						
400/72	29	m	r—f	0	14	A 2						
258/72	34	f	r—f	+	14	A 2	+	14	A 2	+	14 →	
154/67	40	m	r—f	+	15	A 2	0	7				
46/66	45	m	l—t	0	16	A 2	+	10	Gbl	0	5	Gbl
20/73	34	m	r—t	0	16	A 2	+	12 →				

Starting group A 2 (continued)

Number	Age	Sex	Loc	Rad	1. Iv	Hist	Rad	2. Iv	Hist	Rad	3. Iv	Hist
58/72	30	f	l—t	+	17	A 2	+	16 →				
265/70	28	m	r—f	0	18	A 2	+	18 →				
468/67	35	m	r—t	0	19	A 2	0	17				
390/68	36	f	r—f	0	19	A 2						
160/57	27	f	r—f	+	23	A 2	+	24	A 2	0	3	
365/70	38	f	r—p	+	23	A 2						
445/72	45	m	l—f	+	23	A 2	0	?				
342/63	35	m	l—f	0	24	A 2	+	22				
407/66	53	m	r—f	0	25	A 2	+	17	A 2			
383/67	37	m	l—p	0	26	A 2						
347/64	42	m	r—p	0	28	A 2						
929/61	37	m	r—f	+	35	A 2	0	2	A 2			
1,521/62	41	m	l—f	+	36	A 2	0	3				
10,244	32	f	r—f	0	40	A 2	+	24				
1,552/62	33	m	l—f	+	44	A 2	+	2				
5,080	41	f	l—t	+	60	A 2						
412/57	27	m	r—f	+	73	A 2	0	3				
7,159	31	f	l—t	+	106	A 2						
4,198	9	m	r—p	0	144	A 2	0	?				
1,345/62	45	m	r—t	+	3	Gbl						
236/74	50	m	l—t	0	3	Gbl	0	5				
7,016	41	m	r—t	+	4	Gbl						
401/55	50	m	l—p	+	5	Gbl						
159/57	45	m	l—t	+	5	Gbl	+	19				
152/59	54	f	l—t	+	5	Gbl						
14,901	54	f	l—t	0	5	Gbl	0	4				
365/55	32	f	r—f	0	6	Gbl						
273/69	35	m	r—f	0	6	Gbl	0	?				
341/58	49	f	r—f	0	8	Gbl						
439/63	38	f	l—f	0	8	Gbl						
182/72	47	m	l—t	+	8	Gbl						
51/69	32	f	r—f	+	10	Gbl	0	2				
6,985	34	f	f	+	10	Gbl						
83/58	37	f	l—t	0	12	Gbl	+	12	Gbl	+	5	
89/69	50	f	l—p	0	13	Gbl	+	18				
6,704	44	m	l—t	+	13	Gbl	+	13				
316/63	30	f	r—f	0	14	Gbl						
388/59	31	m	l—f	+	20	Gbl	+	5	Gbl			
53/68	27	m	l—t	0	21	Gbl	0	2				
37/69	44	m	r—f	0	21	Gbl						
963/56	30	f	r—t	+	22	Gbl	0	3	Gbl			
S 288	23	f	l—t	0	23	Gbl						
148/71	33	m	r—f	0	24	Gbl	+	5	Gbl			
32/68	26	m	r—t	+	24	Gbl	0	2				
1,205/61	37	m	r—f	+	26	Gbl	+	7				
217/69	60	f	l—t	+	37	Gbl	0	3				
173/57	35	f	l—f	+	40	Gbl						
639/56	29	f	l—p	+	144	Gbl	0	6				

Histological investigation of the first recurrences in group A 1 results in the following classification: 10 cases (14%) were not changed, 40 (55.5%) were graded as A 2, and 22 (30.5%) as Gbl (Fig. 3 a). In group A 2 36 cases (55.4%) were unchanged, and 29 cases (44.6%) were Gbl (Fig. 3 b). Taking groups A 1 and A 2 as a whole, 46 cases (37.2%) were histologically unchanged. Later

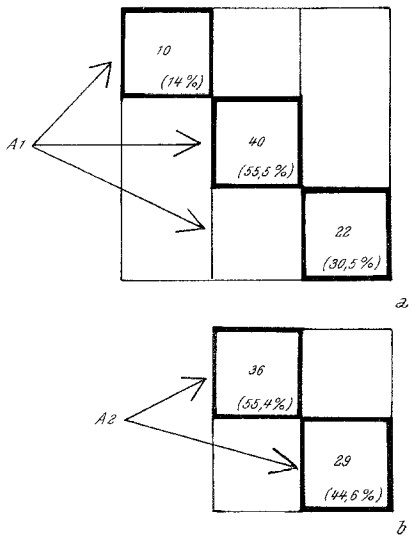

Fig. 3. Histological classification of the first recurrences in the A 1 (a) and in the A 2 (b) group. Forty six cases in both groups (27.2%) were unchanged

recurrences were also studied. There were 14 of these from the combined A 1 and A 2 series. Three remained as A 2 and 6 as Gbl. Four were reclassified as Gbl (Fig. 4). No tumour became more benign. The time relations between the first operation and reoperation or death are important. Both groups were analysed with special regard to these intervals and the histological changes. It follows from Fig. 5 and the appendix, that the first interval shows marked variations. The median time intervals for the two groups are 31.5 and 15 months. The corresponding frequency distributions are signif-

Fig. 4. a) Not irradiated and b) irradiated cases of the group initially A 1; c) not irradiated and d) irradiated cases of the initial group A 2. The order of succession corresponds with the sequence in the appendix. Black = first, hatched = second, and open = third interval. Arrow-shaped end of the file = further fate of the patient unknown

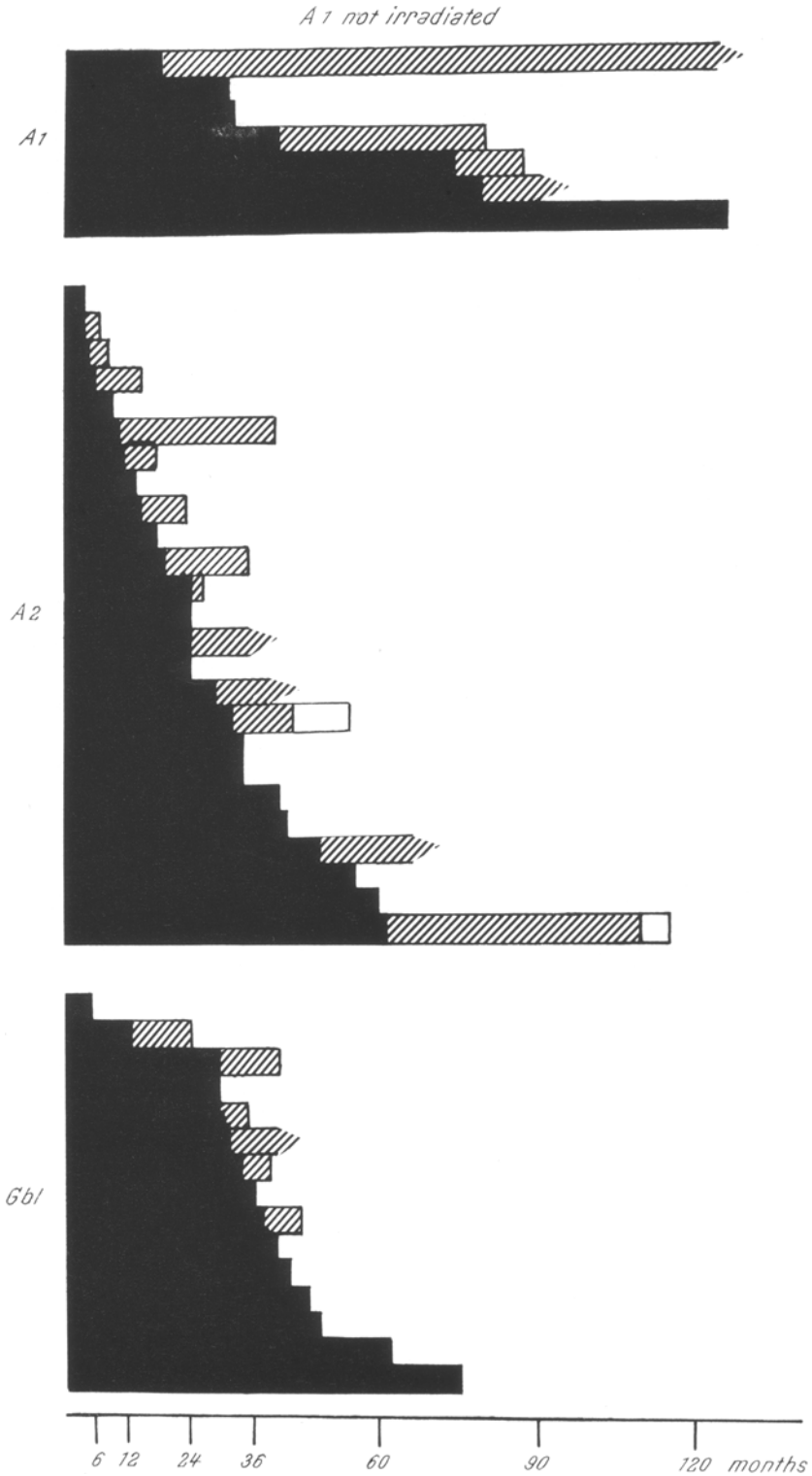

Fig. 4 a

icantly different ($p < 0.001$). Further division of the A 1 group shows in those cases which remain as A 1 a long first interval (median 57 months) and long further survival after the second operation. The

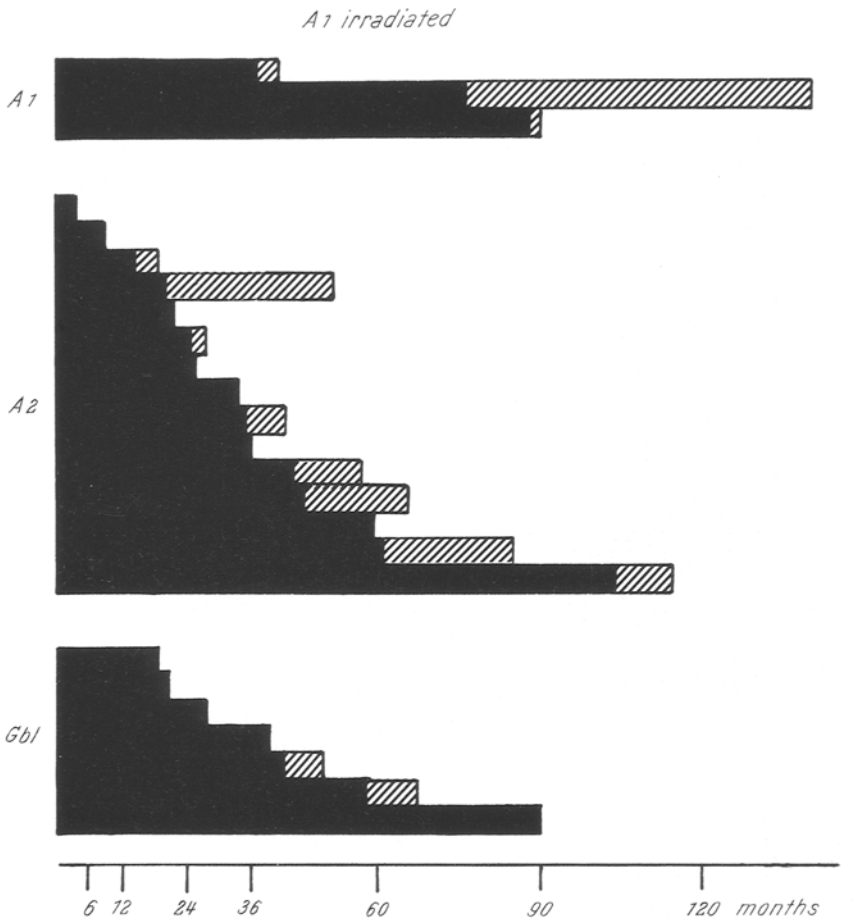

Fig. 4 b

tumours of the A 1 group regraded as A 2 or even als Gbl after reoperation have very different first intervals. Their median values (24 and 37 months) indeed differ, but without significance in the statistical test. The first intervals in the A 2 group show similar deviations. Their median values are 17.5 and 12 months but the statistical significance is not sufficient ($p < 0.10$). One may infer from the median times of the A 1 group that the transformation to

a Gbl takes a longer time than does change to an A 2. But a statistical test demonstrates that this is probably a fallacy, because the probability of error is greater than 10 percent. Despite the insufficient

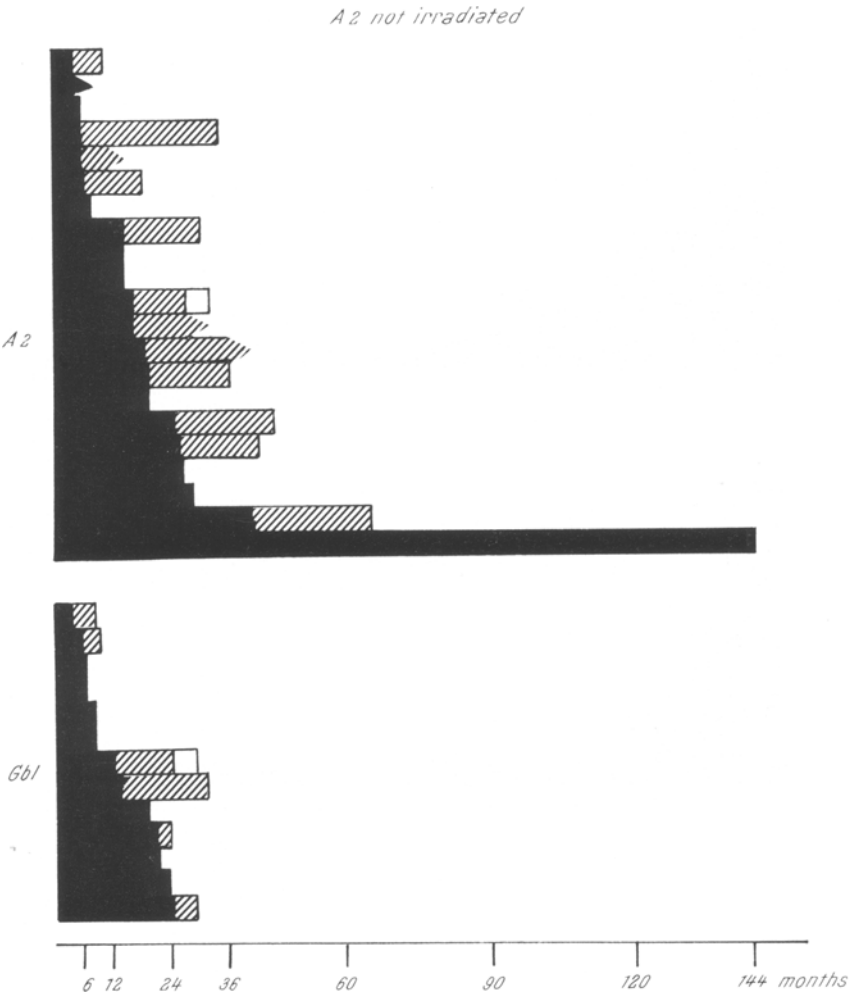

Fig. 4 c

significance of $p < 0.10$, one can presume a difference between the tumours remaining unchanged and those becoming A 2 in the original A 1 group. The material is statistically too small, however.

Now we compare the first interval of patients with a recurrence

diagnosed as Gbl in regard to the classification of the primary tumour. Those cases, which were originally A 1, have a significantly longer interval ($p < 0.001$), with a median time of 37 months, compared to

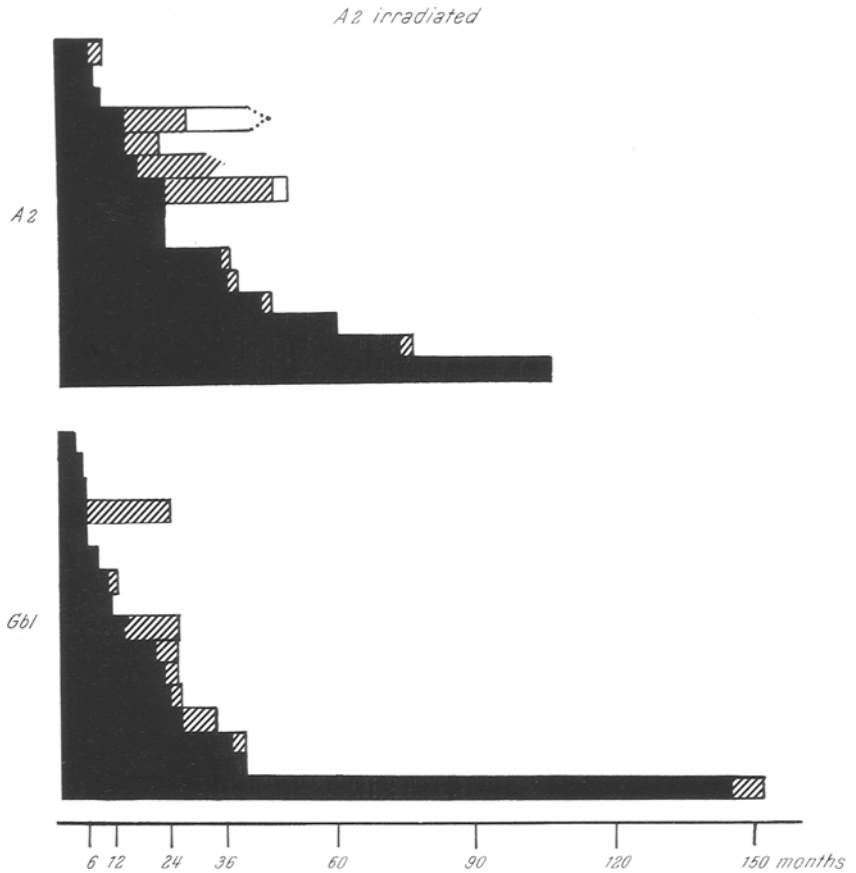

Fig. 4 d

patients with primary A 2 tumours. Their median interval is 12 months. From the statistical point of view we have in this material a sample of a limited collective. It is advisable to give a range of reliability, in which would lie the median value based upon an infinite, number of cases. These ranges of confidence with a 95 per cent probability for the groups already discussed are 24 to 43 months and 6 to 21 months. When we compare the tumours of the primary A 1 group, which are either unchanged or transformed to A 2, with

the unchanged recurrences of the A 2 group, we can see a statistically significant difference ($p < 0.05$). The corresponding median values are 32 and 17.5 months. Their 95 per cent ranges of confidence are 23 to 35 and 14 to 23 months.

The differences in the distribution of the single values are especially prominent on probability plotting. Here the form of the

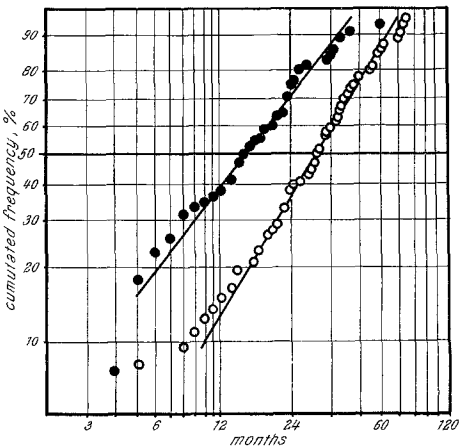

Fig. 5. Cumulated frequencies of the recurrence-time distribution plotted in the Weibull net. Filled circles represent the values of 65 primary A 2 tumours, open circles the values of 72 primary A 1. The A 1 figures suggest longer periods up to the second operation. Their median times are to be read in the 50% line. The points of both distributions show approximately a linear arrangement in this type of diagram

Weibull net has been used for survival times (Sachs 1972). These diagrams (Figs. 5 and 6) show an arrangement of the singular points round the mean value, which indicates approximatively the probable linearity of the distribution curves, despite the insufficient number of cases.

The distribution in histologically different groups in Fig. 4 also took into account whether or not irradiation was given during the first intervals. We come to the conclusion that irradiation does not play a rôle in malignant transformation.

Discussion

For a long time it has been known that grading of tumours is a necessary condition for a better understanding between surgeon and morphologist. Therefore it is not surprising that a number of such grading systems with very different criteria exist in the specialty of

neurooncology. A comparable consideration of different statistics is made more difficult or even impossible because proper documentation is inadequate or absent. The usefulness and practicability of our grading system has been confirmed over many years of practice (Schröder *et al.* 1968, 1970, Walter *et al.* 1969). A similar classification with three stages has been used by Løken (1952), Khominsky

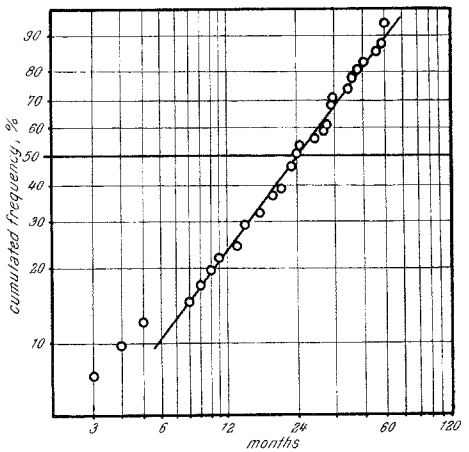

Fig. 6. Cumulated frequencies of the recurrence time of the 40 primary A 1 tumours transformed into A 2. The points also show an approximately straight line in the Weibull net

(1957, 1963) and Vorreith *et al.* (1963). Schiffer and Fabiani (1970) used a classification into three stages, benign, intermediate, and malignant. The suggested WHO classification is in good approximation to ours (meeting of investigators on the histological classification of tumours of the central nervous system, Geneva, 20.–24. 9. 1976).

Nevertheless it is clear that misinterpretations in some cases are inevitable. In our view there are two reasons for this. Firstly, for the occasional investigator misinterpretations are possible. Secondly it is well known that even in very large blocks of tissue important areas can be missed. Compensation for these limitations is achieved by the use of large series of examinations.

There was an increase of malignancy astrocytomas classified in most of our A 1 cases, only 14% remaining unchanged after the first operations. Nearly half were regarded as A 2 and nearly one third became Gbl. With group A 2, after the first interval nearly half became Gbl. Although the time period for the increase of malignancy

in particular cases shows considerable differences, the calculation of the median values indicates a high significance between the groups starting as A 1 and A 2. This means that transformation from A 1 to a more malignant form takes longer than is the case with A 2. But a further subdivision whitin these both groups corresponding to the degree of malignancy of the recurrence does not result in demonstrable significant changes in the time intervals. Therefore, a shortening of the recurrence time by the development of malignancy cannot be established. This aspects needs additional studies with more material. It seems from our results that statistically the recurrence time is chiefly dependent on the type of the primary tumour, and to a lesser extent on the postoperative increase in malignancy.

We confirm that in two thirds of all astrocytomas (A 1 or A 2) an increase of malignancy is to be expected. But it is not possible on the basis of the histological picture in a single case to predict the certainty and the rapidity of the malignant change.

In comparing our results with the communication by Gullotta *et al.* there is moderate conformity. An exact comparation, however, is not possible, because these authors used a grading system with four stages. But if we take into consideration only the unchanged tumours of both initial groups A 1 and A 2, then we find a satisfying conformity: 33.5% to 37.2%. The extensive investigations of recurrent supratentorial gliomas by Alwasiak (1970) are not comparable, because his classification (Gluszcz 1972) is based on another system. An about one third of the recurrences the author found proliferation of fibrous-vascular stroma which caused disorganisation of the structure of neoplastic tissue, and fibrous tissue barriers separating the tumour tissue from the unchanged brain. Such clear proliferation of fibrous tissue in the course of malignant chance we cannot confirm.

The statement by Tooth on the instability of the histological picture of the gliomas is based on two cases. This author came to the conclusion that malignant change is probably provoked by operative intervention. In Ostertag's opinion (1941) surgery plays a role in malignant change by stimulating tumour multipotency. Globus (1931), however, thought the opposite. From our results, we see no evidence for thinking that surgery influences malignant change. In agreement with Scherer (1939), Scheinker (1938), Zülch (1956), and other authors (Schiffer and Fabiani). We support the concept of an inherent tendency in tumour tissue towards malignant transformation, irrespective of external influences.

On the question of the effect of irradiation therapy we draw attention to the communication in 1928 from Bailey *et al.* regarding 62 irradiated gliomas. These authors came to the conclusion that it is not possible exactly to detect histological effects of irradiation. Globus drew attention in 1931 to the possibility of malignant change due to irradiation. In our communication of 1959 (Walter and Müller) we reported on 12 irradiated gliomas. In eight we found in comparison to the primary tumour, signs of increased malignancy. At that time we came to the

conclusion that these findings suggested an effect of irradiation, but that they were not convincing. Without anticipating clinical details in a further communication we can now conclude from the histological results of a greater number of cases that radiotherapy most probably does not cause malignancy. Because we can generally expect increased malignancy in every third astrocytoma. This does not mean automatic rejection of radiotherapy for astrocytomas.

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