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Original paper

Prognostic value of the interval from surgery to initiation of radiation therapy in correlation with some histo-clinical parameters in patients with malignant supratentorial gliomas

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Aim of the study: To determine the relationship between the interval from surgery to initiation of radiation therapy (ISRT) and prognostic factors, such as age, performance status, tumour location, extent of surgical resection and tumour histology in patients with malignant gliomas.

Materials and methods: From 1995 to 2005, 308 adults patients with supratentorial malignant gliomas (198 glioblastomas, and 110 anaplastic astrocytomas) received postoperative radiotherapy with radical intent. A total tumour dose of 60 Gy in 30 fractions in 6 weeks was delivered. ISRT varied from 15 to 124 days, with median time of 37 days, and it was a cut-off value to assess the results. The end point in our study was two-year overall survival.

Results: The two-year overall survival rate in the whole group was 17%, with 24% for patients with ISRT value ≤ 37 days, and 14% for patients with an interval longer than 37 days (p = 0.042). Univariate analysis showed that delayed initiation of radiotherapy influenced the outcome of patients with glioblastoma older than 40 years, and with other than frontal location of tumour. Two-year overall survival rates for ISRT ≤ 37 days were 15%, 18% and 22% respectively, compared to 8%, 4% and 11% for ISRT > 37 days. In a multivariate analysis (Cox's model) the only variables that were significantly associated with worse survival were older age and ISRT prolonged for more than 37 days.

Conclusion: The study showed longer than 37 days waiting time from surgery to initiation of radiotherapy to be a significant predictor of overall survival for adult patients with malignant supratentorial gliomas.

Key words: malignant gliomas, radiotherapy, timing of radiation, prognostic factors.

Introduction

Malignant supratentorial gliomas (MSG) are the most common primary brain tumours in adults. Recently standard treatment consists of maximum safe surgical excision followed by external beam radiotherapy with concomitant and adjuvant chemotherapy with temozolomide. Commonly radiotherapy should start 3-4 weeks after surgery, but in our institution, due to resource and staffing constraints the waiting time for MSG patients fluctuated widely, and very often was much longer than four weeks. The relationship between the delay in radiotherapy and the outcome of patients has been explored in several tumour types and especially in head and neck cancers [1-7], but only a few communications have specifically addressed the delayed initiation of irradiation for MSG [8-17]. The current investigation was undertaken to explore this relationship by analysing the database of our centre, which provides prolonged follow-up of patients with MSG treated with postoperative irradiation.

The purpose of our data is to study the effect on survival of the interval from surgery to initiation of radiotherapy (ISRT), and appraise whether ISRT influenced outcome for patients with MSG, in correlation with different patho-clinical features (patient's age and gender, Karnofsky performance status, tumour's histology and location, extent of resection).

Materials and methods

The study population was derived from neurosurgical centres which referred patients to the Maria Skłodowska-Curie Memorial Centre in Kraków for radiation therapy. Surgery consisted of as complete tumour removal as possible. All surgical specimens were evaluated, by the same pathologist, according to the WHO classification as described by Louis *et al*. [18]. Between January 1997 and December 2007, 308 unselected patients with MSG were postoperatively irradiated. The tumour dose of 60 Gy in 30 fractions in six weeks was delivered. The ISRT varied from 15 to 124 days with a median value of 37 days, and this timing is taken in our study as a cut-off value for ISRT. We determined two ISRT values: ISRT1 ≤ 37 days, and ISRT2 > 37 days. Neurological function and Karnofsky performance status (KPS) [19] of each patient were carefully recording before starting radiotherapy as well as immediately after termination of treatment and on each follow-up examination. The end point for this study was two-year overall survival. Patients were checked monthly after completion of therapy for one year and every 3 months thereafter. Both univariate and multivariate analysis were performed. Cox's proportional hazard mod-

Table 1. Patient characteristics by the ISRT values

Characteristics	ISRT1 (n = 156)		ISRT2 (n = 152)	
	n	%	*n*	%
Gender				
Male	82	52	90	59*
Female	74	48	62	41
Age (years)				
40 or less	44	28	39	26
More than 40	112	72	113	74
Karnofsky status				
60 or more	49	32	47	31
Less than 60	107	68	105	69
Resection				
Total	47	30	47	31
Partial	109	70	105	69
Histology				
Glioblastoma	94	60	94	62
Anaplastic astrocytoma	62	40	58	38
Tumour location				
Frontal	50	32	56	37
Others	106	67	96	63

*ISRT – interval from surgery to irradiation. ISRT1 ≤ 37 days, ISRT2 > 37 days. *There is some disparity between the patient characteristics with more males and relatively more frontal tumours in the ISRT2 group.*

Table 3. Univariate analysis

Characteristics	2-year overall survival (%)	*P*
Age (years)		
40 or less	40	0.000
More than 40	9	
Gender		
Male	16	0.33
Female	19	
Karnofsky status		
60 or more	17	0.54
Less than 60	17	
Resection		
Total	18	0.56
Partial	17	
Histology		
Glioblastoma	10	0.000
Anaplastic astrocytoma	30	
Tumour location		
Frontal	22	0.049
Other than frontal	16	
ISRT		
ISRT1	24	0.042
ISRT2	14	

el was applied to evaluate the strength of influence of examined variables and was expressed as relative risk of hazard (RRH). The values were standardized so that the final model contains only features which are significant for shaping the probability of survival ($p \leq 0.05$) [20, 21].

The distribution of patient characteristics by the ISRT values is given in Table 1.

Table 2. Results according to ISRT values

Characteristics	2-year overall survival ISRT1 (%)	survival ISRT2 (%)	*P*
Age (years)			
40 or less	45	39	0.32
More than 40	18	4	0.003
Gender			
Male	20	14	0.12
Female	29	15	0.18
Karnofsky status			
60 or more	25	12	0.467
Less than 60	23	16	0.519
Resection			
Total	35	13	0.06
Partial	22	15	0.15
Histology			
Glioblastoma	15	8	0.036
Anaplastic astrocytoma	35	28	0.91
Tumour location			
Frontal lobe	28	22	0.64
Others	22	11	0.009

Table 4. Multivariate analysis (Cox's model)

Characteristics	RRH	P
Age		
40 years or less	1	
More than 40	2.78	0.000
ISRT		
ISRT1	1	
ISRT2	1.54	0.007

RRH – relative risk of hazard

Results

The two-year overall survival in the whole group of 308 MSG patients was 17%, and it was 10% for glioblastomas and 30% for anaplastic astrocytomas. Corresponding survival rates for ISRT1 and ISRT2 were 15%, 8% and 35%, 28% respectively. The results of treatment according to the ISRT values are presented in Table 2.

Results of univariate and multivariate analysis are given in Table 3 and 4.

In our study the univariate analysis showed that delayed initiation of radiotherapy influenced the outcome of patients with glioblastoma older than 40 years, and in other than frontal location of tumour. Two-year overall survival rates for ISRT ≤ 37 days were 15%, 18% and 22% respectively, compared to 8%, 4% and 11% for ISRT > 37 days. In a multivariate analysis (Cox's model) the only variables that were significantly associated with worse survival were older age (more than 40 years), and ISRT prolonged for more than 37 days.

Discussion

Fractionated external beam radiotherapy is an important component of standard treatment for MSG. In every therapy schedule comprising postoperative irradiation, it seems of importance to determine the optimum mo-

ment for starting irradiation. The recent technological progress has paradoxically lengthened the interval from surgery to initiation of radiotherapy (ISRT). Complex treatment planning and procedures associated with providing proper radiation therapy quality (quality assurance) require much more time from a radiotherapist and a medical physicist. At the same time the number of irradiated patients has also increased because of the increased number of indications for this treatment. Longer waiting times can cause anxiety in both patients and physicians, who may be concerned about tumour progression before treatment commences. Due to the lack of evidence as to the effect of longer ISRT, it has been difficult to convince funding bodies of the extent of this problem. It may seem that in the case of MSG, which are rapidly growing tumours, the ISRT should be as short as possible. Nevertheless, the literature provides conflicting data on this theme.

Burnet *et al*. devised a complex mathematical model using pathological and radiobiological concepts, based on survival data from 154 glioblastoma patients treated with radiation therapy after surgery. Timing was taken from the date of the first oncology consultation rather than surgery. Their model showed a steep in median survival after a delay of 40 days. The deleterious effect of delay of survival became more marked if patients intended for treatment were also included [9]. In a study from Westmead Hospital (Sydney) in cooperation with the National Health Service and the Medical Research Council, the authors used multivariate analysis to assess the effect of radiotherapy delay on survival in a group of 182 patients with MSG. They found a significant relationship between survival and the time from first assessment in the radiotherapy. The risk of death increased 2% for every day of delay. A delay of 4 weeks from the time of referral resulted in a 10-week reduction in median survival. However, no statistically significant relationship between survival and the time from surgery to the start of radiotherapy was found. An interesting finding of the authors was the fact that older patients, those with poorer performance status, and those with less than total resection had shorter median time from presentation to radiotherapy. One could suppose this was the effect of an attempt to "compensate" for those patients' poor prognosis with "faster" postoperative irradiation [10]. Irvin *et al.* found that a delay in radiotherapy results in a clinically significant reduction in survival. In a group of 172 patients with MSG, time to radiotherapy after surgery varied from 7 days to over 16 weeks. Every additional week of delay until the start of radiotherapy increases the risk of death by 8.9%. A 6-week delay in starting radiotherapy (from 2 weeks to 8 weeks) reduces median survival by 11 weeks. These data emphasize the importance of minimizing delays at every step in the process, including rapid histological diagnosis and reliable early communication between the neurosurgical and oncology teams [12]. Nöel *et al.* retrospectively analysed 94 consecutive patients with histologically proven glioblastoma postoperatively irradiated. For all patients median ISRT was 46 days. The median overall survival for patients with ISRT up to 46 days, and over this period, was 14.3 and 13.6 months respectively. The difference in survival was not statistically significant (p = 0.8) [14]. Similarly, Thomson *et al.* did not find a relationship between the ISRT and treatment outcome in a group of 40 patients with glioblastoma [15].

The above data show that lengthening of ISRT affects, more or less significantly but generally negatively, the survival of patients with MSG receiving postoperative irradiation. In this context the report from the Radiation Therapy Oncology Group (RTOG) seems to be controversial. A large number of patients (2855) with histologically confirmed supratentorial glioblastoma were included in that analysis. Four patient groups were selected based on the interval from surgery to the start of radiotherapy: ≤ 2 weeks, 2 to 3 weeks, 3 to 4 weeks, and more than 4 weeks up to the protocol eligibility limit of 6 weeks. No decrement in survival could be identified with increasing ISRT. Median survival time was unexpectedly and significantly greater in the group with the longest interval (> 4 weeks) than in those with the shortest delay (≤ 2 weeks): respectively, 12.5 months versus 9.2 months (p < 0.0001). On multivariate analysis, with overall survival as the end point, time interval more than 4 weeks was one of the significant predictors of improved outcome. It is difficult to propose a plausible mechanism for an association between delayed therapy and improved survival in the treatment of glioblastoma. Finally, there may be a detrimental effect to the brain when treated with radiation too soon after the primary insult of surgery. Hypoxia from surgical manipulation and oedema in the immediate postoperative period may diminish radiosensitivity. It is unclear that the retrospective nature of this review allows sufficient power to exclude the possibility that delays in ISRT may have had small but clinically meaningful deleterious effects [8].

Our study suggests that longer than 37 days delay in receiving radiotherapy after surgery decreases survival of patients with malignant supratentorial gliomas. However, our data suffer from the well-known shortcomings and potential bias of a retrospective study.

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