Radiol Oncol 2001; 35(2): 127-31.

Dividing patients with brain metastases into classes derived from the RTOG recursive partitioning analysis (RPA) with emphasis on prognostic poorer patient groups

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Background. *The aim of our study was to investigate whether selecting the patients with brain metastases by classifying them into three classes according to the results of the recursive partitioning analysis (RPA) of the Radiation Therapy Oncology Group (RTOG) is useful or not for further decision concerning altered treatment schedules in patients.*

Patients and methods. *The investigated group included 57 male and 48 female patients having received whole brain radiotherapy in a total dose of 30 Gy / 3 Gy daily / 5 days a week. Patients who had surgical excision of brain metastases or had radiosurgical intervention were excluded. All patients were stratified according to the findings of RPA (Class I: Karnofsky Performance Status (KPS) =70, age <65, controlled primary tumour, no other metastases; Class II: not Class I or III; Class III KPS <70).*

Results. *The six/twelve months survival probability for classes I to III was 80 %/44 %, 43 %/17 % and 6 %/0 %, respectively. KPS and extracerebral tumour activity, but not age (<>65) had an impact on survival according to multivariate analysis.*

Conclusions. *Selecting the patients by dividing them into the three RPA classes seems to be useful. Considering the short survival time in RPA Class III, those patients might be well treated with a shorter treatment course.*

Keywords: brain neoplasms-secondary-radiotherapy, brain metastases; survival analysis; Karnofsky performance status; recursive-partitioning analysis, prognostic groups

Received 23 January 2001
Accepted 15 February 2001

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Introduction

The Radiation Therapy Oncology Group (RTOG) performed a recursive partitioning analysis on 1200 patients from three consecutive RTOG trials which tested different dose fractionation schemes and radiation sensitizers.[1] The goals of this analysis were a) to analyse the relative contributions of pre-treatment variables to the survival of patients with brain metastases using an interactive, non-parametric statistical technique known as recursive partitioning analysis; b) to define the influence of treatment variations on survival among patients enrolled on three consecutive RTOG randomised trials and c) to identify patient subgroups or stages.[1]

Based on this analysis, a classification in three classes was suggested to test new treatment techniques on homogeneous patient groups.

To learn more about the survival characteristics, we retrospectively analysed a homogenous group of 105 patients with brain metastases treated by whole brain radiotherapy. The highest emphasis was placed on the prognostically poorer groups to find out if it might be reasonable to enter these patients into shorter treatment courses with higher single doses and a higher probability of late toxicity reactions.

Methods and materials

To gain a homogenous patient group, only patients without previous treatment, like surgical resection or radiosurgical intervention, were accepted. The investigated group included 57 (54.2 %) male and 48 (45.8 %) female patients, who were irradiated at our Department between 1987 and 1997. All patients had received whole brain radiotherapy of 30 Gy in ten fractions within two weeks. Following CT-assisted treatment planning, irradiation was administered using a linear accelerator with 18 MV photon beams. Reproducible patient positioning was achieved by using a thermoplastic mask system. During irradiation, all patients received corticosteroids as prophylaxis of cerebral oedema. All patients were stratified into three classes according to the findings of Gaspar et al.: Class 1: Karnofsky Performance Status (KPS) = 70, age < 65 years with controlled primary and no evidence of extracranial metastases (16 pts, 15.2 %), class 3: KPS < 70 (37 pts, 35.2 %) and class 2: all remaining patients (52 pts, 49.5%).

Patients' characteristics and class characteristics are provided in Table 1.

Statistics

The survival curves were calculated using the Kaplan Meier method and the log rank test was used for univariate comparison. Prognostic factors were analysed using Cox's regression model.

Results

The mean follow up time of the whole group was 6.9 months (0.4-53.3). The median survival of all 105 patients was 3.2 (95 % confidence interval (CI), ±0.98) months. The median survival of the classes one to three was 10.7 (95 % CI, ±1.6), 4.7 (95 % CI, ±1.2) and 2 (95 % CI, ±0.79) months, respectively. The six/twelve months survival probability of classes one to three was 80 %/44 %, 43 %/17 % and 6 %/0 %, respectively. Comparing the survival times of the three classes, a distinct difference was seen ($p < 0.0001$)

Univariate analysis of the whole group showed significant differences in the survival of patients with a Karnofsky Performance Status = 70 or < 70 ($p < 0.001$), of the patients with or without extracerebral tumour activity ($p < 0.001$) and of the patients with or without

Table 1. Patient characteristics according to classes resulting from recursive partitioning analysis (RPA)

	Class 1		Class 2		Class 3		Total	
	n	%	n	%	n	%	n	%
Gender								
Female	8	50	20	39	20	54	48	46
Male	8	50	32	61	17	46	57	54
Age								
< 65	16	100	35	67	17	46	67	64
> 65	0	0	17	33	20	54	38	36
Performance Status								
< 70	0	0	0	0	37	100	37	35
> 70	16	100	52	100	0	0	68	65
Neurological symptoms								
No	13	81	34	65	12	32	59	56
Yes	3	19	18	35	25	68	46	44
Number of brain lesions								
< 3	8	50	24	46	18	49	50	48
> 3	8	50	28	54	19	51	55	52
Primary tumour								
Lung cancer	6	38	28	54	15	40	49	47
Breast cancer	5	31	14	27	12	32	31	30
Melanoma	3	19	3	6	4	11	10	9
Renal cancer	0	6	1	2	1	3	3	3
Gynaecological cancer	1	0	0	0	1	3	1	1
Unknown primary	0	0	0	0	1	3	1	1
Others	1	6	6	11	3	8	10	9
Active primary tumour								
Yes	16	100	35	67	23	62	74	71
No	0	0	17	33	14	38	31	29
Extracerebral metastases								
No	16	100	24	46	15	40	54	51
Yes	0	0	28	54	22	60	51	49

neurological symptoms stage 3 and 4 ($p = 0.01$). Details of neurological function status are given in Table 2. Age did not seem to have an effect on survival with a p-value of 0.8. A multivariate Cox regression model revealed the Karnofsky Performance Status ($p < 0.001$, relative risk (RR), 3.2) and extracerebral tumour activity ($p = 0.004$; RR, 2.4) as significant prognostic factors.

Discussion

According to the findings of the RTOG[1] and validating studies [2,3], we saw a distinct and significant ($p < 0.0001$) difference in the survival of the three prognostic classes. Age, however, did not show statistically significant impact on survival. Selecting patients according to the parameters derived from the RPA analysis might be a good way of predicting

Table 2. Neurological function status[1]

Stage	Symptoms
0	No neurological symptoms; fully active at home/work without assistance
1	Minor neurological symptoms; fully active at home/ work without assistance
3	Moderate neurological symptoms; less than fully active at home/work and requires assistance
4	Severe neurological symptoms; totally inactive requiring complete assistance at home or in institution. Unable to work

the survival time not only for the patients with favourable prognosis but also for those with poor prognosis. Identifying this group of patients gives the possibility to adept the treatment to their needs. In Table 3, the survival times of four studies on the RPA findings are shown. The six/twelve months survival ranged between 6-20 % and 0-6 %, respectively for patients of the RPA class III. The median survival ranged between 2 to 2.3 months. Considering these short survival times we should apply the shortest and least demanding scheme of therapy possible.

Haie-Meder et al.[4] performed a randomised trial on two radiation schedules comparing 18 Gy in 3 fractions versus the same fractionation followed by a second course of radiotherapy with a one-month time interval. The second course was identical to the first one or delivered 25 Gy/10 fractions/14 days. The neurological improvement was similar in both treatment arms; no neurological complications were observed. Concerning the survival, the two treatment arms were equivalent with 4 to 5 months of median survival. The authors conclude, that a radiation schedule as short as 18 Gy in 3 fractions can provide good palliation with the advantage of saving time spent by the patient in the hospital and smaller cost and the maintenance of the same level of palliation. It has also been indicated that the patients might not have lived long enough to experience serious complications.

Short fractionation programs have also been tested by the RTOG.[5-7] The investigation on 10 Gy in one fraction or 12 Gy in two fractions showed comparable results with those of the patients receiving 20 to 40 Gy, single fraction 2-4 Gy, concerning response rates, promptness of neurological improvement,

Table 3. Survival in different studies on RPA classification

		RPA Classes		
		I	II	III
Gaspar et al. 19961	6 mo (%)	59	36	~16
	12 mo (%)	32	16	~6
	median (mo)	7.1	4.2	2.3
Nieder et al. 19993	6 mo (%)	~70	~30	~20
	12 mo (%)	~38	~16	~5
	median (mo)	10.5	3.5	2
Gaspar et al. 20002	6 mo (%)	51	33	-
	12 mo (%)	29	12	-
	median (mo)	6.2	3.8	-
Present study	6 mo (%)	80	43	6
	12 mo (%)	44	17	0
	median (mo)	10.7	4.7	2

treatment morbidity and median survival. However, the duration of improvement, time to progression of neurological status and rate of complete disappearance of neurological symptoms were generally less for those patients who received 10 or 12 Gy, suggesting that ultra rapid high dose irradiation schedules might not be as effective as higher-dose schedules in the palliation of patients with brain metastases.[5]

Conclusion

It still has to be considered, that there are long time survivors among the patients with brain metastases and longer schedules still should be routine. But considering the short survival times of patients in the RPA class III, the use of a short schedule might give precious time at home to the patient with the same palliation and reasonable small risk of more complications than from longer schemes.

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