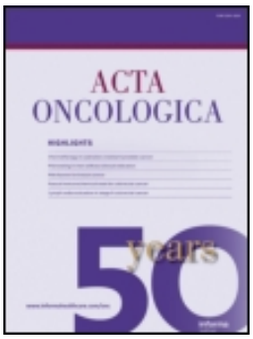

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ORIGINAL ARTICLE

Results of the whole-brain radiotherapy for patients with brain metastases from lung cancer: The RTOG RPA intra-classes analysis

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Abstract

We evaluated the overall survival with respect to prognostic factors in patients with brain metastases (BM) from lung cancer in order to assess the RTOG RPA (Recursive Partitioning Analysis) classification value and to perform intra-classes analyses including pretreatment and treatment-related variables. Between 1986 and 1997, 322 consecutive patients with BM from lung cancer were treated with whole-brain radiotherapy. Patients' distribution according to the RTOG RPA classes was: Class 1 – 13%, Class 2 – 67% and Class 3 – 20%. Prognostic value of the following variables was tested: RTOG RPA classes, performance status, age, extracranial metastases, control of the primary tumour, gender, histology, number of BM and interval from diagnosis to the development of BM. Intra-classes analyses were performed including radiation dose and surgery of BM. Median survival was 4.0 months. Median survival for RTOG RPA classes 1, 2 and 3 were 5.2, 4.0 and 2.5 months, respectively ($p = 0.003$). Extracranial metastases, performance status, control of the primary and RTOG RPA classes were prognostic for survival. Within class 2 higher radiation dose, female, no extracranial metastases and surgery of BM were related to the improved survival. RTOG RPA classes maintain their prognostic significance for patients with BM from lung cancer not participating in clinical trials.

Introduction

Lung cancer is the most frequent primary among patients treated for brain metastases (BM) in both conservative manner, like steroids or whole-brain radiotherapy (WBRT) and more aggressive methods as surgery or radiosurgery [1–3]. Younger patients and those responding better to the treatment of the primary tumour have higher risk than others for developing BM, probably because of the increasing cumulated risk for this event related to the prolonged survival [4]. Wide implementation of new, more aggressive treatment methods like radio-chemotherapy or accelerated irradiation gives a survival advantage for a number of patients with lung cancer. The incidence of BM for this group of patients will probably be growing. Patients with BM from lung cancer are a heterogeneous group, many of them have very limited life expectancy and not only aggressive treatment methods, but even the use of WBRT is questionable [1]. Although WBRT has remained a mainstay of the therapeutic strategy for BM, the results are disappointing with the median survival of 2–6 months [1,2,5–9]. The addition of the surgery or radiosurgery of BM offers a survival advantage when comparing with the WBRT alone, but such a treatment could be beneficial only for a small number of patients. Although the reported median survival after the use of radiosurgery or surgery increases, the prognosis of patients with BM is strongly determined by variables other than therapeutic [10–14]. Improvement of the treatment results could be related to the selection bias. The RPA (Recursive Partitioning Analysis) prognostic classes derived from the RTOG prospective trials on BM were identified as a tool for comparison of treatment results and stratification of patients for clinical studies. This classification is based on the presence of three prognostic factors: performance status, presence of extracranial disease and age [15,16]. RPA prognostic classes are not unanimously accepted, especially for patients not participating in

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clinical trials. Therefore, many modifications and sub-classifications of the respective classes have been proposed [2,17–19]. Patients treated in the randomized clinical trials may differ in their characteristics from patients of general population [20]. First, we evaluated retrospectively the survival of patients with BM from lung cancer treated with WBRT with respect to prognostic factors in order to assess the RPA classification value in our population. Next, we performed intra-classes analysis including both pre-treatment and treatment-related variables in order to better define the respective classes and to try to correct for uncontrolled factors.

Material and methods

Between 1986 and 1997, 322 consecutive patients with brain metastases (BM) from lung cancer were treated with whole-brain radiotherapy (WBRT). Histology of primary was non-small-cell lung cancer (NSCLC) for 190 (59%) and small-cell lung cancer (SCLC) for 132 (41%) patients. Total dose was 20 Gy (5 fractions of 4 Gy, 5 days a week) for 33% patients, 30 Gy (10 fractions of 3 Gy, 5 days a week) for 57% of patients and 40 Gy (10 fractions of 4 Gy, 5 days a week, in 2 courses of 20 Gy with planned gap of 1–2 months between 2 courses) for 10% of patients. WBRT was delivered using Co60 (80%) or 4–15 MV X-rays (20%). As a general rule, patients with better performance status, with previous surgery of BM and without evidence or with minimal extracranial disease received higher doses (30 or 40 Gy), while others received 20 Gy. Characteristics of irradiated patients are summarised in Table I.

Response to WBRT was assessed in terms of palliation of symptoms (headaches or/and neurological impairment) at the first follow-up visit, usually 1–2 months following radiotherapy. Evaluation of response was possible in 248 (77%) patients with symptoms to palliate and available data on symptoms before and after WBRT. Thirty (9%) patients were without any symptoms for palliation before WBRT. There were no sufficient data on palliation for 44 (14%) patients.

Patients were retrospectively grouped into the RTOG RPA prognostic classes [16,17], as follows: Class 1: patients younger than 65 years and with Karnofsky performance status (KPS) ≥ 70, without extracranial metastases and with controlled primary tumour, Class 3: patients with KPS < 70, Class 2: all others.

For most patients (80%) the diagnosis of extracranial metastases was based on clinical examination, chest X-ray, blood count and serum chemistry only. If there was no suspicion of extracranial metastases or local recurrence, other investigations were usually not performed. Such patients were considered as without extracranial metastases for the purpose of this analysis. Primary tumour was considered as controlled, if lung cancer was managed with curative surgery and there was no clinical and/or radiological suspicion of local recurrence. For patients initially managed with conservative treatment, control of the primary was defined as a complete tumour response or a lack of local progression for at least 6 months before WBRT. BM were defined as synchronous, if they appeared before or

Table I. Characteristics of patients.

Characteristic	Number (%)
Gender	
Male	232 (72)
Female	90 (28)
Age	
Range (Median)	31–79 (59)
<65 years	241 (75)
≥ 65 years	81 (25)
Histology	
SCLC	132 (41)
NSCLC	190 (59)
Squamous carcinoma	67 (35)
Adenocarcinoma	76 (40)
Large cell carcinoma	3 (2)
Without type specification	44 (23)
RTOG RPA prognostic class	
Class 1	41 (13)
Class 2	215 (67)
Class 3	66 (20)
KPS	
≥ 70	256 (80)
<70	66 (20)
Previous surgery of BM	
Yes	44 (14)
No	278 (86)
Presence of extracranial metastases	
Yes	83 (26)
No	229 (71)
Unknown	10 (3)
Control of the primary tumour	
Yes	88 (27)
No	222 (69)
Unknown	12 (4)
Number of BM	
Single	124 (39)
Multiple	190 (59)
Unknown	8 (2)
Interval from diagnosis of the primary to development of BM	
Synchronous	147 (46)
Metachronous	175 (54)
Surgery in the treatment of the primary	
Yes	30 (9)
No	292 (91)

within 3 months following the diagnosis of the primary. Diagnosis of single or multiple BM was based on the report of radiological examinations (CT or MRI) performed before radiotherapy or before craniotomy for patients irradiated after surgery.

Survival was evaluated from start of WBRT using Kaplan-Meier method. Possible prognostic factors influencing survival were tested in the univariate and multivariate analysis. Patient-, and tumour-related variables available from the data set included in the univariate analysis were following: RTOG RPA prognostic classes (class 1, 2, 3), KPS (≥ 70 vs. < 70), age (< 65 vs. ≥ 65 years and separately as a continuous variable), presence of extracranial metastases, control of the primary tumour, gender, histology (SCLC vs. NSCLC), number of BM (single vs. multiple), interval from diagnosis of the primary to the development of BM (synchronous vs. metachronous). Factors influencing survival at the significance level $p < 0.10$ (except RPA classes) in Peto and Peto modified Wilcoxon test were included in the multivariate analysis with backward stepwise selection Cox's regression method. RPA prognostic classes were tested separately using Cox's model (with exclusion of factors taken into account in the tested classification). Two separate multivariate analyses were necessary, because RTOG RPA classes consist of the variables tested in the first analysis. Similar method was employed by Weltman et al. [19], when the authors tried to better define prognostic factors for patients with BM treated by aggressive methods.

Additionally, the evaluation of probable prognostic value of patient-, and tumour- related variables was performed in the univariate and multivariate analysis for NSCLC and SCLC separately. For NSCLC the possible prognostic value of adenocarcinoma histology was tested in the univariate analysis (adenocarcinoma vs. other NSCLC types and separately adenocarcinoma vs. squamous carcinoma).

We separately performed univariate analyses using Peto and Peto modified Wilcoxon test for each RTOG RPA class including beyond the pretreatment variables as for the whole group, the treatment related factors, as total dose, use of surgery in the treatment of BM and use of surgery in the treatment of the primary. Factors influencing survival at the significance level $p < 0.10$ were included in the multivariate analysis performed separately for each RPA class.

Results

For 248 evaluable patients there were 173 (70%) improvements of symptoms at the first follow-up visit. Symptoms of 65 (26%) evaluable patients did not change and in 10 (4%) cases neurological status deteriorated.

All but two patients died. Follow-up for living patients was 68- and 96-months. One- and two-year survival rates for the entire group were 14% and 3%, respectively. Median survival was 4.0 months. Median survival was 5.2, 4.0 and 2.5 months for patients from 1, 2 and 3 RTOG RPA prognostic classes, respectively ($p = 0.003$).

It was possible to assess a cause of death in 172 patients (with complete clinical data and CT or MRI of the brain performed after WBRT). Progression in the brain in 98 (57%), extracranial progression in 57 (33%), both extra- and intracranial progression in 14 (8%) evaluable cases led to the death. Three patients (2%) died from cancer and treatment unrelated causes without clinical progression in the brain.

Results of the univariate analysis for the entire group are shown in the Table II. Absence of detected extracranial metastases, KPS ≥ 70, better RPA prognostic class, single BM, control of the primary tumour were associated with improved survival. Interval from diagnosis of the primary to the diagnosis of BM, age (with cut-off of 65 years and considered as continuous variable), gender and histology had no prognostic value. In the multivariate analysis presence of extracranial metastases, KPS, control of the primary and RPA prognostic classes (tested independently) maintained their prognostic significance for survival (Table III). Although there was no difference in survival for NSCLC and SCLC histology, the differences in the disease course and treatment incited us to perform the separate analyses for both histologic types (Tables IV, V and VI). There was no significant difference in survival between adenocarcinoma and other NSCLC, but in the latter group 23% patients had no histologic type specified. The improvement of survival for adenocarcinoma was detected, while comparing adenocarcinoma with squamous carcinoma ($p = 0.02$). In the multivariate analysis no detected extracranial metastases and metachronous presentation were associated with improved survival for NSCLC. RTOG RPA classes did not retain significant prognostic value (Table VI). For SCLC the number of BM, KPS and detected extracranial metastases retained their prognostic significance for survival in the multivariate analysis (Table VI). The small number of patients in RPA prognostic class 1 (5%) and evident worsening of survival with lower KPS did not justify an inclusion of the RTOG RPA classes in the multivariate analysis for SCLC.

Results of univariate analysis for each RPA prognostic class are presented in Tables VII, VIII and IX. Results of multivariate analysis performed separately

Table II. Results of univariate analysis of 322 patients with brain metastases (BM) from lung cancer.

Analysed factor (number of patients)	1-year survival (%)	Median survival (months)	p-value
Presence of extracranial metastases:			
Yes (83)	4	2.0	
No (229)	16	5.0	>0.00001
KPS			
≥70 (256)	15	4.0	
<70 (66)	3	2.5	0.002
RTOG RPA prognostic class:			
Class 1 (41)	12	5.2	
Class 2 (215)	14	4.0	
Class 3 (66)	3	2.5	0.003
Number of BM:			
Single (124)	18	5.0	
Multiple (190)	9	3.0	0.003
Control of the primary tumour:			
Yes (88)	13	4.5	
No (222)	12	3.0	0.03
Gender:			
Female (90)	18	4.0	
Male (232)	11	3.0	0.11
Age:			
≥65 (81)	11	3.0	
<65 (241)	13	4.0	0.13
Interval from diagnosis of the primary to development of BM:			
Synchronous (147)	10	3.5	
Metachronous (175)	14	3.7	0.16
Histology:			
NSCLC (190)	11	4.0	
SCLC (132)	14	3.5	0.93

for each RPA class are summarised in Table X. Surgery of the BM influenced positively survival within class 1 and 2. The understandable small number of patients with the BM surgery in class 3 did not enable any influence of such treatment on survival to be shown. Another treatment related variable – total dose was positively related to survival for classes 2 and 3. In class 1 total doses given to patients were rather homogenous (mostly 30 Gy), which did not allow any differences in survival to be

Table III. Factors positively correlated with prognosis in the multivariate analysis of 322 patients with brain metastases (BM) from lung cancer (* in stepwise selection method, ^ when tested independently).

Variable (number of patients)	Relative risk of death	95% Confidence interval	p-value
Presence of extracranial metastases*:			
Yes (83)	1.32	1.16–1.49	0.00002
No (229)	1.00		
Karnofsky performance status*:			
≥70 (256)	0.63	0.47–0.82	0.003
<70 (66)	1.00		
Control of the primary*:			
Yes (88)	0.98	0.97–0.99	0.02
No (222)	1.00		
RTOG RPA prognostic class^:			
Class 1 (41)	1.00		
Class 2 (215)	1.27 (per Class)	1.02–1.59	0.03
Class 3 (66)			

Table IV. Results of univariate analysis of 190 patients with brain metastases (BM) from NSCLC.

Analysed factor (number of patients)	1-year survival (%)	Median survival (months)	p-value
Control of the primary:			
Yes (73)	16	5.0	
No (117)	7	3.0	0.001
Presence of extracranial metastases:			
Yes (39)	2	2.0	
No (146)	13	4.0	0.002
Interval from diagnosis of the primary to the development of BM:			
Synchronous (95)	5	3.0	
Metachronous (95)	16	4.0	0.01
RTOG RPA Class:			
Class 1 (34)	19	6.0	
Class 2 (117)	11	3.5	
Class 3 (39)	3	3.0	0.02
Histology:			
Adenocarcinoma (76)	15	4.0	
Squamous (67)	5	3.0	0.02
Histology:			
Adenocarcinoma (76)	12	4.0	
Other histologies (114)	9	3.0	0.06
Karnofsky performance status:			
$\geq$70 (151)	13	4.0	
$<$70 (39)	3	3.0	0.10
Number of BM:			
Single (94)	13	4.0	
Multiple (92)	8	3.0	0.10
Age:			
$\geq$65 (59)	11	3.5	
$<$65 (131)	11	4.0	0.29
Gender:			
Female (44)	20	4.0	
Male (146)	8	4.0	0.32

shown. For class 2, with the largest number of patients, the multivariate analysis showed that higher radiation dose, female, absence of extracranial metastases, surgery of BM positively influenced survival.

Discussion

For patients with BM the principal goal of the short-course WBRT is the palliation of symptoms. Significant (70%) improvement of symptoms in the evaluated population of our study is in agreement with other retrospective studies [9]. There are, however, three major limitations of this finding: difficulties to distinguish improvement of symptoms due to radiotherapy from response to steroids, lack of objective criteria of evaluation and a large number of patients without assessment of symptoms after treatment. It is very probable that patients not evaluated had no benefit from the WBRT. Taking into account a number of patients without evaluation of palliative response on WBRT in our study, 54% of the total patient population had a confirmed improvement. Another limitation of our finding is the evaluation of palliative response to treatment at different intervals within 1–2 months, which for patients with short life expectancy could be a problem. In the data evaluating response to the WBRT in the prospective manner, a disappointingly low rate of responses (19%) was seen [1]. A revision of palliative value of WBRT for patients with BM by prospective evaluation is needed, especially for class 3 with very poor survival. In the other hand, the progression in the brain was cause of death in about 60% of evaluated patients, while an evident extracranial disease was present in 76% at the diagnosis of BM. It indicates that the occurrence of BM is a directly life-threatening event and the intensification of treatment in such clinical conditions could improve results.

Table V. Results of univariate analysis of 132 patients with brain metastases (BM) from SCLC.

Analysed factor (number of patients)	1-year survival (%)	Median survival (months)	p-value
Presence of extracranial metastases:			
Yes (44)	6	2.4	
No (83)	20	5.4	0.0004
Karnofsky performance status:			
≥70 (105)	17	4.0	
<70 (27)	4	2.0	0.003
RTOG RPA prognostic class:			
Class 1 (7)	0	3.0	
Class 2 (98)	18	4.5	
Class 3 (27)	4	2.0	0.003
Number of BM:			
single (30)	35	7.0	
multiple (98)	9	2.9	0.005
Age:			
≥65 (22)	14	2.5	
<65 (111)	15	3.5	0.24
Gender:			
Female (45)	15	5.0	
Male (87)	13	3.0	0.26
Control of the primary tumour:			
Yes (15)	6	3.8	
No (105)	16	3.5	0.53
Interval from diagnosis of the primary to development of BM:			
Synchronous (52)	20	4.0	
Metachronous (80)	11	3.0	0.60

In the presented study, there are a relatively lower proportion of patients in RTOG RPA class 3 and a higher proportion of patients with SCLC compared to other materials. It reflects a clinical practice in the 80's and early 90's in our country when, due to limited resources of the public health care system, the patients with especially poor prognosis were rarely addressed to the radiation oncology units.

Table VI. Results of multivariate analysis performed separately for patients with brain metastases (BM) from NSCLC and SCLC.

Variable (number of patients)	Relative risk of death	95% Confidence interval	p-value
NSCLC (190)			
Presence of extracranial metastases:			
Yes (39)	1.35		
No (146)	1.00	1.23–1.62	0.001
Interval from diagnosis of the primary to development of BM:			
synchronous (95)	1.00		
metachronous (95)	0.68	0.59–0.92	0.01
SCLC (132)			
Number of BM			
Single (30)	1.00		
Multiple (98)	1.82	1.55–2.83	0.007
Karnofsky performance status:			
≥70 (105)	0.55		
<70 (27)	1.00	0.35–0.87	0.01
Presence of extracranial metastases:			
Yes (44)	1.28		
No (83)	1.00	1.06–1.56	0.01

Table VII. Results of univariate analysis of 41 patients from RPA class 1.

Analysed factor (number of patients)	Median survival (months)	p-value
Surgery in the treatment of the primary		
Yes (8)	5.0	0.58
No (33)	5.0	
Gender		
Female (9)	4.0	
Male (32)	5.0	0.98
Histology		
SCLC (7)	3.0	
NSCLC (34)	6.0	0.32
Number of BM		
Single (24)	6.5	
Multiple (15)	3.5	0.08
Previous surgery of BM		
Yes (19)	7.0	
No (22)	4.0	0.03
Interval from diagnosis of the primary to development of BM:		
synchronous (12)	5.0	
metachronous (29)	5.0	0.4
Total dose		
20 Gy (8)	3.0	
30 Gy (29)	6.0	
40 Gy (4)	6.0	0.24

Table VIII. Results of univariate analysis of 215 patients from RPA class 2.

Analysed factor (number of patients)	Median survival (months)	p-value
Age		
<65 years (155)	3.0	
≥ 65 years (60)	4.0	0.19
Control of the primary:		
Yes (29)	6.0	
No (180)	4.0	0.21
Presence of extracranial metastases:		
Yes (61)	3.0	
No (148)	5.0	0.0004
Surgery in the treatment of the primary		
Yes (15)	3.0	
No (200)	4.0	0.19
Gender		
Female (62)	5.5	
Male (153)	3.5	0.01
Histology		
SCLC (99)	4.0	
NSCLC (116)	3.5	0.25
Number of BM		
Single (81)	4.0	
Multiple (131)	4.0	0.22
Previous surgery of BM		
Yes (17)	7.0	
No (198)	3.0	0.007
Interval from diagnosis of the primary to development of BM:		
synchronous (99)	3.5	
metachronous (116)	4.0	0.4
Total dose		
20 Gy (75)	2.5	
30 Gy (116)	5.0	
40 Gy (22)	5.5	0.00005

Patients with SCLC received chemotherapy in our institution before brain relapse and therefore had an easier access to other treatments in the same institution at the brain relapse.

Poor overall survival shown in this analysis is in agreement with other reports. Median overall survival for patients with BM from lung cancer after WBRT amounts from 2 to 5 months [2,5–9,21]. It does not differ significantly from results for patients with BM from other primaries managed with WBRT [2]. Some reports indicated that metastases from lung cancer have worse prognosis, which may be due to occult extracranial metastases related to the high metastatic potential of the disease [15]. This opinion is not unanimously accepted, however the worsening of results in comparison with the breast primary is reported [2].

Survival of SCLC patients did not differ significantly from this of NSCLC. It is in agreement with other data [5,20]. Adenocarcinoma was not found as prognostic parameter in our study, but there was a high rate of non-otherwise specified NSCLC histology. Whilst comparing two well established histologies, adenocarcinoma vs. squamous carcinoma, a better survival of the former was seen. There is a higher risk of BM from adenocarcinoma than from squamous histology. It is possible, that even a small component of the former histology in the lung primary can spread to the brain. Biopsy of metastases in case of the known histology of lung tumour is rarely performed and finally it is possible that there are more adenocarcinomas in BM than is reported. This also should be a possible explanation of no confirmation of positive prognostic value of this histologic type in large studies [2,7,8], when the long-term survivors have preponderantly adenocarcinoma [22].

As the impact of prognostic factors on survival is known, the RTOG RPA classification of patients with BM has a goal to enable historical comparisons [15,16]. In our analysis the RTOG RPA classes retained prognostic significance for the entire group. The age was the only variable taken into account in the RTOG RPA classification without prognostic

Table IX. Results of univariate analysis of 66 patients from RPA class 3.

Analysed factor (number of patients)	Median survival (months)	p-value
Age		
<65 years (45)	3.0	
≥65 years (21)	2.0	0.24
Control of the primary:		
Yes (19)	3.5	
No (42)	2.5	0.11
Presence of extracranial metastases:		
Yes (22)	2.0	
No (41)	3.0	0.009
Surgery in the treatment of the primary		
Yes (5)	4.0	
No (61)	3.0	0.06
Gender		
Female (19)	2.5	
Male (47)	3.0	0.56
Histology		
SCLC (26)	2.0	
NSCLC (40)	3.0	0.11
Number of BM		
Single (17)	5.0	
Multiple (46)	3.0	0.04
Previous surgery of BM		
Yes (8)	4.0	
No (58)	3.0	0.06
Interval from diagnosis of the primary to development of BM:		
synchronous (36)	3.0	
metachronous (30)	3.0	0.86
Total dose		
20 Gy (22)	2.5	
30 Gy (38)	3.0	
40 Gy (6)	10.0	0.05

significance in our analysis. Indeed, the most controversial in the RTOG RPA classification is finding that the age of 65 is a cut-off for change of prognosis. Other studies found age with cut-off of 60 [11,19,23] or 70 years [2] as an independent prognostic factor. Reliable evaluation of extracranial disease is not possible to perform in the retrospective manner. Patients with BM not participating in clinical trials, have usually less examinations performed in view of the disease extent evaluation than patients from controlled studies. We should consider this as the limitation of our study, especially for the primary tumour, where an evaluation of the control of the primary was somewhat arbitrary and based often on time without progression from the initial treatment. It was probably the reason for the loss of prognostic significance in the status of primary when analysed in smaller groups. However, the confirmation of the value of RTOG RPA classification for patients treated outside clinical trials is in favour of the strong clinical value of this classification.

In the original RTOG data set for RPA classification there was only 4% of small-cell histology [15], comparing with 41% in our study. All but ten analysed SCLC patients had an active extracranial disease, which confirms other data indicating that BM are very frequently a sign of disease progression in general [24]. This led to the very small number of patients in class 1 and made further reliable analyses of the RTOG RPA classification for this subset of patients impossible. RTOG RPA classification is of limited value for the SCLC histology.

The observed improvement of survival with the use of surgery for BM within class 1 and 2 is in agreement with prospective studies, where adjunction of surgery or radiosurgery to the WBRT was associated with better survival [11,12,14]. An aggressive treatment, like surgery or radiosurgery, addressed to patients with single metastases and without extracranial disease activity prolongs median survival [10,11,13,14].

The size of the subgroup of patients in the RTOG RPA class 2 was large enough to allow the authors to better define this population of patients with BM, as Lutterbach et al. [17] has shown for class 3. We identified higher radiation dose, female, absence of detected extracranial metastases and BM resection before WBRT as independent prognostic factors in class 2. Better survival of female with lung cancer has been already reported by others [25] and it is interesting to see also the influence of gender within the group of patients with similar prognosis.

It has not been proven that dose escalation and/or any radiation schedule give superior results [8,15,16], however for patients with single metastases the dose escalation to 54.4 Gy using hyperfractionation was beneficial [26]. Our finding of the improvement of survival with increased dose within RTOG RPA classes 2 and 3 is debatable, because of the retrospective nature of the study. One could say that physicians were more willing to prescribe higher doses for patients with longer life expectancy, in their opinion, which meant better than reported performance status and/or lower probability of the extracranial disease.

The number of BM (single vs. multiple) did not maintain prognostic significance in the multivariate analysis. Single metastases were not prognostic in the RTOG RPA classification, either. It is in contrast with the findings of more recent data [14,18,19]. It could be explained by the use of unreliable diagnostic tools in earlier data, like ours, namely CT

Table X. Results of multivariate analyses performed separately for all three RPA classes.

Variable	Relative risk of death	95% confidence interval	p-value
RPA Class 1			
Surgery of brain metastases			
Yes (19)	1.00		
No (22)	1.99	1.03–3.82	0.04
RPA Class 2			
Total dose			
20 Gy (75)			
30 Gy (116)			
40 Gy (22)	0.97 by Gy	0.95–0.99	0.002
Gender			
Female (62)	0.62		
Male (153)	1.00	0.46–0.81	0.003
Extracranial metastases			
Yes (61)	1.27		
No (148)	1.00	1.09–1.48	0.003
Surgery of BM			
Yes (17)	1.00		
No (198)	1.76	1.07–2.93	0.03
RPA Class 3			
Extracranial metastases			
Yes (22)	1.40		
No (41)	1.00	1.07–1.82	0.01
Total dose			
20 Gy (22)			
30 Gy (38)			
40 Gy (6)	0.96 by Gy	0.73–0.99	0.02

instead of MRI, which is inappropriate in the evaluation of the real extent of disease in the CNS.

In summary, the results of this study should be interpreted cautiously, especially for prognostic significance of the therapeutic variables, because of the retrospective nature of our data. However, we have shown that RTOG RPA classification could be applied in clinics and also for historical comparisons. The rarity of the occurrence of BM without evidence of extracranial disease decreases the value of the RTOG RPA classification for SCLC.

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