Available online at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Evaluation of results of linac-based radiosurgery for brain metastases from primary lung cancer☆

Dorota Jezierska[a,*], *Krystyna Adamska*[a], *Włodzimierz Liebert*[b]

[a] *Greater Poland Cancer Centre, Garbary 15 Str., 61-866 Poznań, Poland*
[b] *Poznań University of Medical Sciences, Poznań, Poland*

ARTICLE INFO

Article history:
Received 25 October 2011
Received in revised form
13 April 2013
Accepted 23 June 2013

Keywords:
Lung cancer
Radiosurgery
Brain metastasis
Prognostic factors

ABSTRACT

Aim: The purpose of our review was to evaluate results of radiosurgery for patients with brain metastases from lung cancer.
Background: Lung cancer is the leading cause of death from cancer and the most common source of brain metastases. Radiosurgery allows the precise focal delivery of a high single radiation dose to brain metastases and results in high rates of local control.
Materials and methods: 83 patients were treated between 2006 and 2008. We evaluated local control and outcome after radiosurgery and identified prognostic factors.
Results: Median survival in the whole group was 7.8 months from radiosurgery and 11 months from diagnosis. Median survival in classes I, II and III was 13.2, 8.2 and 2.2 months. For 94% of patients symptoms improved or stabilised at the first follow-up visit and this status did not change during 7.1 months. According to the univariate analysis, factors associated with improved survival included: RPA class 1 compared with RPA 2 and 3, RPA class 2 compared with RPA 3, KPS > 70, control of the primary disease, radiosurgery performed more than once, level of haemoglobin >7 mmol/1, absence of extracranial metastases, volume of the biggest lesion <11 cm^3. The multivariate analysis confirmed a significant influence on survival for the following factors: RPA class 1 as compared with RPA 3, KPS > 70, absence of extracranial metastases, multiplicity of radiosurgery.
Conclusions: Stereotactic radiosurgery is a safe and effective treatment. It proved to be effective and safe in older patients. Selection of patients who are likely to benefit most should be based on prognostic factors. KPS proved to be the most important prognostic factor. In the RPA III group (patients with KPS < 70) survival time was similar to that achieved after symptomatic medical management.

1. Introduction

Lung cancer is currently the most prevalent malignancy in the world, accounting for 34% of all cancer deaths. It is also the most prevalent cancer in Poland. Treatment results for lung cancer are still unsatisfactory. This is due to the fact that the disease is usually diagnosed at later stages, with 70% of patients with locally advanced or metastatic cancer. Therefore, a large proportion of patients are not eligible for radical

☆ This article is based on doctoral dissertation of Dorota Jezierska.

* *Corresponding author*. Tel.: +48 618850654; fax: +48 618850657.
E-mail address: dorota.jezierska@wco.pl (D. Jezierska).

1507-1367/$ – see front matter
http://dx.doi.org/10.1016/j.rpor.2013.06.006

Table 1 – Prognostic factors by RPA classes.

RPA classes	Mean survival in months
RPA class I KPS ≥ 70, age < 65, primary disease controlled, no extracranial metastases	7.1
RPA class II KPS ≥ 70 and at least one of the following: age≥65, uncontrolled primary disease, extracranial metastases	4.2
RPA class III KPS < 70	2.3

therapy and are given palliative treatment instead. Such treatment is aimed to improve their quality of life by mitigating pain and to prolong survival. The five-year survival rate with such patients is only around 10%. In patients with stage IV (metastatic) non-small cell lung cancer, the five-year survival rate is below 5%. In extensive disease small cell lung cancer, it is merely 1–2%. Brain metastases develop in 30% of all non-small cell lung cancer patients.[1] In approximately 10% of SCLC patients, metastases to the central nervous system are found at diagnosis.[2] As the disease progresses, brain metastases occur more often (in 60–80% of patients with two-year survival). Of all cases of brain metastases, those from lung cancer represent 40–50%. Brain metastases have a strong negative impact on prognosis and quality of life. It usually requires urgent treatment. The most important aim of such treatment is to improve neurological performance and prolong survival. The choice of a therapeutic method is based on individual assessment of prognostic factors.

Modern brain metastases therapy is based on individual assessment of prognostic factors.[3,4] These include: age, general status as Karnofsky performance scale, type of primary tumour, number of brain metastases (single or multiple) and progression of extracranial processes. The analysis of those factors based on three clinical trials conducted by the RTOG (1200 patients) allowed to distinguish three prognostic classes.[5] Gaspar[3] used the RTOG database to perform a recursive partitioning analysis (RPA). The Karnofsky performance status proved to be the most significant prognostic factor in an univariate analysis. Among patients with KPS 70 or lower, the primary tumour status was the second key prognostic factor, preceding age and extracranial metastases. Three prognostic classes were distinguished: RPA class I consisted of patients with KPS > 70 and higher, aged 65 or younger with controlled primary cancer and no extracranial metastases, whose mean survival period was 7.1 months. RPA class II consisted of patients who had not been qualified into classes I or III (with KPS > 70 and met one of the following criteria: age > 65, uncontrolled primary disease or presence of extracranial metastases). Mean survival time in class II was 4.2 months. Class III covered patients with performance status <70, mean survival time in that class was 2.3 months.

Prognostic factors by RPA classes are shown in Table 1.

The RPA classification may be used to select a small group of patients for radical local treatment (surgery, radiosurgery). There are several important prognostic factors which are not included in the RPA classification. All prognostic factors should be taken into account while selecting a treatment method. Very intensive treatment methods should be considered for patients with favourable prognostic factors, while less intensive or symptomatic treatment for those with unfavourable prognosis. Quality of life, alongside with the length of life, is an important aspect for assessment of treatment efficacy (particularly in the context of short survival time of brain metastases patients).

Considering a small number of Polish studies concerning prognostic factors in brain metastases radiosurgery, we decided to base this evaluation on treatment results for patients with brain metastases from lung cancer treated with radiosurgery in the period from February 2006 to September 2008.

2. Radiosurgery

Radiosurgery is performed with a so-called gamma knife or with the aid of a linear accelerator (LINAC). This method, in contrast to conventional radiation therapy, involves a one-off delivery of high-dose irradiation to a strictly limited area in order destroy it, wherein it resembles a surgical procedure (hence the name radiosurgery). In radiobiological terms, a delivery of a single high dose prevents a repair of post-radiation damage to cancerous cells occurring between fractions of conventional radiation therapy. Depending on a radiosurgery technique, the focus is supplied with doses with different levels of inhomogeneity (higher with a gamma knife). A high dose not only causes damage to tumorous cells, but also to blood vessels that feed them.[11,12]

The linac system uses photon radiation. Many fields of different angles are focused and dosage is precisely adjusted to the volume of a tumour. The application of a multi-leaf collimator reduces the need to use many isocentres and enables a decrease of dose to critical organs.[13]

In stereotactic radiation therapy, the therapeutic index depends on the size of a tumour. The RTOG study on dose escalation showed that a maximum tolerated dose is relative of the size of a tumour. RTOG researchers determined maximum tolerated doses for particular tumour sizes. For tumours of less than 20 mm, it is 24 Gy; for tumours of 21–30 mm, 18 Gy; for tumours of 31–40 mm, 15 Gy.[14] The study by Mehta et al. showed that local control decreases with the size of tumour.[6] In patients with tumours of less than 2 cm^3 in volume, the complete response rate was 61% and the partial response rate was 17%, for tumours of more than 10 cm^3 in volume, the complete response rate was 10%, and the partial response rate was 40% (Table 2).

3. Side effects of radiosurgery

Radiosurgery is usually well tolerated and can be carried out in an ambulatory setting. Therapy-related complications are relatively rare and moderately severe. The advantage of radiosurgery over traditional methods of radiation lies in the possibility to achieve total conservation of healthy tissues owing to lower toxicity of radiation therapy. Nausea, vomiting, alopecia and headaches are among most prevalent

Table 2 – Retrospective studies on radiosurgery in treatment of brain metastases from primary lung cancer.

References	Method	NoP[a]	NoM	%NSCLC	%SCLC	Mean dose (Gy)	%LC	Mean survival (months)
Kim et al.[21]	GN	77	115	100	0	16	85	10
Williams et al.[22]	Linac	30	45	47	0	16	100	7.9 NSCLC 8.4 other
Hoffman et al.[23]	GN	113	301	95	5	18	81	12
Sheehan et al.[24]	GN	273	627	100	0	17	84	7
Kong et al.[28]	GN	35	166	100	0	18.8	93	12[a]
Noel et al. [29]	Linac	92	145	89	11	14	93	9
Chidel et al.[31]	Linac and GN	Linac 73, GN 62	218	48	0	18	ns.	7.9 RPA1 – 11.2 RPA2 and RPA3 – 6.9
Boosheng et al.[25]	Linac	41	ns.	100	0	20	83	9.3(RS) 10.6(RS + WBRT)
Zabel et al.[30]	Linac	86	110	100	0	20	96	4.5
Serizawa et al.[27]	GN	245	ns.	86	14	21	98% in NSCLC, 95% in SCLC	8.6 NSCLC 9.1 SCLC
Gerosa et al.[26]	GN	804	1307	57	0	20	93	13.5

NoP, number of patients; NoM, number of metastases; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LC, local control; ns., not stated; KPS, Karnofsky performance status; CPD, controlled primary disease; GN, Gamma knife.
[a] From diagnosis of metastasis.

side symptoms, their intensity levels ranging from low to moderate.[15–17] Severe complications are divided by their occurrence into acute (early), subacute and late. Early complications (occurring within hours or days following treatment) involve headaches, nausea, vomiting and seizures. Subacute symptoms (occurring within first six months) involve oedema, exacerbation of already existing neurological deficiencies and seizures.[15,18] Post-radiation necrosis may occur as an early complication, but in most cases it is a late complication.[15,16,18] Larger tumours and WBRT relate to a higher risk of complications.[17,19]

Early and late complications following radiosurgery of brain metastases are relatively few.[15,18,20] Acute reactions induced by brain oedema occur in 7–10% of patients within two weeks following treatment.

4. Aims

The aim of this study was to assess treatment results and selected prognostic factors in patients with brain metastases from lung cancer treated with linac-based radiosurgery.

The following factors were subject to analysis:

- Age
- Gender
- Karnofsky performance status
- Primary disease status (controlled or uncontrolled)
- Local stage of primary disease
- Presence of extracranial metastases
- RPA class
- Histological type
- Type of metastases with regard to the time between the occurrence and diagnosis of primary disease (premature, synchronous, metachronous)
- Number of brain metastases
- Location of brain metastases
- Dose in Gy
- Volume of the largest brain metastases
- Hb level
- Multiplicity of radiosurgical procedures
- WBRT applied before or after radiosurgery
- Chemotherapy applied after radiosurgery
- Lung cancer surgery applied before or after radiosurgery

5. Materials and methods

5.1. *Material*

The study sample consisted of 83 patients with single or few (2–4) intracranial metastases from lung cancer treated with radiosurgery from February 2006 to September 2008. The study was retrospective in nature.

All patients were treated with a linear-based radiosurgery system (BrainLab) with immobilisation using a frameless stereotactic thermoplastic mask. After mask fixation, all patients underwent computed tomography simulation. MRI scans with T1 postgadolinium were fused to CT and used to delineate the tumour with 2 mm margin. The dose was prescribed to the 100% isodose line. Dose selection was determined by target volume, previous radiation, location and nearby critical structures.

The age of the patients ranged from 40 to 82, the mean age was 61. Males accounted for 69% of the study group.

The most prevalent histopathological type was adenocarcinoma occurring in 37 patients (47%), followed by squamous cell carcinoma, with 20 patients (25%) affected. Patients with non-small cell lung cancer accounted for 91% of cases (76 patients), while those with small cell lung cancer represented

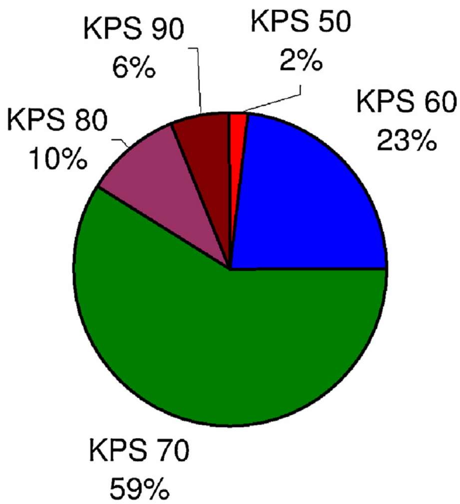

Fig. 1 – Karnofsky performance status.

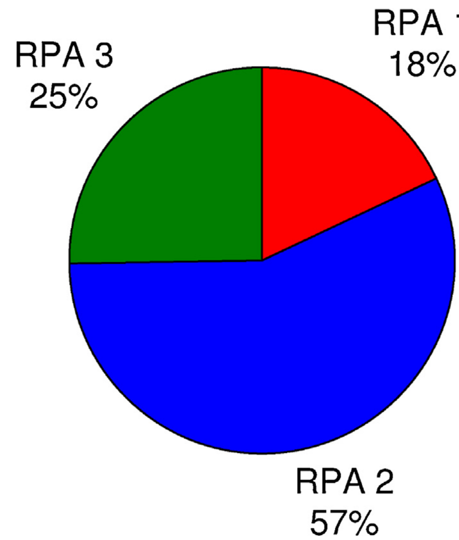

Fig. 2 – RPA classes.

9% (7 patients). The group of SCLC patients was small in our study and radiosurgery in this group was used not as a first line treatment, but only when WBRT was previously used (prophylactically or for cure).

Most of the patients had locally advanced lung cancer at diagnosis, 54% had stage IIIB and 18% stage IIIA cancers. The presence of brain and extracranial metastases, which as well known is a stage IV qualification criterion, was not taken into consideration while evaluating local stage of disease. The disease was in progression in as many as 64% of patients being subjected to radiosurgery.

Extracranial metastases occurred in 29 patients (35% of cases), mostly to the bones, liver and adrenals. In 55% of cases (46 patients), brain metastases occurred within two months following the diagnosis of lung cancer (premature in 12% and synchronous in 43%), metachronous metastases occurred in 45% of cases (37 patients).

Brain metastatic foci were treated mostly with doses of 18 Gy (37% of treated foci), 91% of patients were treated with doses ranging from 14 to 24 Gy. The volume of the largest focus was mostly up to 5 cm^3 (33%), foci of up to 15 cm^3 represented 82% of the total.

Single foci were managed in 69% of cases, two foci in 24% of cases, three in 6% and four in 1% of cases. Metastases were most commonly located in the parietal lobe (54%) and frontal lobe (25%).

The most patients showed Karnofsky performance status of 70 (59%) (Fig. 1). The largest proportion of them (57%) fell into the RPA class II (Fig. 2).

The study involved a univariate and multivariate analyses of selected survival prognostic factors and the time before deterioration of neurological status. The univariate analysis was performed using the Kaplan–Meier method. The statistical variation of the factors was assessed with the log-rank test with significance at $p = 0.05$. The multivariate analysis used the Cox's proportional hazards model with significance at $p = 0.05$.

6. Results

Mean survival for the whole group of 83 patients was 7.8 months from radiosurgery and 11 months from the diagnosis of brain metastases. The survival probability from radiosurgery and diagnosis of brain metastases for the whole group is shown in Figs. 3 and 4.

6.1. *Univariate analysis*

Univariate analysis showed the following factors to have a statistically significant impact on patients' survival:

- RPA class
- Karnofsky performance status
- Primary disease status (controlled or uncontrolled)
- Multiplicity of radiosurgical procedures
- Haemoglobin level
- Dose in Gy
- Presence of extracranial metastases
- Volume of the largest metastases

No statistical variation was found for the following factors:

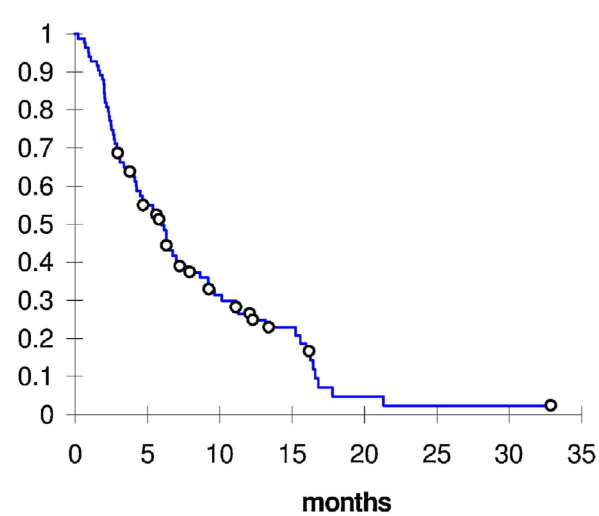

Fig. 3 – Survival probability in relation to the time from RS.

Table 3 – Prognostic factors whose statistically significant impact was shown by the univariate analysis.

Factor	Mean survival (months)	95% confidence interval	*p* value
RPA prognostic class			<0.0001
RPA1	13.2	10.1–16.4	
RPA2	8.2	6.7–9.7	
RPA3	2.2	1.6–2.7	
Karnofsky performance status			0.001
≥70	9.9	8.2–11.6	
<70	5.7	3.8–7.7	
Primary disease status			0.001
Controlled	10.7	8.1–13.3	
Uncontrolled	5.9	4.6–7.1	
Multiplicity of radiosurgery			0.002
Multiple RS	13.4	9.0–17.7	
Single RS	6.9	5.6–8.1	
Haemoglobin level			0.02
≥7 mmol/l	8.4	6.7–10.0	
<7 mmol/l	4.7	2.0–7.4	
Dose			0.03
>18 Gy	9.9	7.0–12.7	
≤18 Gy	6.8	5.4–8.2	
Presence of extracranial metastases			0.04
No	9.1	7.3–10.9	
Yes	4.9	3.5–6.4	
Volume of the largest brain metastasis			0.05
≤11 cm^3	8.7	6.9–10.8	
>11 cm^3	6.1	4.2–8.1	

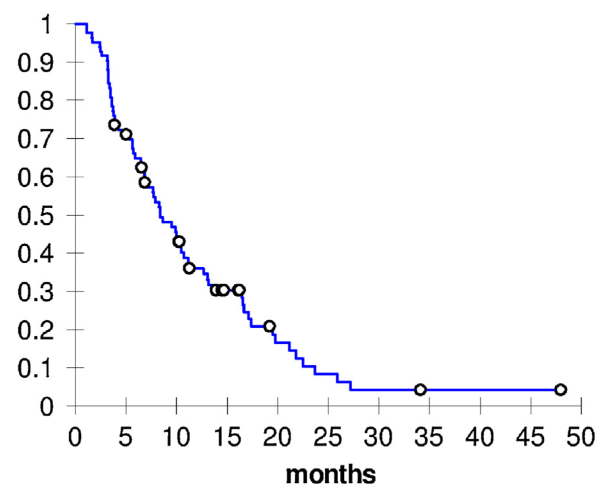

Fig. 4 – Survival probability in relation to the time to diagnosis of metastasis.

- Type of metastases with regard to the time between the occurrence and diagnosis of primary disease (premature, synchronous, metachronous)
- WBRT applied before or after radiosurgery
- Chemotherapy applied after radiosurgery
- Lung cancer surgery
- Histological type (adenocarcinoma vs. squamous cell carcinoma)
- Age
- Main histological type (non-small cell vs. small cell cancer)
- Number of brain metastases
- Local stage of primary disease
- Location of brain metastases
- Gender

The results of the univariate analysis are summarised in Tables 3 and 4.

The analysed sample showed a statistically significant relationship between survival and RPA class ($p < 0.0001$). Mean survival for the RPA class 1 was 13.2 months; for the RPA class 2, 8.2 months; and for the RPA class 3, 2.2 months. The diagram of survival to RPA class relationship is shown in Fig. 5.

We found a statistically significant impact of Karnofsky performance status ($p = 0.001$). Mean survival in patients with KPS < 70 was 5.7 months, while in the group with KPS > 70 it was 9.9 months. The diagram of survival to KPS relationship is shown in Fig. 6.

In our study group, we showed a statistically significant impact of primary disease control on survival time ($p < 0.001$). Mean survival in patients with controlled primary disease was

Table 4 – Prognostic factors whose statistically significant impact was not shown by the univariate analysis.

Factor	*p* value
Type of metastasis with regard to the time between the occurrence and diagnosis of primary disease	0.17
WBRT applied before or after radiosurgery	0.18
Chemotherapy applied after radiosurgery	0.20
Lung cancer surgery	0.23
Histological type (adenocarcinoma vs. squamous cell carcinoma)	0.24
Age	0.58
Main histological type (non-small cell vs. small cell cancer)	0.65
Number of brain metastases	0.65
Local stage of primary disease	0.7
Location of brain metastasis	0.81
Gender	0.98

reports of practical oncology and radiotherapy 19 (2014) 19–29

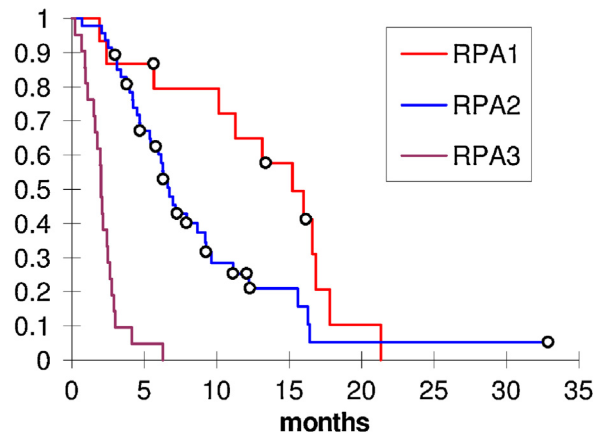

Fig. 5 – Survival probability in relation to RPA class.

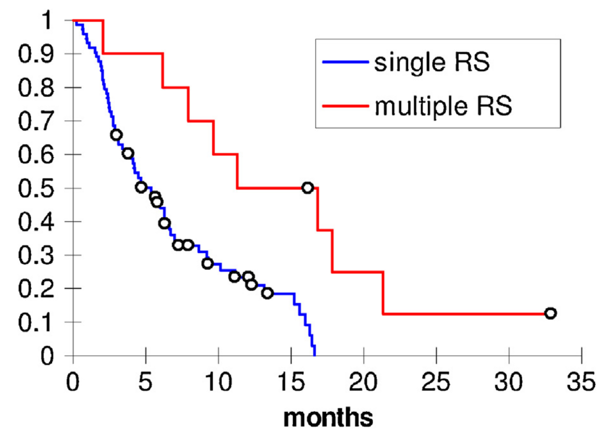

Fig. 8 – Survival probability in relation to RS multiplicity; $p = 0.002$.

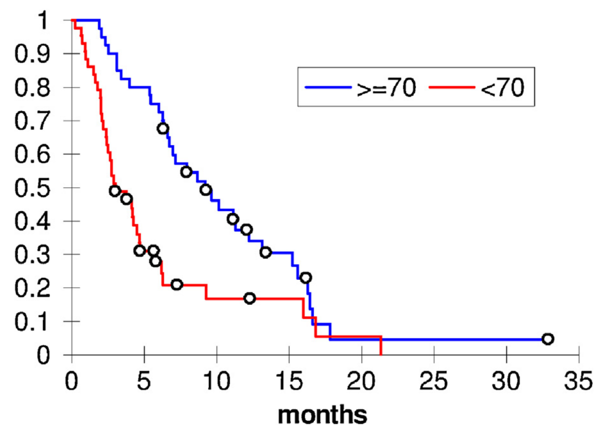

Fig. 6 – Diagram of survival in relation to Karnofsky performance status.

10.7 months, while in the group with uncontrolled primary disease it was 5.9 months. The diagram of survival to primary disease status is shown in Fig. 7.

In our study group, we showed a statistically significant impact of the multiplicity of radiosurgical treatments on survival time ($p < 0.002$). Mean survival in patients who had undergone a single radiosurgery was 6.9 months, while in the group treated with multiple treatments it was 13.4 months. Radiosurgical treatment of the patient which was used more than once was applied because of appearance of new lesion during follow up. We never treated the tumour previously irradiated by radiosurgery. The diagram of survival to multiplicity of treatment is shown in Fig. 8.

We found a statistically significant favourable effect of Hb level ≥7 mmol/l on survival ($p = 0.02$). Mean survival in patients with haemoglobin ≥7 mmol/l was 8.4 months vs. 4.7 months in those with haemoglobin <7 mmol/l. The diagram of survival to haemoglobin level is shown in Fig. 9.

We found a statistically significant impact of dose on survival ($p = 0.03$). Mean survival in patients treated with dose >18 Gy was 9.9 months vs. 6.8 months in those treated with dose ≤18 Gy. The diagram of survival to dose is shown in Fig. 10.

We also found a statistically significant favourable effect of the absence of extracranial metastases ($p = 0.04$). Mean survival in patients without extracranial metastases was 9.1 months, while in the group with extracranial metastases it was 4.9 months. The diagram of survival to occurrence of extracranial metastases is shown in Fig. 11

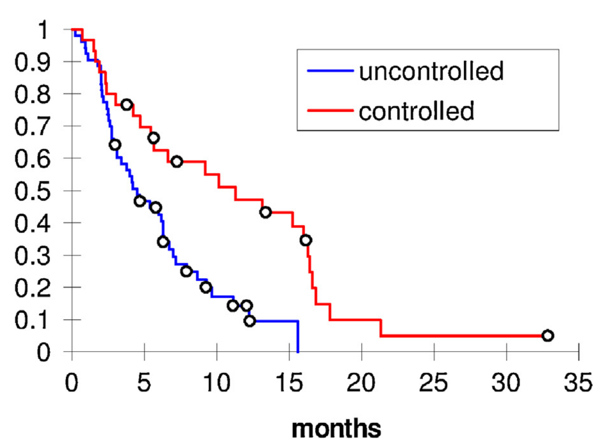

Fig. 7 – Survival probability in relation to primary disease status; $p = 0.001$.

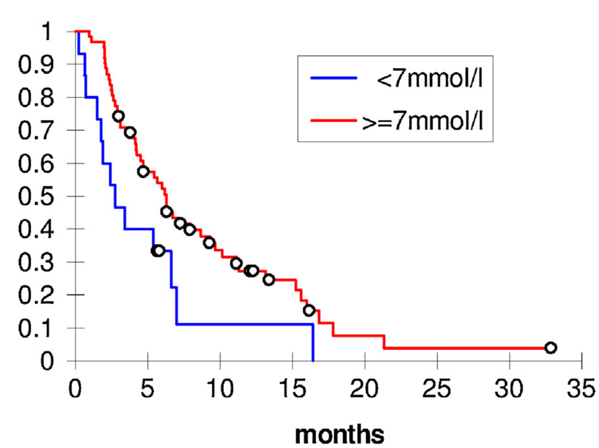

Fig. 9 – Survival probability in relation to haemoglobin level; $p = 0.02$.

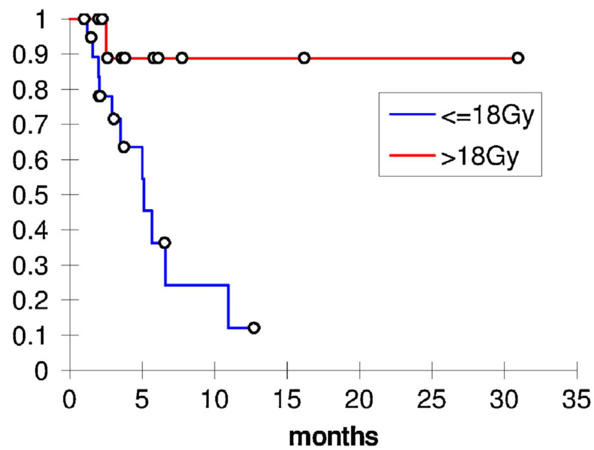

Fig. 10 – Survival probability in relation to dose; $p = 0.03$.

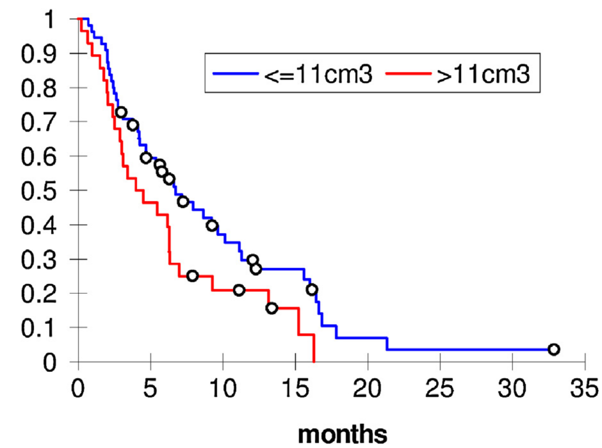

Fig. 12 – Survival probability in relation to the volume of the largest metastasis; $p = 0.05$.

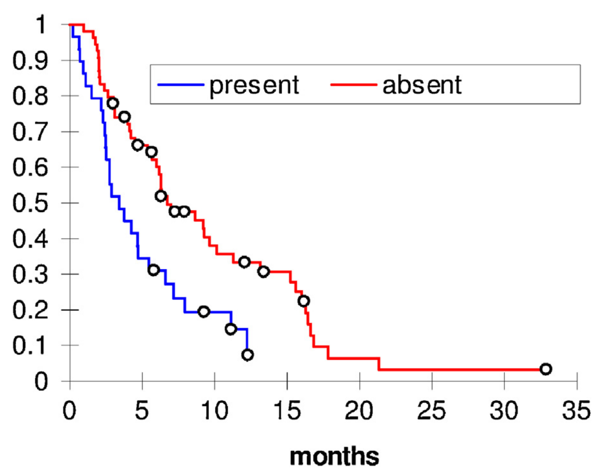

Fig. 11 – Survival probability in relation to the presence of extracranial metastases; $p = 0.04$.

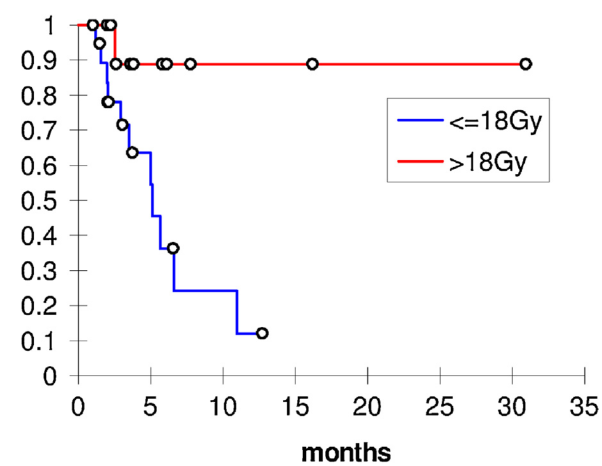

Fig. 13 – Probability of prolonging the time to brain local progression in relation to dose; $p = 0.02$.

In our study group, we showed a statistically significant favourable impact of the largest metastatic focus <11 cm^3 on survival ($p < 0.05$). Mean survival in patients in whom the volume of the largest metastases was less than or equal to 11 cm^3 was 8.7 months vs. 6.1 months in patients in whom the volume of the largest metastases was more than 11 cm^3. The diagram of survival to the largest metastases volume is shown in Fig. 12.

It was found that dose >18 Gy is a significant factor influencing improvement of local control in the brain ($p = 0.02$), as shown in Fig. 13. The mean time to progression after the administration of dose >18 Gy was 7.2 months vs. 5.7 months after a dose <18 Gy. A probability of a six-month local brain progression-free survival was 90% in the case of a dose >18 Gy vs. 80% for a dose <18 Gy.

A mean time to progression of controlled focus or emergence of new metastatic foci was 7.9 months. That time is similar to the mean time to deterioration of neurological symptoms, that is 7.1 months. In our sample, the mitigation or stabilisation of neurological symptoms was achieved in 94% of patients. This effect carried on for an average of 7.1 months.

Notably, no statistically significant relationship was found between age and survival time ($p = 0.58$). In our study, patients aged >65 account for 34% of the total sample.

6.2. *Multivariate analysis*

Due to the complexity of the RPA classification, two multivariate analyses were made under the study. The first multivariate analysis comprised all factors whose statistical significance was proved in the univariate analysis, except for assignment to a particular RPA class. The other multivariate analysis reflected the assignment to a RPA class and all factors except those covered by the RPA classification. The multivariate analysis used the Cox's proportional hazards model with significance at $p = 0.05$. Results of the multivariate are shown in Table 5. The first multivariate analysis showed a positive statistically significant impact on survival of the following factors: KPS > 70, lack of extracranial metastases, multiplicity of radiosurgical treatment. Death risk in patients with KPS < 70 was 10 times higher than in those with KPS > 70. Death risk in patients affected with extracranial metastases was 1.9 times

Table 5 – Multivariate analysis results.

Factor	Analysis without RPA		Analysis with RPA	
	Risk of death (CI[a])	p value	Risk of death (CI[a])	p value
RPA prognostic class	Not included			
RPA1			1	
RPA2			1.7 (0.9–3.6)	0.12
RPA3			15.1 (6.1–37.6)	<0.0001
Karnofsky performance status			Not included	
≥70	1			
<70	10.0 (5.1–19.7)	<0.0001		
Presence of extracranial metastases			Not included	
No	1			
Yes	1.9 (1.1–3.2)	0.02		
Multiplicity of RS				
Multiple RS	1		1	
Single RS	3.1 (1.2–8.3)	0.03	2.9 (1.1–7.9)	0.04
Haemoglobin level				
≥7 mmol/l	1		1	
<7 mmol/l	1.6 (0.9–3.0)	0.13	1.73 (0.9–3.2)	0.09
Volume of the largest brain metastasis				
≤11 cm^3	1		1	
>11 cm^3	1.4 (0.8–2.4)	0.23	1.3 (0.7–2.6)	
Primary disease status			NOT INCLUDED	
Controlled	1			
Uncontrolled	1.5 (0.8–2.8)	0.26		
Dose				
>18 Gy	1		1	
≤18 Gy	1.2 (0.6–2.4)	0.55	1.1 (0.5–2.3)	0.93

[a] 95% confidence interval.

higher than in those free of extracranial metastases. Death risk in patients treated with single radiosurgery was 3.1 times higher than in those treated with multiple radiosurgery treatments. The other multivariate analysis showed a statistically significant impact on survival of the following factors: assignment to the RPA class 1 as opposed to the RPA class 3 and multiplicity of radiosurgical treatment. Death risk in patients of the RPA class 3 was 15.1 times higher than in those of the RPA class 1. Death risk in patients treated with single radiosurgery was 2.9 times higher than in those treated with multiple radiosurgery.

7. Discussion

Mean survival in patients with brain metastases from lung cancer treated with radiosurgery, as reported in literature, ranges from 4.5 to 13.5 months.[21–31] Those data apply to patients treated with both a gamma knife and accelerator. Some studies, where higher survival times were achieved, tended to assume certain exclusion criteria.[21–23,25,26,28,29,31] For example, patients with low Karnofsky performance status were excluded. Our study covered all patients who had undergone radiosurgery in the above indicated period. Our mean survival times differed substantially from survival times of patients untreated (approx. 1 month) and of those treated with steroids (approx. 2 months)[32] or WBRT alone (approx. 3–5 months).[7,33] Rodrigus et al.[34] reported results for 250 patients with brain metastases from primary lung cancer treated with WBRT in 1993–1998. They reported a mean survival time of only 3.1 months. Also in Fernandez et al. study[40] median survival time for group of 39 patients (14 with lung cancer) treated with WBRT was only 3 months. Those results varied considerably from mean survival times in our study sample and other investigations of radiosurgical treatment. The outcome of radiosurgery, on the other hand, is similar to that of surgery. Wroński et al.[1] published results for surgery of brain metastases from primary lung cancer in 231 patients managed in 1976–1991. Mean survival time in that group was 11 months, and post-operative mortality rate was 3%. In that study, 61% of patients exhibited KPS > 80.

Statistically significant relationship between survival and RPA class ($p < 0.0001$) which was found in our study was also demonstrated by other authors.

Mean survivals for particular RPA classes are different than those reported by Gaspar. They are higher in the RPA classes I and II and comparable in the RPA class III. Therefore, a conclusion may be drawn that radiosurgical treatment is superior to other types of therapy only for patients representing the RPA classes I and II, i.e. those with KPS > 70. Mean survival was 13.2 months (7.1 months in Gaspar's study) for the RPA class I; 8.2 months (4.2 months in Gaspar's study) for the RPA class II; and 2.2 months (2.3 months in Gaspar's study) for the RPA class III. The results demonstrate benefit of radiosurgery in properly selected patients.

Comparably to other authors' studies,[24,27,29,31] we found a statistically significant impact of Karnofsky performance status ($p = 0.001$). Mean survival in patients with KPS < 70 was 5.7 months, while in the group with KPS > 70 it was 9.9 months.

Hoffman et al. reported a mean survival time of 9.3 in the KPS 50–60 group, 7 months in the KPS 70–80 group and 13.9 months in the KPS 90–100 group.

This correlation accounts for the difference in the mean survival between particular authors' reports as arising from different proportions of patients representing specific performance statuses. A relatively high proportion of patients in our sample (25%) had KPS < 70, which certainly affected the mean survival time being somewhat lower than in other studies.

In our study group a statistically significant impact of primary disease control on survival time ($p < 0.001$) was demonstrated. Mean survival in patients with controlled primary disease was 10.7 months, while in the group with uncontrolled primary disease it was 5.9 months. The impact has also been proved in many other studies.[21,23,24,27,29–31] Sheehan et al. reported a mean survival of 16 months in a controlled primary disease group vs. 7 months in an uncontrolled group. In the study by Kim et al., the values are 12 and 2 months, respectively.

In our study group, we showed a statistically significant impact of the multiplicity of radiosurgical treatments on survival time ($p < 0.002$). Multiplicity of radiosurgical treatments means treatment by radiosurgery new lesion found during follow up. This impact may be due to the fact that most of the patients subjected to multiple radiosurgery had initially been qualified to better RPA classes. Consequent longer survival enabled the patients to be observed longer and treated with radiosurgery as a life-saving treatment in cases of brain progression (management of a new metastatic focus).

Statistically significant favourable effect of Hb level ≥7 mmol/l on survival ($p = 0.02$) is likely to be due to the fact that the level of haemoglobin affects a patient's general health status and tumour oxidation, thus making it more sensitive to radiation.

Statistically significant impact of dose on survival ($p = 0.03$) which was found in our study was not confirmed in studies of other authors.[21,23,30]

Statistically significant favourable effect of the absence of extracranial metastases ($p = 0.04$) which was found in our study was also reported by Hoffman et al.[23] who showed that a mean survival in patients without extracranial metastases was 13.9 months vs. 8.6 months in patients with extracranial metastases.

The impact of dose on local brain progression-free survival which was found in our study was also demonstrated by Hoffman et al.[23] In this study, the probability of a six-month local brain progression-free survival was 95% in the case of a dose >18 Gy, 82% for a dose between 15 Gy and 18 Gy, 28% for a dose <15 Gy.This impact seems to be obvious because the dose is connected with tumour volume.

A mean time to progression of controlled focus or emergence of new metastatic foci was 7.9 months. That time is similar to the mean time to deterioration of neurological symptoms, that is 7.1 months. Mitigation or stabilisation of symptoms is the main objective behind treatment of brain metastases, leading to the improvement of the quality of life. In our sample, the mitigation or stabilisation of neurological symptoms was achieved in 94% of patients. This effect carried on for an average of 7.1 months. This result is similar to the mean survival, meaning that most of the patients, owing to the treatment, did not suffer from deterioration of neurological symptoms. The result is comparable to those reported by other authors. In the study by Zabel et al.,[30] an improvement or stabilisation was found in 95% of patients in a retrospective analysis of 86 patients with brain metastases from NSCLC treated with radiosurgery using an accelerator.

No statistically significant relationship was found in our study between age and survival time ($p = 0.58$). It is very interesting and useful outcome.

Life expectancy constantly rises both in the Western countries and Poland. Older people are exposed to an increased risk of cancer. Cancer incidence grows with age. The incidence of brain metastases is also correlated with age. Around 15% of patients with brain metastases from various types of cancer are over 65 years of age.[4] Older patients are often treated with less radical methods, compared to younger patients, due to a commonly shared belief that their treatment tolerance may be lower and expected survival time, shorter. Although 50% of cancers occur in patients aged over 70,[35] the knowledge on treatment tolerance in older people is limited, as such patients tend to be excluded from prospective randomised trials due to their age or concomitant diseases. Therefore, data derived from retrospective studies are of great importance.

Noel et al.,[36] responding to this need, carried out a retrospective analysis of 117 patients aged >65 with brain metastases treated with radiosurgery using accelerators (45% of the study group consisted of lung cancer patients). Mean survival in that group was 8 months, which is more than in the RTOG 9508 study (6.5 months) where patients over 65 years of age represented only 35% of the study sample. Local control was 95%. This treatment was well tolerated. This leads to a conclusion that patient's age should not be a disqualifying criterion for radiosurgical treatment.

Opposite to other authors we did not proved the female gender and histological type of adenocarcinoma to be independent favourable prognostic factors in lung cancer patients.[39]

8. Treatment tolerance

Radiosurgery is well tolerated by patients. Only 5% of our study group showed exacerbation of any of earlier occurring neurological symptoms within the first month. Four patients (5%) had to be operated for foci that had earlier been given radiosurgical treatment. It is hard to establish, however, whether the increase in tumour volume producing serious clinical symptoms was caused by post-radiation necrosis or tumour progression due to the loss of local control. Patients in our study group did not complain about difficulties in memorising or deterioration of cognitive abilities, which is quite a frequent (occurring in 11% of cases) symptom following WBRT.[37,38]

9. Conclusion

1. Radiosurgery performed with a linear accelerator is a safe and effective treatment modality for brain metastases from primary lung cancer. It allows a radical treatment of metastases even in the critical structures of the brain, such as the brain stem, which are inaccessible for surgery, and treatment of old patients.

2. Survivals achieved owing to radiosurgery were much longer than those following whole brain radiation therapy and comparable to those reported for patients treated with surgery. We demonstrated a clear favourable effect of radiosurgery on survival following radiosurgery applied to the RPA1 and RPA2 patients, but not the RPA3 patients (with Karnofsky performance status <70), for whom symptomatic treatment should be considered.
3. Our study did not find a statistically significant relationship between age and treatment outcome. Age should not be a reason for disqualifying patients from radiosurgical treatment.
4. Our results proved that Karnofsky performance status is the factor of the strongest impact on prognosis. The multivariate analysis confirmed after the univariate analysis that the following factors have a statistically significant impact on patients' survival:
- Karnofsky performance status >70,
- Assignment to the RPA class 1 as opposed to the RPA class 3,
- Absence of extracranial metastases,
- Multiplicity of radiosurgical procedures (treatment of new lesions)
5. The factors whose statistically significant positive impact on survival was shown in the univariate analysis, but not confirmed by the multivariate analysis, include:
- Controlled primary disease,
- Haemoglobin level >7 mmol/1,
- Dose >18 Gy,
- Volume of the largest brain metastases $\leq$11 cm^3.

The multivariate analysis did not confirm a prognostic value of those factors probably due to their impact on patient's performance status.
6. Dose >18 Gy is a significant factor in improvement of brain local control.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Wronski M, Arbit E, Burt M, Galicich JH. Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. *J Neurosurg* 1995;**83**(4):605–16.
2. Simon G, Wagner H. Small cell lung cancer. *Chest* 2003;**123**:259–71.
3. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;**37**(4):745–51.
4. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999;**43**(4):795–803.
5. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys* 2000;**47**(4): 1001–6.
6. Mehta MP, Rozental JM, Levin AB, et al. Defining the role of radiosurgery in the management of brain metastases. *Int J Radiat Oncol Biol Phys* 1992;**24**(4):619–25.
7. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1980;**6**(1):1–9.
11. Kjellberg RN, Davis KR, Lyons S, Butler W, Adams RD. Bragg peak proton beam therapy for arteriovenous malformation of the brain. *Clin Neurosurg* 1983;**31**:248–90.
12. Pozza F, Colombo F, Chierego G, et al. Low-grade astrocytomas: treatment with unconventionally fractionated external beam stereotactic radiation therapy. *Radiology* 1989;**171**(2):565–9.
13. Shiu AS, Kooy HM, Ewton JR, et al. Comparison of miniature multileaf collimation (MMLC) with circular collimation for stereotactic treatment. *Int J Radiat Oncol Biol Phys* 1997;**37**(3):679–88.
14. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;**47**(2):291–8.
15. Alexander E, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. *J Natl Cancer Inst* 1995;**87**(1):34–40.
16. Breneman JC, Warnick RE, Albright REJ, et al. Stereotactic radiosurgery for the treatment of brain metastases. Results of a single institution series. *Cancer* 1997;**79**(3):551–7.
17. Joseph J, Adler JR, Cox RS, Hancock SL. Linear accelerator-based stereotaxic radiosurgery for brain metastases: the influence of number of lesions on survival. *J Clin Oncol* 1996;**14**(4):1085–92.
18. Flickinger JC, Kondziolka D, Lunsford LD, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. *Int J Radiat Oncol Biol Phys* 1994;**28**(4):797–802.
19. Majhail NS, Chander S, Mehta VS, Julka PK, Ganesh T, Rath GK. Factors influencing early complications following Gamma Knife radiosurgery. A prospective study. *Stereotact Funct Neurosurg* 2001;**76**(1):36–46.
20. McKenzie MR, Souhami L, Caron JL, Olivier A, Villemure JG, Podgorsak EB. Early and late complications following dynamic stereotactic radiosurgery and fractionated stereotactic radiotherapy. *Can J Neurol Sci* 1993;**20**(4):279–85.
21. Kim YS, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for patients with nonsmall cell lung carcinoma metastatic to the brain. *Cancer* 1997;**80**(11):2075–83.
22. Williams J, Enger C, Wharam M, Tsai D, Brem H. Stereotactic radiosurgery for brain metastases: comparison of lung carcinoma vs. non-lung tumors. *J Neurooncol* 1998;**37**(1):79–85.
23. Hoffman R, Sneed PK, McDermott MW, et al. Radiosurgery for brain metastases from primary lung carcinoma. *Cancer J* 2001;**7**(2):121–31.
24. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control. *J Neurosurg* 2003;**98**(2):342–9.
25. Li B, Yu J, Suntharalingam M, et al. Comparison of three treatment options for single brain metastasis from lung cancer. *Int J Cancer* 2000;**90**(1):37–45.
26. Gerosa M, Nicolato A, Foroni R, et al. Gamma knife radiosurgery for brain metastases: a primary therapeutic option. *J Neurosurg* 2002;**97**:515–24.

27. Serizawa T, Ono J, Iichi T, et al. Gamma knife radiosurgery for metastatic brain tumors from lung cancer: a comparison between small cell and non-small cell carcinoma. *J Neurosurg* 2002;**97**(5 dodatek):484–8.
28. Kong DS, Lee JI, Nam DH, et al. Prognosis of non-small cell lung cancer with synchronous brain metastases treated with gamma knife radiosurgery. *J Korean Med Sci* 2006;**21**(3):527–32.
29. Noel G, Medioni J, Valery CA, et al. Three irradiation treatment options including radiosurgery for brain metastases from primary lung cancer. *Lung Cancer* 2003;**41**(3):333–43.
30. Zabel A, Milker-Zabel S, Thilmann C, et al. Treatment of brain metastases in patients with non-small cell lung cancer (NSCLC) by stereotactic linac-based radiosurgery: prognostic factors. *Lung Cancer* 2002;**37**(1):87–94.
31. Chidel MA, Suh JH, Reddy CA, Chao ST, Lundbeck MF, Barnett GH. Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases. *Int J Radiat Oncol Biol Phys* 2000;**47**(4):993–9.
32. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF. Intracerebral metastases in solid-tumor patients: natural history and results of treatment. *Cancer* 1981;**48**(2):384–94.
33. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;**322**(8):494–500.
34. Rodrigus P, de Brouwer P, Raaymakers E. Brain metastases and non-small cell lung cancer. Prognostic factors and correlation with survival after irradiation. *Lung Cancer* 2001;**32**(2):129–36.
35. Fentiman IS, Tirelli U, Monfardini S, et al. Cancer in the elderly: why so badly treated? *Lancet* 1990;**335**(8696): 1020–2.
36. Noel G, Bollet MA, Noel S, et al. Linac stereotactic radiosurgery: an effective and safe treatment for elderly patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2005;**63**(5):1555–61.
37. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology* 1989;**39**(6):789–96.
38. Nieder C, Schwerdtfeger K, Steudel WI, Schnabel K. Patterns of relapse and late toxicity after resection and whole-brain radiotherapy for solitary brain metastases. *Strahlenther Onkol* 1998;**174**(5):275–8.
39. Niemiec M, Głogowski M, Tyc-Szczepaniak D, Wierzchowski M, Kępka L. Characteristics of long-term survivors of brain metastases from lung cancer. *Rep Pract Oncol Radiother* 2011;**16**(2):49–53.
40. Fernandez G, Pocinho R, Travancinha C, Netto E, Roldao M. Quality of life and radiotherapy in brain metastasis patients. *Rep Pract Oncol Radiother* 2012;**17**(5):281–7.