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ORIGINAL ARTICLE

Survival and prognostic factors in patients treated with stereotactic radiotherapy for brain metastases

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ABSTRACT

Background. Stereotactic radiation therapy (SRT) of brain metastases is used with good effect around the world, but no consensus exists regarding which prognostic factors that are related to favourable or unfavourable prognosis after the treatment. A better definition of these factors will ensure a more precise application of the treatment.

Material and methods. A consecutive cohort of the 198 patients treated for brain metastases with SRT without concurrent whole-brain radiation therapy at our department from 2001 to 2012 was retrospectively analysed.

Results. Median survival was seven months and median time to clinical cerebral progression was eight months. The multivariate analysis revealed age ≥ 65 years, Performance Status ≥ 2, extracranial metastases and size of metastasis > 20 mm as independent prognostic factors related to shorter survival. No factors were independently related to clinical cerebral progression.

Conclusion. We identified four prognostic factors related to survival after SRT for brain metastases. The grouping of patients by these factors is useful to determine the level of treatment. We discourage the delivery of SRT to patients with 3–4 unfavourable prognostic factors because of the very short median survival of two months.

Metastasis to the brain is observed in up to 40% of all patients with metastatic cancer and it is the most common malignant neoplasm in the brain [1]. Patients with brain metastases are at risk of rapid deterioration of neurological and neurocognitive functions in addition to having a very short life expectancy, most often just 1–2 months [2–4]. High dose corticosteroid treatment and whole-brain radiation therapy (WBRT) has been the mainstay in the treatment of brain metastases, providing an increase in median survival to about four months [5]. Steroids often provide instant relief of the patients' symptoms, but have only little, if any, effect on overall survival [4]. WBRT is easy to deliver, but provides most patients with only a short-lived disease control and only a few months of prolonged survival [6,7].

The therapeutic focus has now moved to more aggressive local therapies, such as surgical resection and stereotactic radiation therapy [2]. Surgery can be used with good effect, but it requires an accessible location of the metastases plus location in a non-eloquent area – two requirements often not met. Surgery remains, however, the best choice for tumours presenting with significant mass effect or tumours causing increased intracranial pressure, due to the immediate effect of removing such tumours [8].

Stereotactic radiation therapy (SRT) is a non-invasive, fast and efficient treatment of brain metastases. The lesion is targeted with a number of radiation beams from different angles, thus delivering a high dose to the target while sparing adjacent healthy tissue. SRT is considered equally effective compared to surgery as treatment for brain metastases in terms of local control and survival, with the added benefit of being able to target lesions deep in the brain, which are not accessible for surgery.

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However, this presumed equality has not yet been demonstrated in a randomised trial. Furthermore, SRT can be delivered on an outpatient basis without the need for hospitalisation.

Even though metastatectomy and SRT of brain metastases are most often considered as palliative treatments, they still allow patients to live for up to several years after the treatment with few or no symptoms from the metastases. Earlier studies have shown a median survival after SRT or surgery of 7–10 months, with some patients surviving much longer [9–12].

It is important to identify patients with a more favourable prognosis who may benefit from aggressive and potentially curable treatment, and patients with a poorer prognosis who should be offered less aggressive and only palliative treatment. This identification is important for the following reasons: It ensures the most appropriate treatment for the individual patients and reduces the risk of side effects in patients who may not benefit from active therapy. Furthermore, it minimises treatment expenses and allows immediate therapy to poor prognosis patients, because WBRT can be delivered right away. Finally, it ensures relevant information to the patients and their families about the prognosis.

Prognostic factors indicating favourable survival after SRT are still not clear-cut, and a further identification and validation of these factors is of tremendous value in selecting the right patients for SRT. The aim of this study was to identify prognostic factors related to overall survival after SRT for oligo-brain metastases in a large heterogeneous patient cohort treated in a single institution.

Material and methods

Patients

This retrospective study included all patients who received SRT for brain metastases at Aarhus University Hospital between 2001 and 2012.

A list of patients was obtained from the electronic Danish National Registry of Patients. Data was extracted from the patients' paper and electronic chart. A few patients' general practitioner was contacted for information regarding disease progression and cause of death. At the time of the decision to offer SRT, all patients had WHO Performance Status (PS) of 0–2, a maximum diameter of the largest metastasis of 30 mm, histologically confirmed cancer and controlled or controllable extracerebral tumour sites. Besides, before 2009 patients with a maximum of two brain metastases were considered eligible for SRT, from 2009 and onwards this was raised to three metastases. We chose to exclude patients treated later than 31 December 2012 to allow for a minimum follow-up time of six months.

Stereotactic radiation therapy

The SRT was delivered using linear accelerator (LINAC) technique. Before 2009, patients were immobilised by an invasive head frame (BrainLAB, Feldkirchen, Germany). After 2009, patients were immobilised by a thermoplastic mask and set-up by cone-beam computed tomography (CT) scan. In 2012, a modified mouth bite system (Elekta, Stockholm, Sweden) was introduced for use in patients with adequate dentition.

For all patients, dedicated treatment planning contrast enhanced CT and magnetic resonance imaging (MRI) scans were acquired. The CT scan was reconstructed with an interslice distance of 2 mm. The MRI was acquired as T1 weighting in the transversal orientation. The MRI was co-registered to the treatment planning CT scan by anatomical fusion using the iPlan software (BrainLAB).

Manual contouring of the tumour and auto-contouring of normal tissues were performed by use of the iPlan TPS and subsequent treatment planning was performed by use of the iPlan, Helax (Helax, Uppsala, Sweden) or Eclipse (Varian, Palo Alto, CA, USA) TPS.

The clinical target volume (CTV) was defined by the gross tumour on the contrast enhanced MRI and the PTV was formed by addition of a margin of 2 mm. The prescription dose was the mean dose to the CTV and minimum doses of 95% and 90% to the CTV and PTV were aimed at.

All patients received prednisolone 100 mg during the treatment period and this was tapered to lowest possible dose a few weeks later.

Statistical analysis

The primary endpoint was overall survival and the secondary endpoint was clinical cerebral progression. Clinical cerebral progression was defined at the time of progression of cerebral symptoms or radiological tumour progression. These were calculated using the Kaplan-Meier method as the time interval between the first day of SRT and either time of death/clinical cerebral progression or last follow-up.

The potential prognostic factors tested were selected from a review of the existing literature. They included age, gender, World Health Organization Performance Status (WHO PS), site of primary disease, primary disease histology, number of involved extracranial organs, whether the patient received systemic anticancer treatment less than two months before the presentation of brain metastasis, time

interval between first diagnosis of cancer and brain metastasis, location of the metastases above or below the tentorium, number of brain metastases, diameter of largest metastasis and SRT fractionation schedule. A separate analysis was performed on the patients' symptoms leading to the diagnosis (seizures, headache, paresis). The status of the factors was determined at the first delivery of SRT (Hence a patient might have worsened and then be classified as WHO PS 3, e.g. or the metastases might have increased in size). The multivariate analysis included the factors that were significantly ($p < 0.05$) related to survival in a univariate analysis. Statistical analysis was performed using the statistics package SPSS 18 (IBM, Armonk, NY, USA).

Results

We identified 198 patients eligible for the study. Characteristics of the patients are shown in Table I.

Table I. Patient and tumour characteristics (N = 198).

Characteristics	No. of patients/median
Gender	
Female	126 (63.6%)
Male	72 (36.4%)
Age	61 years (range 25–85 years)
< 65 years	128 (64.6%)
≥ 65 years	70 (35.4%)
Primary tumour site	
Lung cancer	95 (48%)
Breast cancer	34 (17.2%)
Renal cancer	23 (11.6%)
Malignant melanoma	13 (6.6%)
Colorectal cancer	13 (6.6%)
Other/unknown primary	20 (10.1%)
WHO performance status	
0–1	176 (88.9%)
≥ 2	22 (11.1%)
Number of extracranial organs involved	
0	120 (60.6%)
1	32 (16.2%)
2	26 (13.1%)
≥ 3	20 (10.1%)
Diameter of largest metastasis	20 mm (range 5–57 mm)
< 21 mm	106 (53.5%)
≥ 21 mm	92 (46.5%)
Number of brain metastases treated	
1	128 (64.6%)
2	51 (25.8%)
3	17 (8.6%)
4	2 (1%)
Supra- or infratentorial location of metastases	
Supratentorial	142 (71.7%)
Infratentorial	56 (28.3%)
SRT fractionation	
1 fraction	121 (61.1%)
> 1 fraction	77 (38.9%)
Median dose per fraction	
1 fraction	20 Gy [range 9–25 Gy]
3 fractions	9 Gy [4–10 Gy]
Clinical presentation	
Seizures	35 (17.7%)
Neurologic deficit	125 (63.1%)
Headache	87 (43.9%)
Asymptomatic	22 (11.1%)
Systemic medical therapy < 2 months before brain dissemination	
Yes	44 (22.2%)
No	154 (77.8%)
Time interval between primary and brain metastasis	
< 1 year	108 (54.5%)
≥ 1 year	90 (45.5%)

One hundred and thirty-nine patients received SRT as initial treatment for brain metastases, whereas 59 patients had previously been treated for brain metastases. Of these 59 patients, nine had previous surgery (4.5%), 18 had WBRT (9.1%), 26 had surgery + WBRT (13.1%) and six had other treatments or combinations of treatment (3%). Five of the 59 patients had small-cell lung cancer and received prophylactic WBRT (25 Gy in 10 fractions except 1 patient receiving 20 Gy in 4 fractions). The remaining 54 patients received WBRT for brain metastasis. The WBRT was given as 30 Gy in 10 fractions in 21 patients, 20 Gy in 4 fractions in 21 patients and 20 Gy in 5 fractions in one patient. Thirty-one patients had local failure of their previously treated brain metastases, whereas 12 patients had new brain metastases. Eleven patients had both local failure and new brain metastases.

One hundred and sixty-six patients received SRT as the only local therapy for metastases, whereas 32 patients received SRT concurrent with surgery (19 patients; 9.6%) or WBRT (7 patients; 3.5%), or surgery and WBRT (3 patients; 1.5%). Ten of these patients received SRT as a boost treatment. For the 19 other patients, the concurrent treatment was given to other synchronous brain metastases not treated with SRT.

One hundred and twenty-six patients did not receive any further treatment for brain metastasis except for corticosteroids, whereas 72 patients received subsequent WBRT, SRT and/or systemic medical treatment for recurrent or new brain metastases. Thirty-one patients had a local failure of at least one metastasis treated with SRT, whereas 25 patients had developed new brain metastases. Sixteen patients had both local failure and new brain metastases.

Survival

At the time of the last follow-up (10 July 2013), 21 patients were alive and 177 patients were deceased. Of these, 114 died with neurologic progression whereas 63 died without neurologic progression, i.e. of systemic disease progression or intercurrent disease. The median overall survival was 7.0 months, and the one- and two-year survival rates were 38% and 17%.

The results of a univariate analysis on the impact on overall survival by primary tumour site and histology are shown in Table II. Only 12 patients with metastases of squamous cell carcinoma histology had significantly shorter median survival than the total group of patients. Patients with breast cancer as primary tumour site showed a tendency for prolonged survival, though not significant.

The results of the univariate analysis of the remaining prognostic factors' impact on overall survival are shown in Table III. Age less than 65 years, PS 0–1, no extracranial metastases and diameter of brain metastasis less than 21 mm were related to improved survival. On multivariate analysis including these four factors, they all remained significantly related to favourable survival (Table IV).

Regarding the presence of extracranial metastases, grouping the patients as 0–1 extracranial metastases versus two or more extracranial metastases had similar significance, but we chose the above mentioned

Table II. Univariate analysis of overall survival according to primary tumour site and histology.

Factor	Median survival in months [95% CI]	Log rank test
Primary tumour site:		
Lung/other sites (N = 95/103)	8.0 [6.0:10.0] vs. 7.0 [4.9:9.1]	p = 0.666
Breast/other sites (N = 34/164)	12.0 [7.8:16.2] vs. 6.0 [4.3:7.7]	p = 0.169
Renal/other sites (N = 23/175)	9.0 [4.6:13.4] vs. 7.0 [5.3:8.7]	p = 0.706
Melanoma/other sites (N = 13/185)	4.0 [1.9:6.1] vs. 7.0 [5.5:8.5]	p = 0.861
Colorectal/other sites (N = 13/185)	6.0 [< 0.0:14.2] vs. 7.0 [5.4:8.6]	p = 0.167
Other or unknown/other sites (N = 20/178)§	4.0 [< 0.0:8.4] vs. 8.0 [6.3:9.7]	p = 0.246
Primary histology:		
Adenocarcinoma/other histologies (N = 145/53)	8.0 [5.7:10.3] vs. 5.0 [2.6:7.4]	p = 0.502
Anaplastic carcinoma/other histologies (N = 14/184)	10.0 [< 0.0:22.8] vs. 7.0 [5.5:8.5]	p = 0.161
Melanoma/other histologies (N = 13/185)	4.0 [1.9:6.1] vs. 7.0 [5.5:8.5]	p = 0.861
Squamous cell carcinoma/other histologies (N = 12/186)	4.0 [< 0.0:9.1] vs. 7.0 [5.4:8.6]	p = 0.007
Non-small cell carcinoma NOS/other histologies (N = 10/188)	5.0 [1.9:8.1] vs. 7.0 [5.4:8.6]	p = 0.927
Other/other histologies (N = 4/194)*	3.0 [1.0:5.0] vs. 7.0 [5.5:8.5]	p = 0.119
Overall (N = 198)	7.0 [5.5:8.5]	N/A

NOS, not otherwise specified.
§Other/unknown: Cardia cancer (N = 6), unknown primary (N = 6), ovarian cancer (N = 3), 1 bladder cancer, 1 cervix cancer, 1 oropharyngeal cancer, 1 rhinopharyngeal cancer and 1 sarcoma; *Other: Neuroendocrine carcinoma (n = 2), urothelial carcinoma (n = 1), sarcoma (n = 1).

Table III. Univariate analysis of overall survival according to other potential predictive factors.

Factor	Median survival in months [95% CI]	Log rank test
Male/female gender (N = 72/126)	7.0 [4.9:9.1]/7.0 [4.7:9.3]	p = 0.333
Age ≥/< 65 years (N = 70/128)	6.0 [4.4:7.6]/9.0 [6.2:11.8]	p = 0.013
WHO PS ≥/< 2 (N = 22/176)	2.0 [1.3:2.7]/9.0 [7.1:10.9]	p < 0.001
Number of involved extracranial organs		p = 0.038
0 (N = 120)	8.0 [5.6:10.4]	
1 (N = 32)	7.0 [2.9:11.1]	
2 (N = 26)	5.0 [2.5:7.5]	
≥ 3 (N = 20)	4.0 [1.1:6.9]	
Systemic treatment ≤/> 2 months before brain metastasis (N = 44/154)	7.0 [5.3:8.7]/7.0 [5.0:9.0]	p = 0.251
≤/> 1 year between primary diagnosis and brain metastasis (N = 108/90)	6.0 [4.6:7.4]/9.0 [5.0:13.0]	p = 0.189
Infratentorial/supratentorial location (N = 56/142)	8.0 [4.9:11.1]/6.0 [4.1:7.9]	p = 0.528
> 1 or 1 brain metastasis (N = 70/128)	9.0 [6.6:11.4]/7.0 [5.3:8.7]	p = 0.624
Largest metastasis ≥/< 21 mm (N = 92/106)	6.0 [4.8:7.2]/10.0 [7.5:12.5]	p = 0.024
> 1 or 1 fraction of SRT (N = 77/121)	6.0 [4.3:7.7]/9.0 [6.7:11.3]	p = 0.058

division of zero versus one or more extracranial metastases because the groups were more equal in size.

The patients were grouped according to numbers of unfavourable prognostic factors and the survival according to prognostic groups is displayed in Figure 1. This shows a pronounced difference in median survival between the prognostic groups of patients with zero prognostic factors (28 patients; median survival 21 months), 1–2 prognostic factors (147 patients; median survival 7 months) and 3–4 prognostic factors (23 patients; median survival 2 months; $p < 0.001$). This is also reflected by the two-year survival rates of 47%, 14% and 0%, respectively. No patients had all four prognostic factors, but if a patient were to have all four, he would have an equally poor survival as patients with three factors or possible worse, so we have included them in the same group.

Steroid usage was separately investigated in the selected groups of patients who had a follow-up visit at three and six months after SRT. Patients who were prescribed a lower dose of steroids three months after SRT had a significantly longer median survival compared to those without any reduction (13 months vs. 8 months; $p = 0.027$), but this difference was not significant six months after SRT (15 months vs. 12 months; $p = 0.181$).

Symptoms of brain metastasis

An analysis of the patients' symptoms of brain metastasis was performed separately. This analysis revealed that seizures were related to favourable survival compared to headache and paresis (11 months vs. 7 months; $p = 0.031$). This also held true in multivariate analysis (hazard ratio 0.571; $p = 0.024$).

Clinical cerebral progression

At the time of last follow-up, 116 patients had experienced clinical cerebral progression, whereas 82 were without progression. Median time to clinical cerebral progression was eight months, and actuarial one- and two-year clinical cerebral progression-free rates were 36% and 18%, respectively.

The only significant factors related to clinical cerebral progression in univariate analysis were size of largest metastasis less than versus more than 21 mm (9 months vs. 6 months; $p = 0.028$) and single fraction versus multi-fraction SRT (9 months vs. 6 months; $p = 0.032$).

These factors did not reach the level of significance in a multivariate analysis.

Discussion

The present study identified four prognostic factors related to the most favourable survival after SRT for brain metastases: Age less than 65 years, a PS of less than 2, no involved extracranial organs and size of largest metastasis less than 21 mm. The importance of these factors is underlined by the large difference in median survival and two-year survival-rate for

Table IV. Multivariate analysis of overall survival in months including the significant factors.

Factor	Hazard ratio	95% CI	Significance test
Age ≥ 65 years (N = 70)	1.55	[1.12:2.11]	p = 0.005
WHO PS ≥ 2 (N = 22)	3.39	[2.09:5.48]	p < 0.001
Largest metastasis ≥ 21 mm (N = 92)	1.51	[1.12:2.04]	p = 0.007
Involvement of one or more extracranial organs (N = 78)	1.40	[1.02:1.91]	p = 0.036

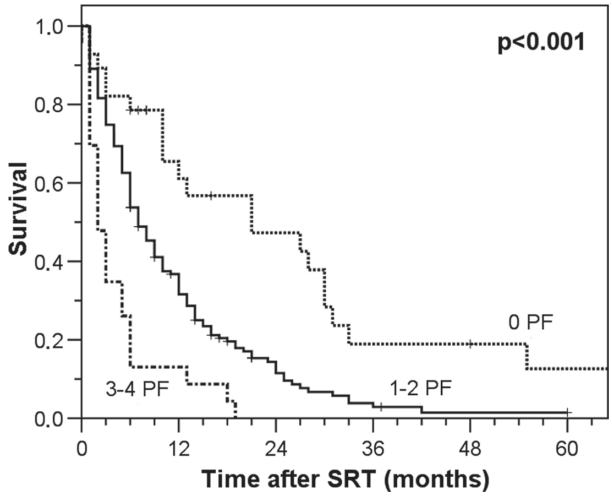

Figure 1. Survival according to number of unfavourable prognostic factors. Two patients still alive 124 and 96 months past SRT, respectively. PF, prognostic factors.

patients with 0, 1–2 and 3–4 unfavourable prognostic factors.

A number of previous studies have been looking at prognostic factors for overall survival after SRT for brain metastases; however, many studies included only a small number of patients [13,14]. With such a heterogenic patient group being treated, it is necessary to include a sufficient number of patients to ensure consistent and clear conclusions that cannot be attributed to other causes.

A similar study from Italy of 206 patients showed a median survival of 14.1 months [15]. Multivariate analysis revealed Karnofsky PS $\geq$ 80 and stable extracranial disease as the only prognostic factors. Performance status also correlated significantly to survival in a study of 172 patients from Pennsylvania, which revealed a median survival of 8.0 months [9]. Multivariate analysis revealed stable primary tumour status, age less than 60 years and Karnofsky PS $\geq$ 90 as prognostic factors. In addition, they also found a poorer survival for melanoma histology. Histology was also an important prognostic factor in a study from Connecticut of 334 patients that showed a median survival of 8.1 months [16]. Prognostic factors indicating improved survival in this study were total tumour volume less than 5 cm^3, controlled systemic disease, less than four brain metastases and breast cancer histology. Number of brain metastases was also of significance in a study from Minnesota [17]. This study involved 73 patients with a median survival of 7.8 months. Absence of extracranial disease, Karnofsky PS $\geq$ 70 and only one brain metastasis were the prognostic factors related to improved survival. In contrast to this, a recent study from Texas showed no survival difference according to the number of brain metastases, but improved survival with smaller total tumour volume [18]. This study on 251 patients showed a median survival of 11.1 months. Absence of extracranial disease, total tumour volume less than 2 cm^3, less than 60 years of age and better diagnosis-specific graded prognostic assessment (DS-GPA) were prognostic factors in multivariate analysis. Age was also a significant factor in an older study from Boston of 248 patients [10]. This study revealed a median survival of 9.4 months. Stable extracranial disease and age less than 60 years were the only prognostic factors in a multivariate analysis.

These previous studies on prognostic factors after SRT have yielded ambiguous results. Not a single factor has consistently shown significance in the literature. We decided to include all previously reported prognostic factors in our survival analysis. The median survival of seven months in the present study was relatively short, but we expect this to be due to differences in the patient selection [15,17]. Each of the factors age, metastasis size and number of extracranial metastatic sites yielded a relative risk of 1.4–1.5. Only WHO performance status was a strong prognostic factor (RR = 3.4) that strongly separated patients into short and average survivors. However, combination of the four prognostic factors yielded strong prognostic information; it allowed identification of subgroups of patients with very poor and patients with more favourable survival.

The present study did not identify any tumour type with unfavourable outcome; however, squamous cell carcinoma as primary histology had a less favourable survival compared to the other histologies, but the low number of patients with this histology discouraged us from ascribing this finding any prognostic value. The tendency for breast cancer patients to experience a prolonged survival is consistent with the findings in other studies, which also show an increased survival for these patients [16,19].

The number of extracranial metastatic sites was directly related to poor survival. This has also been shown in patients with various primary tumours receiving WBRT for brain metastases [20–22].

There was a tendency for better outcome in patients treated with 1 fraction (typically of 20 Gy) compared to more than 1 fraction (typically 27 Gy in 3 fractions), but the difference did not reach the level of significance in univariate analysis. Patients treated with fractionated SRT had lesions that were too large for single-fraction or they were located in an eloquent area that did not allow single-fraction SRT. These patients are therefore expected to have a poor survival and the findings of the present study indicate that fractionated SRT is feasible for patients with large metastases and metastases located close to the brain stem or other critical structures. This has also been shown in earlier studies [23].

The patients with seizures as symptoms of brain metastasis had a better survival than the other patients, a finding we attribute to the fact that fairly small metastases can cause seizures, allowing for early discovery of brain metastasis. Symptoms of brain metastasis are not tumour-associated prognostic factors, however, so we chose not to include this parameter in our multivariate analysis.

This study underlines the fact that prognostic factors indicating survival after SRT do exist and are useful to distinguish which patients to offer aggressive treatment with SRT in the hope of long-term survival. Cho et al. found a median survival of 17.7 months in patients with zero unfavourable prognostic factors compared to a median survival of only 1.5 months in patients with all three unfavourable prognostic factors identified in their study [17]. Hasegawa et al. found a median survival of 28 months in their patients with zero unfavourable prognostic factors [9]. Based on the large survival difference found in our study we discourage the delivery of SRT to patients with 3–4 unfavourable prognostic factors due to the poor median survival of just two months. These patients are better off just receiving WBRT right away and are not at risk of developing long-term neurocognitive decline because of their short life expectancy. On the contrary, patients with zero unfavourable prognostic factors should not be treated with WBRT initially, because of their long life expectancy and risk of developing neurocognitive decline after WBRT, but instead be treated with SRT and followed closely with regular scans to enable early detection of recurrence [24].

Compared to other proposed scoring systems (RPA, BSBM, SIR etc.), the strength of our system lies in its simplicity. The status of all four factors can be easily determined at the initial clinical evaluation and the most appropriate treatment can be initiated immediately.

The use of SRT as a boost to WBRT was tested against SRT without WBRT in a randomised clinical trial [25]. The study revealed that addition of WBRT reduced the risk of brain tumour recurrence, but it did not translate into a survival benefit. A second randomised study, as discussed above, was prematurely interrupted due to excess cognitive dysfunction measured at four months after therapy in patients receiving WBRT in addition to SRT [24]. Whether SRT should be used alone or as a boost to WBRT is still a matter of controversy. We decided to use SRT alone without WBRT and if this affects the survival outcome of the present study is unknown, but not expected.

Shortcomings of this study include the long time span of 12 years from which the patients were gathered. Furthermore, it was not possible to obtain the images of all scans of the patients. Therefore, local control could not be included as an endpoint for the analysis. The study is limited by its retrospective study design and the cohort size of 198 patients, which is most clearly reflected in the paucity of patients with brain metastases from the more rare primary sites such as ovary, bladder, cervix etc.

The scoring system with four prognostic factors introduced in this study and the different survival times found should be verified in a study on a separate cohort of patients with brain metastases.

However, our study still showed a sizable difference in survival among the groups of prognostic factors. We encourage the use of this knowledge in the decision-making and selection of patients with brain metastases for SRT.

Conclusion

This study shows that prognostic factors related to improved survival after SRT for brain metastasis do exist and should be taken into consideration when selecting the best treatment for patients with brain metastasis. We introduced a scoring system based on four prognostic factors that allowed identification of patients with poor, average and more favourable survival. Based on the results of our study, we discourage delivering SRT to patients with 3–4 unfavourable prognostic factors, due to the poor median survival of only two months for this group of patients.

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