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Symptom response after palliative radiotherapy for patients with brain metastases

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Abstract

Whole brain radiotherapy (RT) is frequently used to palliate symptoms in patients with brain metastases, but the palliative benefit to patients has not been well documented. We conducted a longitudinal observational prospective study of patients receiving standard RT (20 Gray (Gy)/5 fractions) for symptomatic brain metastases. End-points were observer rating of neurological symptoms, patient-rated symptoms, performance status, neurological functional status, cognitive function and quality of life (QOL). Median survival for the 75 patients was 86 days (95% confidence interval (CI): 65–101 days). At 1 month, 19% of patients showed an improvement or resolution of presenting symptoms, 23% were stable and 55% had progressed or died. Patient-rated symptoms were increased at 1 month in comparison to baseline data. Only 4 patients had an improved performance status and 22 were stable. Many patients with brain metastases have a short life expectancy and may not benefit from even short duration radiation schedules. Further effort is needed to optimise patient selection and tailor treatment appropriately.

Keywords: Brain metastasis; Radiotherapy; Palliation; Symptom response; Quality of life

1. Introduction

Brain metastases occur in approximately 25% of patients with cancer [1]. They are a cause of major morbidity and greatly shortened life expectancy. Treatment for most patients with multiple brain metastases consists of palliative radiotherapy (RT) to the brain, supplemented by steroids [2,3]. Solitary brain metastases in patients with good performance status and controlled extracranial disease may be amenable to a more aggressive approach, such as surgery with postoperative radiotherapy [4,5] or stereotactic radiosurgery [6]. Occasional patients do not receive RT, usually if they have poor performance status or if they are entirely asymptomatic [2].

In studies of RT, radiological imaging, observer-rated neurological symptoms, performance status and survival have all been used to assess response to RT [7–11]. The degree of benefit to the patient in terms of quality of life (QOL) and patient-rated symptoms has been less well described.

Many RT schedules are utilised, including 20 Gray (Gy) in five fractions, 30 Gy in 10 fractions, 36 Gy in 12 fractions and, in some countries, 12 Gy in 2 fractions [4,8,10]. The 20 Gy in five fractions schedule is the one most commonly employed in Canada [12]. No one RT schedule has been shown to have superior efficacy.

At a Canadian Consensus workshop on priorities in palliative RT held in 1995 [13], the existing evidence was discussed and a randomised study of observation versus palliative brain RT (20 Gy in five fractions) was proposed as the priority study for patients with multiple brain metastases [14]. Further discussions, however,

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revealed feasibility problems, most notably the perception that limited numbers of patients would be willing to be randomised to a RT versus no RT study. Similar issues and concerns about accrual to such a study were also being debated by UK oncologists [10]. Rather, a need was identified to better document the palliative benefit from the standard treatment policy of RT to patients with symptomatic brain metastases, utilising patient-based outcomes. To address that need, this longitudinal observational prospective study was commenced, with the following objectives: (i) to standardise the treatment and assessment of patients with brain metastases, (ii) to assess symptom response of patients following treatment with palliative RT of 20 Gy in five fractions to the whole brain, and (iii) to determine changes in QOL, performance status and survival following RT.

2. Patients and methods

2.1. Patients

From October 1997, all patients with symptomatic brain metastases referred to the Palliative Radiation Oncology Program (PROP) at the Princess Margaret Hospital were considered for the study. Inclusion and exclusion criteria are listed in Table 1. A control group of patients was identified by a retrospective chart audit of all patients with brain metastases from non-haematological malignancies treated with palliative whole brain RT over a concurrent 3 month period (July–September 1998) at our institution. In order to obtain a comparative cohort, patients who had undergone surgical excision and those entered into our study were excluded.

2.2. Details of treatment

All patients received RT consisting of 20 Gy in five daily fractions to the whole brain, usually on a cobalt unit. Field edges were determined through clinical mark-up, utilising bony landmarks of superior orbital ridge anteriorly and external auditory meatus or, in the case of posterior fossa tumours, inferior pinna of the ear posteriorly. Verification films on the treatment unit were taken on day 1 of RT to assure that they covered the target volume. Patients had already been prescribed steroids when assessed by the Radiation Oncologist. The dose and tapering of dexamethasone were standardised at 4 mg four times daily (qid) during RT and a uniform reduction over a 3 week period. The date of commencing steroids, response to steroid treatment, and steroid dose at initial and subsequent contacts was recorded.

Table 1
Inclusion and exclusion criteria

Inclusion criteria
Known diagnosis of cancer
Brain metastases confirmed by imaging
Neurological symptoms due to brain metastases
No contradiction to whole brain RT
Able to give informed consent
Literacy in English
Exclusion criteria
Prior surgical excision of solitary brain metastasis
Primary diagnosis of lymphoma or leukaemia
Previous radiotherapy of the brain

2.3. Outcome measures

All outcome measures were clinical, not radiological. The primary outcome measure for the study was symptom response as reported by the patient at 1 month following RT and recorded by an observer (clinical research nurse or oncologist). The 1 month time point was chosen as it is a common time for assessment following RT. Secondary outcome measures were patient-rated symptoms, performance status, neurological functional status, cognitive function, QOL and survival.

Assessment of neurological symptoms was performed at the initial clinic appointment prior to RT. The presenting neurological symptoms that prompted investigation for cerebral metastases were noted. One month following RT, information regarding status of neurological symptoms was recorded, and this information used to categorise symptoms as resolved, improved, stable or worse.

At the time of the commencement of this study, there was no existing symptom assessment tool specific for brain metastases. A symptom checklist was created for use in the study (Table 2), which was modelled after symptom items included in QOL questionnaires specific for brain cancer patients (Functional Assessment of Cancer Therapy brain subscale (FACT-Br) [15] and the European Organisation for Research and Treatment of Cancer brain cancer module (EORTC BCM 20) [16]) and supplemented by symptom information from the literature, with input from the investigators. The aim was to capture changes in symptoms associated with brain metastases and raised intracranial pressure, as well as to identify symptoms associated with treatment (RT and steroids). The resulting list of symptoms was piloted in a small group of patients to check for wording and comprehension. The symptom checklist consisted of 17 items, each scored on a four-point categorical scale (0 = not at all, 3 = very much). The maximum score attainable was 51, a higher score representing a greater level of symptoms. For analysis, symptoms were subdivided into those commonly associated with raised intracranial pressure (three items: headache, nausea,

Table 2
Patient completed symptom checklist

MONTHLY DIARY CARD Please circle the number that best describes HOW MUCH EACH OF THE FOLLOWING BOTHERED YOU IN THE PAST 24 H	NOT AT ALL	A LITTLE	MODERATELY	VERY MUCH
1. Headaches	0	1	2	3
2. Nausea (feeling sick to your stomach)	0	1	2	3
3. Vomiting (being sick to your stomach)	0	1	2	3
4. Burning in the stomach	0	1	2	3
5. Poor sleeping at night	0	1	2	3
6. Restlessness/irritability	0	1	2	3
7. Weight gain	0	1	2	3
8. Tiredness (fatigue)	0	1	2	3
9. Poor appetite	0	1	2	3
10. Hair loss	0	1	2	3
11. Decreased hearing	0	1	2	3
12. Leg weakness	0	1	2	3
13. Problems with balance	0	1	2	3
14. Difficulty walking	0	1	2	3
15. Arm or hand weakness	0	1	2	3
16. Speech problems	0	1	2	3
17. Other (please state)	0	1	2	3

vomiting); those associated with steroid use (four items: dyspepsia, poor sleep, restlessness, weight gain); possible sub acute side-effects of RT (four items: fatigue, anorexia, hair loss, decreased hearing); and those associated with brain metastases (five items: leg weakness, arm/hand weakness, balance problems, walking and speech difficulties). Of note, the symptoms associated with whole brain RT are not specific to RT treatment and could be construed as constitutional symptoms. Patients were given the opportunity to list additional symptom(s) (one item). Patients were asked to complete the checklist prior to RT, at weekly intervals for 1 month following RT and monthly thereafter for 6 months. This report is confined to the information gained at 1 month. A change in score from baseline to 1 month was calculated for all symptom groups.

Performance status was graded according to the Eastern Cooperative Oncology Group (ECOG) classification [17], and neurological functional status using the classification employed by the Radiation Therapy Oncology Group (RTOG) [8]. The 'Mini-Mental State' Examination (MMSE) was used to document cognitive function [18]. The Functional Assessment of Cancer Therapy (FACT) questionnaire with its validated brain subscale (FACT-Br) was chosen to assess QOL [15]. Survival was calculated from the date of entry into the study until death. Patients alive at the time of analysis were censored.

All patients were to be assessed at baseline (before RT, but after starting steroids) and 1 month following RT. Subsequent study contacts were to be carried out either at follow-up clinic appointments, if clinically feasible, or by telephone on a monthly basis for 6 months. If a telephone interview was undertaken, questions were asked about functional ability, neurological symptoms and current treatment, and the symptom checklist was completed. It was not possible to complete a MMSE during telephone contacts, but an attempt was made to record QOL data by mailing out the FACT-Br questionnaire, which the patient was asked to mail back when completed.

2.4. Statistical methods

The study sample size was not based on *a priori* considerations of statistical power, as there was no information in the literature on the expected symptom response after 20 Gy of RT given in five fractions. A target of 70 evaluable cases was set; accrual of 85 patients was completed in October 1999.

The 95% confidence interval (CI) for the proportion with symptom improvement was produced using the Normal approximation to the Binomial distribution.

Changes from baseline to 1 month in the overall symptom score and its four components were assessed for statistical significance using the paired t-test. The 95% confidence interval (CI) for the change in overall symptom score utilised Student's t distribution. The same test was also used to compare differences in overall QOL scores and MMSE changes from baseline to 1 month. To assess changes in neurological functional status, and ECOG performance status, the non-parametric equivalent of the paired t-test, the Wilcoxon matched pairs signed rank sum test [19], and the sign test (with continuity correction) were used.

The association between presence of oedema and response to steroids, and neurological symptom response and response to steroids, was tested in a 2×2 contingency table using Fisher's Exact test.

The survival plots were produced using the Kaplan–Meier estimate. RTOG classes were compared for overall survival using the log-rank test. The CI for the median survival time amongst study patients employed the method of Brookmeyer and Crowley [20].

Numerous endpoints were analysed (albeit, all specified in advance). One of the effects of this multiple testing is to increase the likelihood of a false-positive result. To mitigate this, we adopted a stricter P value (i.e. $P<0.01$) before claiming statistical significance.

Analyses were performed with SAS, while all plots were generated in S-Plus.

3. Results

3.1. Patients

A total of 85 patients were recruited onto the study. 10 patients were excluded from analysis: 3 patients chose to withdraw from the study soon after the baseline assessment, 1 could not complete forms due to communication problems, 5 patients did not receive a complete course of RT due to a deterioration in their clinical condition and 1 patient declined RT. The details of primary diagnosis and patient characteristics for the 75 remaining patients are shown in Table 3. This includes classification of patients into prognostic classes, based on the recursive partitioning analysis (RPA) of RTOG brain metastases trials [21,22]. Characteristics of the brain metastases, derived from pretreatment imaging, are shown in Table 4.

The number of patients available for the monthly assessments dropped off rapidly, due to death or frailty. At 1 month follow-up, information was available for 52 patients (69% of the study group). At 2 months, 22 patients (29%) had some or all assessments completed. At 3 months, the number was 16 (21%); at 4 months, 13 (17%), at 5 months, 7 (9%) and at 6 months, 6 (8%).

Median follow-up among the 7 cases still alive at the time of analysis was 224 days (range 172–640 days).

3.2. Observer-rated response to treatment

The symptom(s) that patients presented with are documented in Table 5. 22 patients (29%) complained of one symptom at presentation, 32 patients (43%) two symptoms, and 21 patients (28%) more than two symptoms.

At baseline, prior to RT, improvement in presenting neurological symptoms with steroid treatment was seen in 63 patients (84%), while 12 (16%) showed no response to steroids. No correlation was seen between the presence of oedema on radiological imaging and response to steroids: 49 out of 56 patients with documented

Table 3
Patient characteristics

Characteristic	$n=75$
Gender	n (%)
Female	44 (59)
Male	31 (41)
Age (years)	
Median (range)	62 (35–84)
ECOG performance status	
0	6 (8)
1	28 (37)
2	26 (35)
3	15 (20)
4	0
Primary tumour	
Lung	49 (65)
Breast	9 (12)
Unknown primary	7 (9)
Renal	3 (4)
Melanoma	3 (4)
Other	4 (5)
Presence of extracranial disease	
Yes	61 (81)
No	14 (19)
RTOG RPA prognostic class	
1	3 (4)
2	31 (41)
3	41 (55)

ECOG, Eastern Cooperative Oncology Group; RTOG RPA, Radiation Therapy Oncology Group, recursive partitioning analysis.

Table 4
Imaging characteristics of the brain metastases

Characteristic	$n=75$
Number of metastases	n (%)
Multiple	55 (73)
Single	20 (27)
Laterality	
Bilateral	41 (55)
Unilateral	33 (44)
Not specified[a]	1 (1)
Position of metastases	
Supra-tentorial	43 (57)
Intra-tentorial	4 (5)
Both	27 (36)
Not specified[a]	1 (1)
Presence of oedema	
Yes	56 (75)
No	9 (12)
Not specified[a]	10 (13)
Evidence of midline shift	
Yes	20 (27)
No	28 (37)
Not applicable	4 (5)
Not specified[a]	23 (31)
Size of largest metastasis	
$\leqslant 2$ cm	18 (24)
>2 to $\leqslant 3$ cm	17 (23)
>3 cm	12 (16)
Not specified[a]	28 (37)

[a] Not specified in computed tomography (CT) or magnetic resonance imaging (MRI) report.

oedema responded to steroids, whereas 7 out of 9 patients with no oedema responded to steroids ($P=0.6$). At the time of baseline assessment, 48 patients (64%) were taking 16 mg or more of dexamethasone daily; 20 (27%) were taking between 8 and 16 mg; and 7 (9%) were taking less than 8 mg. The median time that patients had been on steroids prior to assessment for RT was 14 days (range 0–51 days).

Change in neurological symptoms at one month following RT compared with baseline (pre-RT, after steroid therapy was commenced) is documented in Table 6. 14 patients showed improvement or resolution of symptoms at 1 month, a response rate of 19% (95% CI: 10–28%). 20 of 75 patients (27%) either died before the 1 month assessment (13 patients) or were too unwell to attend follow-up at 1 month (7 patients died 5–8 weeks following RT). 3 patients did not attend at 1 month, but were assessed subsequently: 1 patient had progressed at 2 months, and 2 patients had some improvement at 2 and 3 months, respectively.

When neurological symptoms at 1 month were compared with symptoms at initial presentation (prior to being started on steroids), a higher proportion of patients showed improvement. Resolution of neurological symptoms at 1 month follow-up was seen in 7 patients (9%), improvement in 15 patients (20%), stable symptoms in 19 patients (25%), and worse symptoms in 11 patients (15%). Reasons for the differences observed can be grouped into the following categories: (i) patients showing a response to steroids when seen pre-RT whose improvement was not sustained, and their symptoms at 1 month were equivalent to presentation (9 patients); (ii) patients whose symptoms had resolved when seen pre-RT, and who remained stable at 1 month (4 patients); (iii) patients whose symptoms had improved when seen pre-RT, and who remained stable at 1 month (3 patients); and (iv) patients showing a response to steroids when seen pre-RT whose improvement was not sustained, but their symptoms at 1 month were still better than at presentation (1 patient).

Patients who have shown no response to steroids are commonly thought less likely to respond to RT. Of 12 such patients (16%), 4 patients had improved neurological symptoms at one month, 4 were stable, 2 had worse symptoms, and 2 were deceased. The proportion of improved symptom responses at one month following RT among patients who had not responded to steroids (4/12) was not statistically significantly different than among patients who had responded to steroids (10/60) ($P=0.23$).

At 1 month, 20 patients had reduced their dexamethasone and 21 patients had discontinued it, although 5 patients were advised to restart in view of ongoing symptoms.

Table 5
Presenting neurological symptoms

Symptom	Number of patients ($n=75$)
	n (%)
Headache	29 (39)
Motor weakness	25 (33)
Altered mental status	23 (31)
Ataxia/balance problem	23 (31)
Dysphasia	11 (15)
Seizure	9 (12)
Nausea/vomiting	8 (11)
Visual problem	7 (9)
Sensory loss	6 (8)
Dizziness	3 (4)
Incoordination/dysarthria	3 (4)
Facial/neck pain	2 (3)
Lethargy	1 (1)

Table 6
Neurological symptom status at one month compared with baseline

Symptom response	$n=75$ *n* (%)
Resolved	3 (4)
Improved	11 (15)
Stable	27 (23)
Worse	21 (28)
Patient deceased at or soon after 1 month	20 (27)
No data	3 (4)

3.3. Symptom checklist

75 patients (97%) completed a symptom checklist at baseline and 42 patients (56%) completed a checklist at 1 month. In 41 cases, both were completed. Table 7 provides information on symptom checklist scores at baseline and 1 month and change in score from baseline to 1 month. Larger positive changes represent worse symptoms at one month compared with baseline.

The mean change in overall symptom score was +7.41 (95% CI: +5.11 to +9.71), indicating a higher symptom burden on average at 1 month compared with baseline. Statistically significant increases from baseline to 1 month are seen in overall symptoms, and in all symptom subgroups apart from those symptoms associated with steroid use. The box plots shown in Fig. 1 illustrate graphically baseline and 1 month scores for overall symptoms and for the four symptom subgroups. They show the median score and inter-quartile ranges for each assessment, and highlight the general worsening in symptoms.

3.4. Performance status

Information on performance status was available for all patients at baseline, and 52 patients at 1 month. The plot in Fig. 2 shows the number of patients at each

Table 7
Symptom checklist scores

Variable	Baseline mean (S.D.)	One month mean (S.D.)	Mean change (SEM)	*P* value
Overall symptoms	12.0 (5.95)	18.4 (8.40)	+7.41 (1.14)	<0.0001
Raised ICP	0.5 (0.93)	1.2 (1.51)	+0.73 (0.21)	0.001
Steroids	3.2 (2.28)	3.5 (2.69)	+0.59 (0.42)	0.17
RT	2.3 (1.67)	5.9 (2.80)	+3.80 (0.43)	<0.0001
Brain metastases	5.2 (3.25)	6.9 (3.94)	+2.20 (0.62)	0.001

S.D., standard deviation; SEM, standard error of the mean; RT, radiotherapy; ICP, intracranial pressure.

assessment with a classified ECOG performance status of 0–4. Of 52 patients with a score at both baseline and 1 month, 26 patients experienced a worsening of performance status and only 4 experienced an improvement ($P < 0.0001$); 22 patients remained stable. With the magnitude of the change incorporated in the analysis, instead of only direction of change, the degree to which patients worsened is statistically significantly more than the degree to which they improved ($P < 0.0001$).

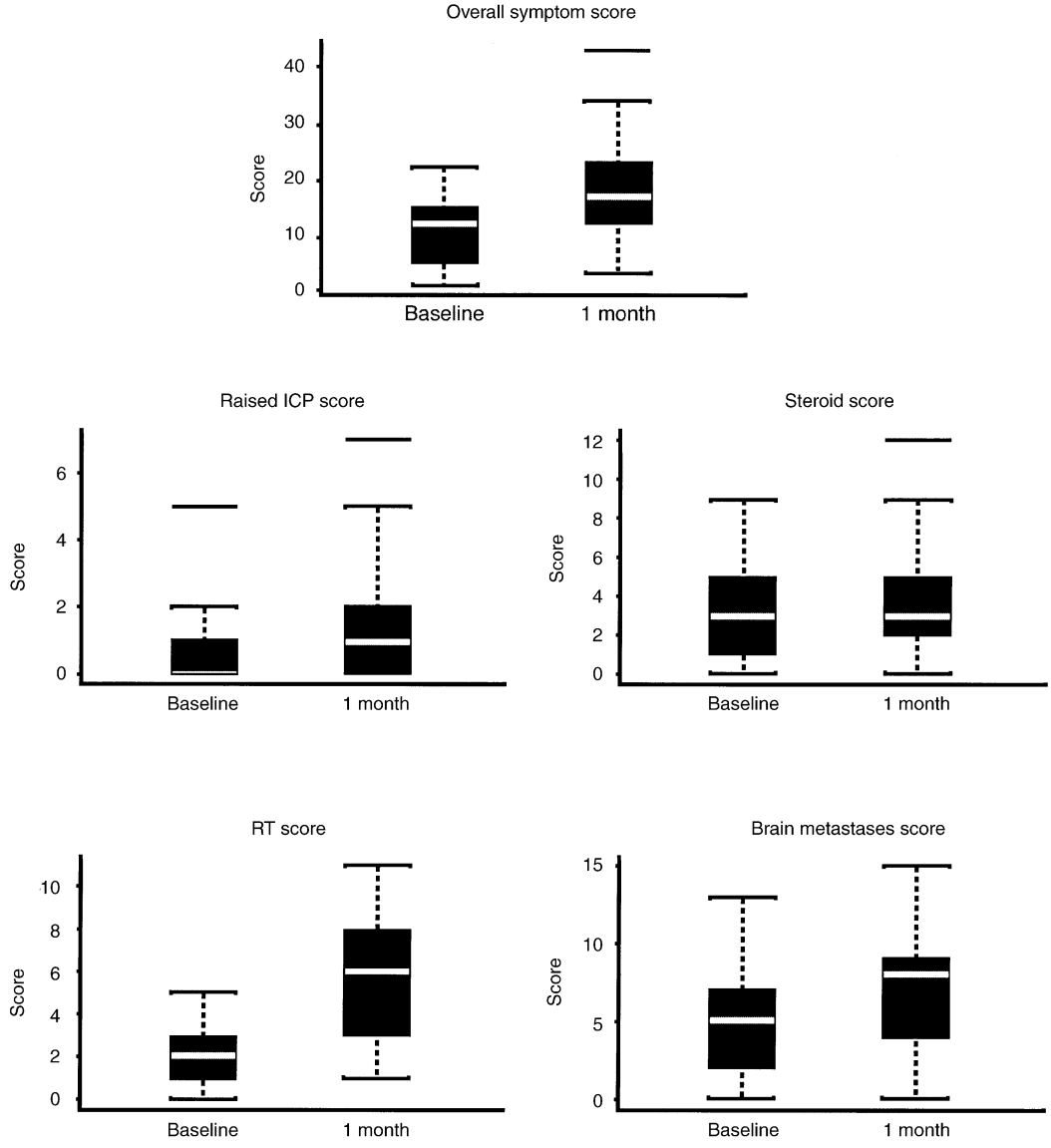

Fig. 1. Symptom checklist scores at baseline and 1 month.

3.5. Neurological functional status

Information on neurological functional status (Table 8) was available for all patients at baseline, and 52 patients at 1 month. The plot in Fig. 3 shows the numbers of patients at each assessment classified neurological functional class 1–4. Of 52 patients with scores at both baseline and 1 month, 24 were graded class 1 (minor or absent neurological findings) at baseline, therefore an improvement was not possible. 12 patients remained in class 1, and 12 had worse neurological functional status at 1 month. Overall, 21 of 52 patients experienced a worsening in score at 1 month, and 8 patients improved ($P=0.02$). In the remaining 23 cases, there was no change. Statistical analysis incorporating the magnitude of the observed changes, instead of simply the direction of change, gives $P=0.008$, i.e. the degree to which patients worsened was statistically significantly more than the degree to which they improved.

3.6. Cognitive function

Details of MMSE results collected at baseline and 1 month and change in score are provided in Table 9. 15 of 33 patients completing two evaluations scored higher at 1 month (median change +2, range +1 to +12); 6 patients scored the same; and 12 patients scored less at the second assessment (median change −2, range −10 to −0.5). Overall, there was no statistically significant change in the MMSE score from baseline to one month ($P=0.51$).

3.7. Quality of life

Details of the FACT-Br results from baseline and 1 month and change in score are provided in Table 9. Only 23 patients completed QOL questionnaires at both assessments. Of these, 8 patients had improved QOL at 1 month (median change +18.5, range +1 to +29), and 15 showed deterioration in QOL (median change −18, range −69 to −1). Overall, there was a mean deterioration in QOL from baseline to 1 month, but this difference was not statistically significant ($P=0.13$).

Table 8
Neurological function classification

1	Able to work or to perform normal activities; neurological findings minor or absent
2	Able to carry out normal activities with minimal difficulties. Neurological impairment does not require nursing care or hospitalisation
3	Seriously limited in performing normal activities. Requiring nursing care or hospitalisation. Patients confined to bed or wheelchair, or have significant intellectual impairment.
4	Unable to perform even minimal normal activities. Requiring hospitalisation and constant nursing care and feeding. Patients unable to communicate or in coma.

3.8. Survival

Median survival among the 75 patients was 86 days (95% CI: 65–101 days). The survival for these patients is shown in Fig. 4, along with survival results for the control group ($n=69$) ($P=0.28$; $X_1^2=1.17$). When the 75 study patients were divided according to RTOG prognostic classes a statistically significant difference in survival ($P=0.01$) was found between class 2 and class 3. Class 1 was not considered because it contained only 3 patients. Survival for class 2 and class 3 patients is shown in Fig. 5.

At study closure, 7 patients remained alive at 6, 7, 7, 8, 11, 13 and 21 months following RT.

3.9. Control group

The demographics of the control group were broadly similar to the study cohort, although there was a higher percentage of patients with breast cancer (35%). Survival is as documented in Fig. 4. There was no information

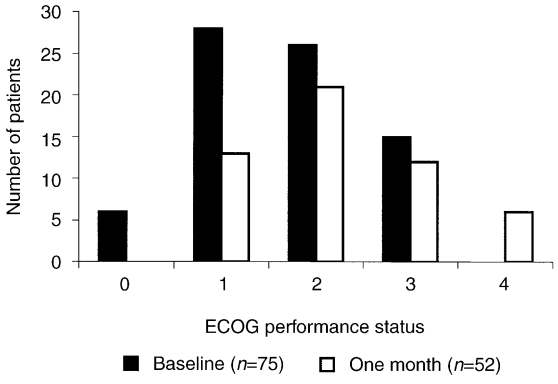

Fig. 2. ECOG performance status at baseline and 1 month.

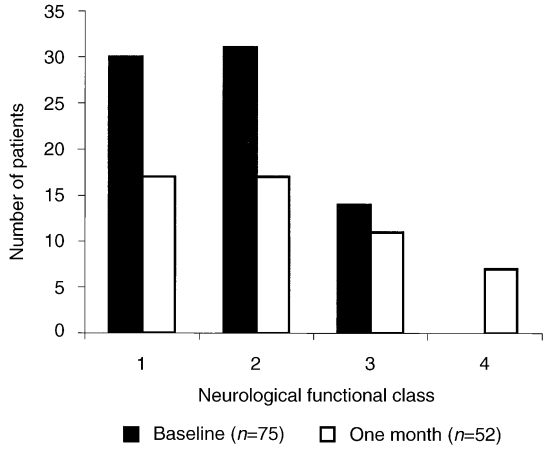

Fig. 3. Neurological functional class at baseline and 1 month.

Table 9
Cognitive function and quality of life (QOL)

	Baseline	One month	Change score
MMSE			
Number of patients	71	34	33
Mean (range)	2.59 (12 to 30)	26.3 (7 to 30)	+0.5 (SEM 0.75) (−10 to +12)
FACT-Br			
Number of patients	61	27	23
Mean (range)	123.1 (67 to 165)	118.7 (78 to 160)	−8.04 (SEM 5.08) (−69 to +29)

SEM, standard error of the mean; MMSE, 'Mini-Mental State' Examination; FACT-Br, The Functional Assessment of Cancer Therapy questionnaire with its validated brain subscale.

available in the charts to judge symptom control at 1 month following RT for most of the control patients.

4. Discussion

4.1. Symptom response after palliative RT

In most patients with brain metastases, especially those with multiple metastases, RT is given with the intent of palliation. Information in the literature is generally focused on reporting survival, radiological response, performance status, physician assessment of neurological status and treatment toxicity [7–11]. This study was conducted to further evaluate symptom control following whole brain RT with input from patients, which is of paramount importance in the assessment of palliative benefit from treatment.

There is no agreed upon method of assessing symptom response in this patient population. We have prospectively recorded the status of neurological symptoms, as recorded by clinician or clinical trials nurse and by patients' own assessment through completion of the symptom checklist. However, despite efforts to obtain a formal record of change in patient-rated symptoms from baseline to 1 month following RT, this information was only available for 55% of our patients. Not surprisingly, most patients (84%) had improvement of presenting symptoms with dexamethasone. However, at follow-up 1 month after whole brain RT, only 19% of patients had either improvement or resolution of their presenting neurological symptoms in comparison to just prior to RT. The low response rate was confirmed by patient reports of more and worse symptoms, worsening of performance status, and lack of improvement in QOL scores at 1 month follow-up. These findings indicate that many of our patients did not benefit from RT, and raises the question of whether some patients should not be treated with RT. It may be that the benefit of whole brain RT has been overstated, given that studies evaluating the effect of RT have generally not distinguished between response to steroids and response to RT [9–11]. In order

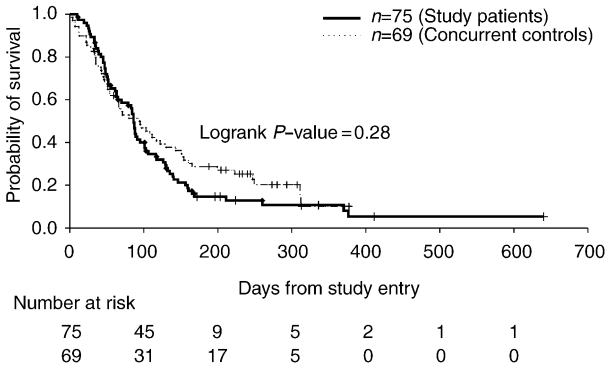

Fig. 4. Overall survival for the 75 study patients and 69 controls.

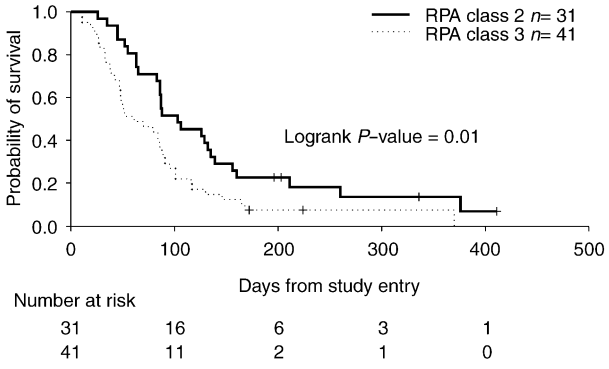

Fig. 5. Overall survival by RTOG RPA prognostic class (3 patients classified class 1 excluded).

to determine the true benefit of RT, its effect needs to be separated from the known effect of steroid therapy. This may indeed be very difficult, especially as steroids are being tapered after RT, and it may be hard to distinguish whether the lack of steroids or lack of RT effect are leading to clinical deterioration.

An alternative goal of RT may be prevention of symptom progression, particularly following an initial response to steroids. One may argue that patients with complete symptom resolution on steroids are not able to improve further with RT, and remaining stable at 1 month should be considered a favourable response. This was the case for 4 of our patients, so it does not greatly affect the conclusions reached.

4.2. Role of steroids in palliation of brain metastases

Interestingly, a randomised prospective study reported in 1971 comparing the use of steroids alone with steroids plus RT, concluded that the latter combination offered only slightly better survival and duration of remission than steroids alone [23]. Treating brain metastases patients with steroids alone is again under discussion: at the Consensus Workshop in Palliative Radiotherapy and Symptom Control held in Spring 2000 it was proposed that some poorer prognosis patients should not receive treatment with RT, although clear criteria were not defined. However, steroid treatment is not without its toxicity [24,25]. Our self-assessment symptom checklist revealed that steroid side-effects were indeed bothersome to our patients, and can occur fairly soon after the commencement of steroid treatment. Therefore, even patients with a survival expectancy of a few months may benefit by being able to reduce steroid dosage following RT, and thus reduce steroid-associated side-effects. However, our study also suggests that RT side-effects (especially hair loss, anorexia and fatigue) are not inconsequential, a fact that should also be taken into account when considering the pros and cons of RT.

4.3. Study limitations

Three potential limitations of our data are the use of a previously unvalidated symptom checklist, the question of internal validity due to lack of information on all patients, and the issue of external validity, i.e. generalisability. Although we did not formally attempt to validate the checklist, results suggested an increased symptom burden at 1 month, a finding that is consistent with the observed worsening of performance status. Data from other validated instruments measuring related constructs, namely QOL and neurological functional status, supported this finding. The symptom checklist does not, however, allow for the comparison of the severity or impact of different symptoms (e.g. radiation or constitutional symptoms versus steroid side-effects), i.e. it is not possible from our data to determine the exact burden of radiation toxicity on our patients.

Almost one-third of patients did not have a 1 month assessment. In an attempt to verify whether results were representative of the full cohort, baseline values were compared between those with and those without missing data and were found to be not statistically different. In most instances, cases with missing data had statistically significantly worse survival compared with those without missing data. This is not surprising given that we know that 20 of the patients who did not have a 1 month assessment were too unwell to attend or had died. This may mean that the results in this study paint a more optimistic picture than is the case in reality.

Patients recruited to our study had been referred to a specialised palliative radiotherapy programme to be assessed by a Radiation Oncologist for the first time. Patients previously treated by RT, e.g. adjuvant breast RT after lumpectomy, would have been seen by their original Radiation Oncologist for management of brain metastases and, thus, are underrepresented in our study population. Asymptomatic patients whose brain metastases were incidentally discovered were not included, as our aim was to assess symptom improvement after palliative RT. Patients treated with surgical resection and postoperative RT, stereotactic RT or higher dose RT were also not included. However, it is our opinion that the results represent a significant proportion of patients with brain metastases, which may be under-reported in studies that concentrate on surgery, high dose RT or other more aggressive therapies.

4.4. Generalisability of results

Are our patients representative of the general population of patients with brain metastases? Comparison of this patient cohort with all patients with brain metastases treated over a concurrent 3 month period at our institution and not entered onto this study revealed an almost identical survival. Thus, a bias towards entering poorer prognosis patients onto our study was not likely. The only notable difference between our study and the control group was the primary tumour type, with 35% of patients in the control group having a primary diagnosis of breast cancer, compared with 12% of the study group. Many of the large series in the literature include similarly high percentages of lung cancer patients [8,10,11,21,26], reflecting the frequency of lung as the primary tumour responsible for brain metastases. Thus, our patient cohort reflects clinical reality.

Why are our results so much poorer than in some RT studies? Applying the RTOG recursive partitioning model [21] to our data revealed that the patients recruited to our study represent a moderately poor prognosis group, which may be excluded from many randomised trials. The patient selection bias for some randomised controlled trials (RCT) likely results in patients with more favourable performance status, disease-free interval and primary diagnosis (breast rather than lung) [8,9,11]. In one recent RCT that included patients with similar characteristics (including performance status) to ours, reported by Priestman and colleagues, the median survival was 79 days [10]. Moreover, the proportion of patients who died before the 1 month follow-up or were too unwell to attend (34%) was similar to ours (27%).

5. Conclusions

The similarity of our results to those from the UK multicentre trial strengthens our observation that many patients with brain metastases have a very short life expectancy and may not benefit from even short duration palliative radiotherapy schedules. Further effort is needed to optimise patient selection for radiotherapy, so that treatment can be tailored appropriately. There is a need for a practical and reliable prognostic index to identify patients' prognosis, as there is a proportion of patients with brain metastases in whom an aggressive approach is warranted. Poor prognosis patients may be more optimally managed with steroids alone; proper assessment and follow-up of these patients in clinical trials continues to be a practical and methodological challenge for research in this area.

Palliative RT should be offered with the intent and assurance that patients' QOL will be maintained or improved, not as a reflex response to offer 'therapy' to a patient with incurable brain metastases.

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