Quality of life in patients with brain metastases receiving upfront as compared to salvage stereotactic radiosurgery using the EORTC QLQ-C15-PAL and the EORTC QLQ BN20+2: a pilot study

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Abstract

Objective The purpose of this study is to investigate quality of life (QOL) outcomes in patients receiving either upfront (no prior whole brain radiation) or salvage (prior whole brain radiotherapy) stereotactic radiosurgery (SRS) for brain metastases using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL and the EORTC QLQ-BN20+2 questionnaires.

Methods Thirty patients who received either upfront or salvage SRS for brain metastases completed the two questionnaires before and 4 weeks following SRS. Scale scores at baseline and at the 1-month follow-up were calculated using the EORTC scoring manual.

Results Fifteen patients were treated with upfront SRS and 15 with salvage SRS. The baseline characteristics of the two groups were balanced with the exception of more patients in the salvage cohort having had received prior systemic therapy (93 % vs. 40 %; $p=0.0052$, respectively). When

comparing QOL outcomes at baseline and at 1 month post-SRS, no significant differences in QOL were observed between cohorts based on the EORTC QLQ C15-PAL and the EORTC QLQ-BN20+2 change scales.

Conclusion Patients receiving salvage SRS maintain a similar QOL profile as compared to patients treated upfront with SRS at 1-month posttreatment. Our findings support the use of salvage SRS in patients with brain relapse following prior WBRT.

Keywords Brain metastases · Stereotactic radiosurgery · Palliative radiation · Quality of life · QLQ-BN20 · QLQ-C15-PAL

Introduction

Metastatic brain tumors are a common complication in patients with advanced cancer occurring in about 20–40 % of all cancer patients [1, 2]. The most common primary cancers that metastasize to the brain include lung, breast, and skin (melanoma) [3].

For the patient presenting with a limited number of brain metastases, several patient and tumor factors are considered prior to recommending a treatment course. These include the patient's performance status, whether solitary or multiple (up to four vs more than four tumors), the presence of systemic metastases, whether or not the primary tumor is controlled, availability of further systemic therapies and age [3–5]. For good performance status patients with a reasonably long life expectancy, controlled systemic disease, and up to four brain metastases, treatment options include whole brain radiotherapy (WBRT) alone, WBRT plus stereotactic radiosurgery (SRS) boost, or SRS alone. A recent meta-analysis reviewed the impact of these options [6] and found

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no survival advantage to the use of WBRT plus a SRS boost as compared to SRS alone. However, fewer distant relapses and local failures were observed with combined WBRT plus SRS boost. These gains from WBRT do come at a cost of impaired neurocognitive functioning [7], and why SRS alone has emerged as a first-line therapeutic option.

For patients who have been previously treated with WBRT and relapsed intra-cranially, treatment options consist of repeat WBRT, SRS as a salvage focal therapy or supportive care alone. Typically, repeat WBRT is avoided and used in those patients with a poor life expectancy or widely disseminated brain disease. Neurotoxicity may be quite significant in the long-term with repeat WBRT and, furthermore, its efficacy is questionable as the dose of radiation is lower the second time such that we do not necessarily expect long-term local tumor control. Therefore, in patients who are fit and have a limited number of tumors to be treated, salvage SRS is a preferred treatment option.

There are limited data with respect to efficacy [6–8] for salvage SRS and no randomized trials comparing outcomes to repeat WBRT or even supportive care alone. In particular, we lack quality of life (QOL) outcomes for this cohort to help us better understand the impact of salvage SRS on our patient's life. QOL outcomes are highly relevant as QOL is a multidimensional construct comprised of physical, psychological, social well-being, and functioning as perceived by the individual. Some argue that QOL is the most relevant factor in guiding patients in their decision making process.

The aim of this prospective study was to conduct a pilot investigation to determine preliminary QOL outcomes in a cohort of patients treated with salvage SRS and to compare outcomes to patients treated with upfront SRS using the validated European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL and the EORTC QLQ-BN20+2 questionnaires.

Methods

Patients

This study included 30 patients with brain metastases treated with SRS from three Canadian cancer centers from May 2009 to August 2010. All patients had to be eligible for SRS according to the treating radiation oncologist and consent to the study. Fifteen patients had been treated with upfront SRS and 15 patients with salvage SRS (Table 1). Patients completed the EORTC QLQ-C15-PAL and the EORTC QLQ-BN20+2 questionnaires before and at 1 month following SRS treatment. All researches were conducted with approval from each institution's research ethics board. Baseline patient data included: age, Karnofsky Performance Status (KPS), sex, primary cancer site, the presence of

co-existing visceral or bone metastases, whether the patient had been treated with SRS upfront or as salvage for relapse following prior WBRT, and each patient was scored according to the Graded Prognostic Assessment (GPA) scale [9]. Patients treated with boost SRS were excluded. Concurrent systemic treatments such as chemotherapy, hormone therapy, and bisphosphonates within 1 week of baseline were also recorded.

Questionnaires

QOL for patients receiving SRS was assessed using the EORTC QLQ-BN20+2 and the EORTC QLQ-C15-PAL questionnaires (Figs. 1 and 2). Patients completed the questionnaires in person at baseline (date of initial SRS consultation) and by telephone with a research assistant at 1 month following the date of initiation of SRS treatment. The QLQ-C15-PAL is a general core QOL assessment tool that can be used in conjunction with various cancer subtype specific questionnaires. The QLQ-C15-PAL [10] consists of 15 questions that encompass multi-item functional scales (for example, physical and emotional functioning), multi-item symptom scales (for example, fatigue and pain), single-item symptom scales (for example, nausea, vomiting, dyspnea, insomnia, appetite loss, and constipation), and a final question evaluating the patients' overall QOL (Fig. 1).

The QLQ-C15-PAL core questionnaire was used in conjunction with the QLQ-BN20+2, which is a brain-specific subtype of the questionnaire. The QLQ-BN20+2 [11] consists of 22 questions that encompass single-item symptom scales (for example, headaches, seizures, drowsiness, hair loss, itchy skin, leg weakness, and bladder control), multi-item scales (for example, future uncertainty, visual disorder, motor dysfunction, and communication deficit), and cognitive functioning (for example, concentration and memory) scales (Fig. 2).

Statistical analysis

To compare demographic characteristics between patients treated with upfront SRS to those with salvage SRS, the Fisher exact test was applied for categorical variables (i.e., gender, marital status, primary cancer site, etc.), and the Student's *t* test for continuous variables (i.e., age, KPS, and GPA). Questionnaire scores were tabulated using the EORTC QLQ C30 Scoring Manual in addition to the manuals' addendum entitled: EORTC QLQ-C15-PAL scoring. Scaled scores (range, 0–100 %) were calculated for the EORTC QLQ-C15-PAL and the EORTC QLQ BN20+2 (cognitive items) questionnaires. For the QLQ-C15-PAL, the higher the functional/global health status QOL scores the better the QOL. However, the higher the symptom score,

Table 1 Baseline demographics of the upfront SRS cohort compared to the salvage SRS cohort

	Upfront SRS cohort	Salvage SRS cohort	<i>P</i> value
Age (years)			0.48
Number	15	15	
Mean±SD	60.3±9.1	57.9±9.8	
Interquartiles	54.0–71.0	49.0–64.0	
Median (range)	59 (48–77)	57 (44–79)	
KPS			0.89
Number	14	14	
Mean ± SD	78.6±15.1	79.3±12.1	
Interquartiles	70–90	70–90	
Median (range)	80 (50–100)	85 (60–90)	
Gender			0.14
Female	6 (40.0 %)	11 (73.3 %)	
Male	9 (60.0 %)	4 (26.7 %)	
GPA			0.51
Number	15	15	
Mean ± SD	1.9±0.8	2.1±0.9	
Interquartiles	1.5–2.5	1.5–3.0	
Median (range)	2.0 (0.5–3)	2.5 (0.5–3)	
Marital status			0.28
Married	10 (66.7 %)	11 (73.3 %)	
Single	1 (6.6 %)	3 (20.0 %)	
Other	4 (26.7 %)	1 (6.7 %)	
Primary cancer site			0.37
Lung	8 (53.3 %)	11 (73.3 %)	
Breast	1 (6.7 %)	2 (13.3 %)	
Colon	1 (6.7 %)	0 (0.0 %)	
Melanoma	2 (13.3 %)	1 (6.7 %)	
Renal cell/kidney	3 (20 %)	0 (0.0 %)	
Ovarian	0 (0.0 %)	1 (6.7 %)	
Number of brain metastases			0.40
1	8 (53.3 %)	4 (26.7 %)	
2 to 3	5 (33.3 %)	8 (53.3 %)	
>3	2 (13.3 %)	3 (20.0 %)	
Previous systemic therapy			0.0052
Yes	6 (40.0 %)	14 (93.3 %)	
No	9 (60.0 %)	1 (6.7 %)	

P value was obtained by Fisher exact test for categorical variables or Student's *t* test for continuous variables (age, KPS, and GPA). *P* value <0.05 was considered as statistical significance

the lower the QOL. For the BN20+2, higher scores indicate worse QOL.

Time periods were split according to prior to SRS (baseline), and 1 month after SRS (follow-up). Descriptive statistics detailed changes (follow-up–baseline) between these two time periods. To compare C15-PAL change scores, or BN20+2 change scores, between patients with two different treatments, the Student's *t* test was used under the assumption of unequal variance. To normalize the distribution, a natural log-transformation was applied for each change score. To adjust for multiple comparisons, a Bonferroni adjusted *p* value of <0.004 (0.05/13 scale scores) was

considered as statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS version 9.2 for Windows).

Results

Baseline demographics for patients treated with upfront SRS

For the 15 patients receiving upfront SRS, six were female and nine male, the median age was 59 years (range, 48–77 years), the median KPS was 80 (range, 50–100), and the

Fig. 1 EORTC QLQ-C15-PAL questionnaire **EORTC QLQ – C15 – PAL (version 1)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no “right” or “wrong” answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much			
1. Do you have any trouble taking a <u>short</u> walk outside the house?	1	2	3	4			
2. Do you need to stay in bed or a chair during the day?	1	2	3	4			
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4			
During the Past Week:							
4. Were you short of breath?	1	2	3	4			
5. Have you had pain?	1	2	3	4			
6. Have you had trouble sleeping?	1	2	3	4			
7. Have you felt weak?	1	2	3	4			
8. Have you lacked appetite?	1	2	3	4			
9. Have you felt nauseated?	1	2	3	4			
10. Have you been constipated?	1	2	3	4			
11. Were you tired?	1	2	3	4			
12. Did pain interfere with your daily activities?	1	2	3	4			
13. Did you feel tense?	1	2	3	4			
14. Did you feel depressed?	1	2	3	4			
For the following question please circle the number between 1 and 7 that best applies to you.							
15. How would you rate your overall <u>quality of life</u> during the past week?	1	2	3	4	5	6	7
	Very poor			Excellent			

median GPA score was 2 (range, 0.5–3). The most common sites of primary cancer included lung (53.3 %), renal cell/kidney (20.0 %), melanoma (13.3 %), colon (6.7 %), and breast (6.7 %); 53.3 %, 33.3 %, and 13.3 % of the patients had 1, 2–3, or >3 brain metastases treated with SRS (Table 1).

Baseline demographics for patients treated with SRS as salvage

For the 15 patients receiving SRS as salvage, 11 were female and four were male, the median age was 57 years (range, 44–79 years), the median KPS was 85 (range,

60–90), and the median GPA score was 2.5 (range, 0.5–3). The most common sites of primary cancer included lung (73.3 %), breast (13.3 %), melanoma (6.7 %), and ovarian (6.7 %); 26.7 %, 35.3 %, and 20 % of the patients had 1, 2–3, or >3 brain metastases treated with SRS (Table 1).

Comparison of baseline characteristics between the upfront SRS and SRS salvage cohort

Patients treated with salvage SRS were more likely to have received systemic therapy as compared to those treated with upfront SRS (93 % vs. 40 %; $p=0.0052$, respectively).

Fig. 2 EORTC QLQ-BN20 + 2 questionnaire

EORTC QLQ–BN20 + 2 Cognitive Items

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at all	A little	Quite a bit	Very much
1. Did you feel uncertain about the future?	1	2	3	4
2. Did you feel you had setbacks in your condition?	1	2	3	4
3. Were you concerned about disruption of family life?	1	2	3	4
4. Did you have headaches?	1	2	3	4
5. Did your outlook on the future worsen?	1	2	3	4
6. Did you have double vision?	1	2	3	4
7. Was your vision blurred?	1	2	3	4
8. Did you have difficulty reading because of your vision?	1	2	3	4
9. Did you have seizures?	1	2	3	4
10. Did you have weakness on one side of your body?	1	2	3	4
11. Did you have trouble finding the right words to express yourself	1	2	3	4
12. Did you have difficulty speaking?	1	2	3	4
13. Did you have trouble communicating your thoughts?	1	2	3	4
14. Did you feel drowsy during the daytime?	1	2	3	4
15. Did you have trouble with your coordination?	1	2	3	4
16. Did hair loss bother you?	1	2	3	4
17. Did itching of your skin bother you?	1	2	3	4
18. Did you have weakness of both legs?	1	2	3	4
19. Did you feel unsteady on your feet?	1	2	3	4
20. Did you have trouble controlling your bladder?	1	2	3	4
21. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
22. Have you had difficulty remembering things?	1	2	3	4

Otherwise no significant differences between the two treatments cohorts were observed (Table 1).

Comparing QOL outcomes based on changes from baseline to the 1 month follow-up in the upfront SRS vs. salvage SRS cohort

Table 2 summarizes the EORTC QLQ-C15-PAL scaled scores from baseline to 1-month follow-up in patients treated with upfront SRS and salvage SRS. When comparing QOL outcomes using the Bonferroni adjusted p value of <0.004 as statistically significant, no significant differences were observed. Table 3 summarizes the EORTC QLQ-BN20+2 scaled scores from baseline to 1 month follow-up in patients treated with upfront SRS and salvage SRS. When

comparing QOL outcomes using the Bonferroni adjusted p value of <0.004 as statistically significant, at baseline and at 1 month post-SRS, no significant differences in QOL were observed.

Discussion

The current literature assessing the impact of SRS for brain metastases tends to emphasize endpoints such as survival, and time to local and distant intracranial recurrence [6, 12, 13]. Although these endpoints are critical considerations to justify the resource intensive and costly therapy of SRS [14], the importance of QOL has been less emphasized and should be considered equally critical in the treatment

Table 2 Comparison of changes in EORTC QLQ-C15-PAL scaled scores from baseline to 1 month follow-up in patients treated with upfront SRS and salvage SRS

Item	Upfront SRS cohort (<i>n</i> =15)			Salvage SRS cohort (<i>n</i> =15)			Comparison <i>p</i> value ^a
	Baseline (mean)	1 month follow-up (mean)	Difference	Baseline (mean)	1 month follow-up (mean)	Difference	
Pain Scale	23.1	28.2	5.1	23.6	16.7	−6.9	0.41
Dyspnea	11.1	17.8	6.7	15.6	11.1	−4.4	0.28
Insomnia	31.1	20.0	−11.1	24.4	22.2	−2.2	0.34
Appetite loss	9.5	22.2	11.9	20.0	15.6	−4.4	0.15
Constipation	17.8	4.4	−13.3	11.1	11.1	0.0	0.27
QOL scale	70.0	65.6	−4.4	65.6	63.3	−2.2	0.60
Physical Functioning	72.9	73.3	0.4	70.2	70.7	0.4	0.99
Fatigue	38.5	45.9	12.0	35.6	39.3	3.7	0.22
Nausea and vomiting	5.6	14.4	8.9	14.4	2.2	−12.2	0.18
Emotional Functioning	84.4	80.0	−4.4	82.2	88.1	6.0	0.23

^a *P* value was obtained by applying the Student's *t* test. A Bonferroni adjusted *p* value of <0.004 was considered as statistically significant. Natural log-transformation was applied for each change score to normalize distribution

decision-making process. In particular, in the salvage SRS patient, there are no randomized trials to justify SRS; however, it is acknowledged that for selected patients, long-term efficacy and survival has been observed [8, 15, 16]. The issue lies in whether we are improving, or at least even maintaining, QOL following this intense treatment. To our knowledge, this study is the first to report defined QOL outcomes using a validated QOL instrument in a population of patients treated with salvage SRS, and compare outcomes to those treated with upfront SRS.

The present pilot study was designed as a feasibility study with respect to collecting QOL outcomes in the salvage SRS population and to gain preliminary outcomes to base a larger study upon. This is why our data collection was limited to the 1-month posttreatment endpoint as a future planned study on a large scale will address long-term follow-up.

We first observed that the two cohorts were well balanced (Table 1). However, patients in the salvage SRS cohort were more likely to have been treated with previous systemic

Table 3 Comparison of changes in EORTC QLQ BN20 + 2 scaled scores from baseline to 1 month follow-up in patients treated with upfront SRS and salvage SRS

Item	Upfront SRS cohort (<i>n</i> =15)			Salvage SRS cohort (<i>n</i> =15)			Comparison <i>p</i> value ^a
	Baseline (mean)	1 month follow-up (mean)	Difference	Baseline (mean)	1 month follow-up (mean)	Difference	
Future uncertainty	23.3	26.7	3.3	31.1	7.2	−23.9	0.035
Visual disorder	11.9	7.1	−4.8	11.1	4.0	−4.8	0.92
Motor dysfunction	17.8	14.1	−3.7	14.8	13.3	−1.5	0.53
Communication deficit	12.8	15.4	2.6	4.8	2.4	−2.4	0.26
Headaches	17.8	20.0	2.2	24.4	13.3	−11.1	0.85
Seizures	2.2	0.0	−2.2	0.0	0.0	0.0	0.33
Drowsiness	31.1	44.4	13.3	21.4	28.9	4.8	0.35
Itchy Skin	7.7	17.9	10.2	23.8	33.3	9.5	0.39
Hair loss	0.0	8.3	8.3	20.0	11.9	−6.7	0.34
Weakness of legs	13.3	17.8	4.4	11.1	7.1	−4.8	0.48
Bladder control	0.0	2.2	2.2	6.7	7.1	2.4	0.88
Concentration	5.9	1.5	−4.4	7.4	3.0	−4.4	0.93
Memory	15.4	23.1	7.7	19.0	19.0	0.0	0.77

^a *P* value was obtained by applying the Student's *t* test. A Bonferroni adjusted *p* value of <0.004 was considered as statistically significant. Natural log-transformation was applied for each change score to normalize distribution

therapies. This result was not unexpected. From our clinical experience, these patients are further along the course of their disease, and following initial treatment of WBRT are often treated with multiple lines of systemic therapy prior to developing intracranial relapse. The overall similarity of the two cohorts highlights that we are in fact selecting our patients for salvage SRS well. Therefore, it is important to note that our findings are specific to a well-selected cohort of patients with intracranial relapse, and may not be generalizable to all patients who suffer relapse post-WBRT.

We observed in both the upfront and salvage SRS cohort a mixture of improvements and declines in QOL outcomes (Tables 2 and 3) at 1 month post-SRS. In the salvage SRS cohort, we also observed that constipation, seizures, and memory scales did not demonstrate any changes at 1 month post-SRS. The common factors that improved 1 month post-SRS in both the upfront and salvage SRS cohorts included insomnia, motor dysfunction, communication deficiency, and concentration. The common factors that deteriorated post-SRS in both the upfront and salvage SRS cohorts included global QOL, fatigue, emotional functioning drowsiness, itchy skin, and bladder control. These data are helpful to gain insight into the positive and negative impact of SRS on patient QOL. Statistical analysis comparing QOL outcomes between the two patient cohorts indicated no significant differences based on either the EORTC QLQ-C15-PAL or EORTC QLQ-BN20+2 QOL assessment tools. Therefore, in a well-selected cohort of patients with intracranial relapse following prior WBRT, a QOL profile similar to those patients treated with upfront SRS was observed 1 month posttreatment.

Conclusion

The current study indicates that patients treated with salvage SRS have a comparable QOL profile to those patients treated with upfront SRS 1 month posttreatment. Therefore, a patient who is fit enough for salvage SRS should not be discriminated upon by the advanced state of their disease and offered this aggressive focal therapy. This study also indicates that collecting QOL outcomes in this population is feasible, and larger studies with long-term follow-up are required in order to appreciate the full extent of the impact of salvage SRS on QOL before final conclusions can be rendered.

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