Review Article on Palliative Care in Neuro-Oncology

Narrative review of neurocognitive and quality of life tools used in brain metastases trials

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Abstract: Development of brain metastases are common in patients with advanced malignancies leading to significant morbidity and mortality. Although overall survival is an important endpoint in these patients, neurocognition and health related quality of life (HRQoL) more accurately highlights the impact of the disease and its treatment on patients. Whole brain radiotherapy (WBRT) has historically played a key role in the management of these patients, especially those with multiple brain metastases. Clinical trials have supported the use of stereotactic radiosurgery (SRS) alone in patients with limited brain metastases sparing neurocognitive function and HRQoL as compared to the combination of SRS plus WBRT. Furthermore, new systemic agents are increasingly being used in clinical practice and have shown promise in patients with brain metastases. The upcoming clinical trials are tasked with defining treatment guidelines that are more specific to patient and tumour factors incorporating radiation, surgery, and systemic therapy. The validity of findings in these trials rest on the rigor of the study methodology and the utilisation of validated assessment tools for neurocognition and HRQoL. This review aims to appraise and summarise the neurocognitive and HRQoL tools used in modern brain metastases trials.

Keywords: Neurocognitive function; quality of life (QoL); brain metastases radiation trials

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Introduction

Brain metastases affect 20% to 40% of all cancer patients and are associated with poor outcomes, as with any form of metastases, the patient transitions from curative to palliative management (1,2). However, advancements in systemic treatment have improved the survival rate in this patient population. As a result, there has been increasing concern regarding treatment effects on neurocognitive function and health related quality of life (HRQoL) (2,3). Clinical radiation therapy trials that compare different treatment regimens have typically included endpoints of survival and toxicity. More recently, studies have begun to report neurological symptoms, functional independence, and quality of life (QoL) metrics (3,4). While the inclusion of these metrics has the potential to improve patient care, there remains a need to evaluate the reliability and validity of these tests (3).

As the predominant route of metastatic dissemination is hematogenous, the entire brain may potentially harvest micro-metastatic disease (5). Consequently, whole-brain radiotherapy (WBRT) has historically been the standard of care in brain metastases to treat both macro and microscopic disease in the brain (1,5). The benefits of WBRT have come under scrutiny in recent years as clinical trials have failed to show a survival benefit while

its deleterious effects on the brain have become more clear (1,4,5). Several randomised studies comparing stereotactic radiosurgery (SRS) with SRS plus WBRT have found an increase in risk of intracranial failure (both local and distant) without WBRT, but no statistically important overall survival difference. Additionally, WBRT was associated with a decline in patients' neurocognitive function and HRQoL (1,4,5). As a result, SRS alone is the current standard of care for patients with limited brain metastases.

Over the years, we could see the shift to replace WBRT with SRS to reduce the long-term neurotoxicity that affects HRQoL and this also allows implementation of salvage treatment in cases of recurrence (6-8). Maintenance of neurocognitive function and HRQoL in patients with brain metastases is important especially in the era of emerging systemic agents, as patients are surviving longer (9). It is therefore pertinent to establish the effects of brain irradiation on neurocognition and HRQoL of patients with brain metastases. The quality and validity of findings in clinical radiation therapy trials rest on the rigor of the study methodology. This review aims to appraise and summarize the neurocognitive function and HRQoL tools used in brain metastases trials. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1036).

Neurocognitive measures

Brain tumour patients typically experience cognitive dysfunction associated with the disease itself and the effects of treatment such as surgery, radiotherapy, and chemotherapy (10). This section will focus on radiation-induced impairment to neurocognitive function. The existing body of research on radiation-induced neurocognitive decline has demonstrated that WBRT impairs learning and memory, as well as functions driven by frontal-subcortical white matter, including verbal retrieval, attention, processing speed, and executive function (10,11). As patients with brain metastases are surviving longer due to current advancements in treatment, numerous clinical trials in radiation therapy have included measures of neurocognitive function as an endpoint (1,4-6,12) (*Table 1*).

A multicentre Japanese randomised study JROSG-99-1 reported by Aoyama *et al*. in 2006 was the very first major comparative trial published. This study looked at 132 patients with 1–4 brain metastases randomised to WBRT plus SRS or SRS alone and found no differences in OS with the addition of WBRT (1). JROSG-99-1 assessed neurological function with the mini-mental state examination (MMSE) and illustrated no differences in MMSE scores between WBRT plus SRS and SRS alone groups before treatment and at the final follow up. Comparably, patients with 1–3 brain metastases enrolled in EORTC 22952-26001 were initially treated with SRS or surgical resection followed by randomization to WBRT or observation. This study found that WBRT resulted in reduction of CNS progression events, however there was no differences in OS (6). The EORTC 22952-26001 trials validated that WBRT did not appreciably affect OS, cognitive effect from WBRT could not be addressed because the collection of rigorous cognitive data was limited.

It is important to highlight that the MMSE is optimized for the detection of dementia, for performance in an abnormal range, and lacks the sensitivity to detect more subtle neuropsychological changes (15). MMSE is an insufficient tool to capture varying degrees of neurocognitive decline in patients with brain metastasis. Comparative assessments to discern the sensitivity of the MMSE have found that the MMSE detects impairment in only 77.6% of patients with a brain tumour (15). The MMSE underperforms when compared a battery of neuropsychological tests, as the MMSE only detected 50% of patients which the test battery found to be functioning abnormally (15). This suggests that the MMSE is an insensitive measure on par with chance (15). Additionally, the components that the MMSE assesses (orientation, attention, aphasia and apraxia) do not align with radiation-induced cognitive decline (executive function, processing speed, fine motor control, learning and memory) (15). Therefore, we should be mindful of clinical trials that assess the neurocognitive impact of WBRT using MMSE, as the metric fails to capture the neurocognitive decline experienced by the patients. MMSE has to be either replaced with or accompanied by other neurocognitive tests. A robust battery of neurocognitive tests has been suggested by the International Cognition and Cancer Task Forces, and these include the Hopkins Verbal Learning Test Revised (HVLT-R) to assess immediate recall, delayed memory, and recognition; Controlled Oral Word Association test (COWA) for verbal fluency and Trial Making Test Part A (TMT-A) for executive functioning; Part B (TMT-B) for delayed memory (3). This array of tests is better aligned with the symptomatology of radiation-induced neurocognitive decline, and there is substantial evidence to

Table 1 Summary of neurocognitive assessments

Study	Modality	n	Overall survival	Neurocognitive test	Neurocognitive outcome
NCCTG N107C/ CEC.3, Brown *et al*., 2017 (12)	SRS alone to surgical cavity	194	SRS:12.2 months	HVLT-R	WBRT is associated with significant cognitive deterioration at 6 months
	WBRT alone		WBRT: 11.6 months	TMT-A/B	
				COWA	
NCCTG N0574, Brown *et al.*, 2016 (4)	SRS alone	213	SRS: 10.4 months	HVLT-R	SRS + WBRT is associated with significant cognitive deterioration at 3 months
	SRS + WBRT		SRS + WBRT: 7.4 months	TMT-A/B	
				COWA	
				Grooved pegboard test	
RTOG 0614, Brown *et al.*, 2013 (13)	WBRT + Memantine	508	WBRT + Memantine: 6.7 months	HVLT-R	MMSE and TMT showed cognitive improvement at 24 weeks in Memantine group
	WBRT + placebo		WBRT + Placebo: 7.8 months	TMT-A/B	
				COWA	COWA showed significant improvement at 8 weeks in Memantine group
				MMSE	
Sun *et al.*, 2011 (14)	PCI	340	NA	HVLT	MMSE showed no significant difference
	OBS			MMSE	HVLT showed significant improvement in immediate recall and delayed recall in OBS group
Chang *et al*., 2009 (5)	SRS alone	58	NA	HVLT-R	At 4 months SRS + WBRT showed reduced learning and memory function (mean posterior probability of decline 52%)
	SRS + WBRT			TMT-A/B	
				COWA	
				WAIS-III digit symbol	
				Grooved pegboard	
JROSG-99-1, Aoyama *et al.*, 2006 (1)	SRS alone	132	SRS: 8.0 months	MMSE	No difference between the two groups
	SRS + WBRT		WBRT: 7.5 months		

SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; PCI, prophylactic cranial irradiation; OBS, observation; n, number of participants; HVLT, Hopkins Verbal learning test; TMT, trial making test; COWA, controlled oral word association; WAIS-III, Wechsler Adult Intelligence Scale-3; NA, not available.

support their reliability and validity (3).

In 2009, Chang *et al*. (5) randomised patients with 1–3 brain metastases to SRS plus WBRT *vs*. SRS alone, importantly, with neurocognitive function as their primary endpoint. Neurocognition was assessed with HVLT-R, TMT-A/B, COWA, with the addition of two other tools; the Wechsler Adult Intelligence Scale-III (WAIS-III) to assess IQ and Lafayette Grooved Pegboard to measure fine motor skills (5). At 4 months, the study was halted early as measures of total recall found SRS alone to be superior to SRS plus WBRT, an effect that persisted beyond 6 months in the follow-up period (5). Evidenced as the mean probability of decline in total recall, delayed recall, and delayed recognition, for SRS alone was 24%, 6%, 0% respectively, compared with 52%, 22%, and 11% for patients treated with SRS plus WBRT (5). This study also found that patients that only received SRS had a higher overall intracranial recurrence compared to patients treated with SRS plus WBRT, which continued at the 6-month follow-up (5).

A multicentre randomised study NCCTG N0574 by Brown *et al*., (4) investigated neurocognitive function as the primary endpoint of SRS plus WBRT *vs*. SRS alone for patients with 1–3 brain metastases. This study employed a rigorous battery of cognitive tests including the HVLT-R, COWA, TMT-A, TMT-B and Grooved Pegboard Test. The authors determined that a decline greater than one standard deviation from baseline on one or more cognitive test was indicative of cognitive deterioration. At 3 months post treatment, they found less cognitive deterioration for patients that received SRS alone compared with SRS plus WBRT (63.5 *vs*. 91.7%, P<0.001). A further assessment of cognitive deterioration was conducted at 12 months in long-term survivors, which found persistent variation in cognitive decline (60 *vs*. 94.4%, P=0.04) (4).

A subsequent study by Brown *et al*., NCCTG N107C/CEC.3 (12) compared WBRT to SRS alone treatment for the surgical cavity in patients with resected brain metastases, by applying a similar battery of cognitive tests. The primary endpoints for this study were overall survival time and cognitive deterioration-free survival. This study found that WBRT decreased cognitive-deterioration-free survival (3.7 *vs*. 3.0 months, HR 0.47, 95% CI: 0.35–0.63, P<0.0001), and increased cognitive deterioration at 6 months in patients who received WBRT (52% *vs*. 85%, P<0.001). Consistent with previous literature presented in this review, there was no significant difference in OS (12).

PCI is a pre-emptive radiation treatment, used commonly in cases of small-cell lung cancer due to high rates of brain metastasis (16). Gondi *et al*. conducted one of the largest analyses of cognitive impact of PCI (17). Their comparative pooled analysis of PCI *vs*. no-PCI outcomes, revealed a decline in cognitive function at 6 and 12 months. The patient-reported cognitive outcomes had a more than threefold decrease in the PCI group (17). Similarly, Sun *et al*. (14) evaluated the effect of PCI on neurocognitive function and HRQoL in patients with stage III non-small cell lung cancer and found no significant differences between the two treatment groups (PCI *vs*. observation) (14). HVLT assessment tool was also included as an additional measure of cognitive function and patients who received PCI were found to have a statistically significant deterioration (P=0.03) in immediate and delayed recall at 1 year (14). The disparity between the two neurocognitive assessment tools may be due to the fact HVLT has superior sensitivity compared to the MMSE in detecting mild dementia (18) and hence a more superior tool to assess neurocognitive function.

In recent years, interest has grown for the use of neuroprotective agents to preserve cognitive function for patients requiring WBRT. The use of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is known for its neuroprotective properties and has been investigated in RTOG 0614 by Brown *et al*. (13) in patients receiving WBRT. This randomized placebo control trial of 554 patients, found that patients treated with memantine had lower cognition function failure 54% compared to 64% in patients treated without memantine, based on HVLT-R assessments. Despite the primary endpoint falling short of significance, there was a strong trend towards significance (P=0.059) supporting the use of memantine in patients receiving WBRT. Their secondary endpoints analysis showed that memantine treated patients had greater cognitive function over time; specifically, memantine was found to delay time to cognitive decline and is associated with a reduction of the rate of memory decline, processing speed, and executive function at 24 weeks (13).

Memory function has been localized to dentate gyrus of the hippocampus, specifically pyramidal and granule cells (19). Mitotically active neural stem cells found in the sub granular zone of the dentate gyrus of the hippocampus, produce new granule cells (20,21). Preclinical work by Monje *et al*. has provided evidence that pathogenesis of radiation induced neurocognitive decline is due to radiation induced injury to this neural stem cell compartment (22). Subsequently, Monje *et al*. showed that inflammation surrounding neural stem cells inhibits neurogenesis (23). Hence, inflammatory injury induced by radiation to the proliferating sub granular neural stem cells compartment of the hippocampus has been hypothesized to represent one of the mechanisms contributing to neurocognitive decline. Notably, the primary driver behind neurocognitive decline is the dose received by the hippocampus, as irradiation results in the deficiency of the progenitor cells (10). Providing evidence in support of these hypotheses, a multi-institutional single-arm phase II trial RTOG 0933 found that hippocampal avoidance WBRT offered superior cognitive preservation on the HVLT-R, compared to traditional WBRT protocols (24).

The NRG oncology CC001, subsequently tested this in a multi-institutional Phase III RCT (25). They confirmed that applying IMRT during WBRT for conformal avoidance of the hippocampal neurodegenerative stem cell resulted in superior conservation of patient's cognitive function and reported symptoms (25). This trial randomized patients with brain metastases to hippocampal avoidance WBRT

Table 2 Ongoing clinical trials comparing SRS with WBRT plus SRS in patients with multiple brain metastases (4–20 lesions)

Trial identifier	Organisation	Modality	Number of lesions treated	Primary outcome
NCT03775330	Sunnybrook Odette Cancer Centre	SRS *vs*. WBRT plus SRS	5–20	Neurocognition
NCT03550391	Canada Cancer Trial Group	SRS *vs*. WBRT plus Memantine	5–15	OS, neurocognition
NCT01592968	MD Anderson Cancer Centre	SRS *vs*. WBRT	4–15	LC, neurocognition
NCT03075072	Brigham and Women's Hospital/Dana Farber Cancer Institute	SRS *vs*. WBRT	5–20	QoL

OS, overall survival; QoL, quality of life; LC, local control; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

plus memantine or WBRT plus memantine. The risk of cognitive failure was significantly lower in hippocampal avoidance WBRT plus memantine (adjusted hazard ratio, 0.74; 95% CI, 0.58 to 0.95; P=0.02). Evidenced at 4 and 6 months as patients experienced less deterioration in executive function (23.3% *vs*. 40.4%; P=0.01), and learning and memory, respectively (11.5% *vs*. 24.7%; P=0.049 and 16.4% *vs*. 33.3%; P=0.02). There was however no significant difference in OS, intracranial PFS, or toxicity between the two treatment arms. Patients who received hippocampal avoidance WBRT plus memantine also noted decreased fatigue (P=0.04), less memory difficulties (P=0.01), less trouble speaking (P=0.049), reduced impact of neurologic symptoms on daily activities (P=0.008), and fewer cognitive symptoms (P=0.01), at 6 months (25).

As discussed above, multiple randomized trials report that WBRT offers improved CNS control rates without OS benefits, albeit are associated with neurocognitive function decline (1,4-6,12). Furthermore, the QUARTZ trial, investigating the value of supportive care plus WBRT *vs*. supportive care alone in patients with non-small cell lung cancer suggested that WBRT can be omitted as there was no important QoL or overall survival benefits between the two groups. The difference in QoL years QALYs for the omission of WBRT was −4.7 days. Equally, the median survival rate between groups was approximately 5 days difference, underlining both the poor prognosis of this patient group and minimal benefit of WBRT (26). An individual patient meta-analysis by Sahgal *et al*. also reported no benefit in overall OS and suggested that WBRT resulted in a decrement in OS for patients <50 years old (27). These studies essentially highlight the clinical importance of neurocognitive decline after WBRT, coupled with improved CNS control but no OS benefit have failed to validate the routine administration of WBRT in patients with limited CNS disease.

The evidence to date demonstrates that management of brain metastases is evolving quickly, since WBRT is no longer the default treatment for patients. Owing to better understanding of the negative effect of WBRT on neurocognitive function, SRS alone is the preferred treatment option particularly in patients with limited brain metastases. The use of SRS has been validated for use in patients with multiple brain metastases (>4). This was investigated by a Japanese multicentre prospective study incorporating patients with <10 brain metastases that showed patients with 5–10 brain metastases who undergo SRS experience comparable survival outcomes to patients with 2–4 brain metastases (28). To further justify the use of SRS in patients with multiple brain metastases (>4), several other studies investigating the efficacy and safety of SRS *vs*. SRS plus WBRT these patients are ongoing (*Table 2*).

QoL measures

Measures of health-related QoL (HRQoL) complement neurocognitive assessments, as it provides context to how cognitive decline affects patient's daily life (29). Given the correlation between neurological morbidity and poor prognosis, it is pertinent to provide effective treatment while being mindful of patients' QoL especially in the current era where life expectancy of patients with brain metastases is increasing as a result of improvements in systemic treatment (30) (*Table 3*).

SRS with adjuvant WBRT translates to significantly greater neurocognitive decline versus SRS alone, and is reputed to a HRQoL detriment (5). It should be noted that baseline HRQoL outcomes in patients with brain metastases are impaired to begin with, in all aspects of daily life, including physical and mental functioning (8) (*Table 4*).

Chang *et al*. (5) utilized the Functional Assessment of Cancer Therapy-Brain (FACT-Br) assessment tool in a

Table 3 Summary of QoL assessments in selected trials

Study	Modality	n	Primary endpoint	Quality of life tool	Quality of life outcome
NCCTG N0574, Brown *et al*., 2016 (4)	SRS alone SRS + WBRT	213	Cognition function	FACT-Br	At 3 months quality of life was higher with SRS alone, including overall quality of life (P=0.001)
EORTC 22952-26001, Soffietti *et al*., 2013 (8)	WBRT OBS	359	Duration of functional independence (WHO performance status deterioration >2)	EORTC QLQ C30 EORTC QLQ-BN-20	OBS only arm reported better HRQOL scores These differences were both statistically significant and clinically relevant seen in early follow-up period (global health status at 9 months, physical functioning at 8 weeks, cognitive functioning at 12 months, and fatigue at 8 weeks)
Slotman *et al*., 2009 (31)	PCI OBS	286	Development of symptomatic brain metastases	EORTC QLQ C30 EORTC QLQ-BN-20	PCI had a negative impact on HRQOL scales. The greatest difference was observed for hair loss fatigue, and global health status at 6 weeks and 3 months in favour of the control arm (OBS)
Chang *et al*., 2009 (5)	SRS alone SRS + WBRT	58	Neurocognition function at 4 months	FACT-Br	At 4 months WBRT was significantly more likely to show a decline in learning and memory function (mean probability of decline 52%) than patients that receive SRS alone (mean probability of decline 24%)
Miller *et al*., 2017 (29)	SRS alone single arm trial	67	Time to health state (EQ-5D index failure)	EQ-5D	At patient's last follow up patients had worse scores on all dimensions (analysed on the basis of 122 treatments)
Bragstad *et al*., 2017 (32)	SRS single arm study	44	HRQoL	FACT-Br	Stable HRQoL up to 12 months after SRS An improved HRQoL was reported by 23 (60.0%) of the 39 patients surviving more than 1-month SRS, an unchanged HRQoL by 6 (15.4%), and a reduced HRQoL by 9 (23.1%)
Skeie *et al*., 2017 (33)	SRS single arm study	97	HRQoL	FACT-Br	Stable HRQoL after up to 12 months after SRS HRQoL was improved or unchanged compared with baseline for 64%, 60%, 66%, 72%, and 60% of the patients at 1, 3, 6, 9, and 12 months, respectively

SRS, stereotactic radiosurgery; WBRT, whole brain radio therapy; PCI, prophylactic cranial irradiation; OBS, observation; n, number of participants; EORTC, European Organisation of Research and Treatment of Cancer; QLQ, quality of life questionnaire; BN-20, brain module; FACT-Br, functional assessment of cancer therapy-brain.

randomized trial of 58 patients, split into 2 cohorts SRS alone or SRS plus WBRT. The HRQoL revealed no difference between the cohorts, despite that the combination group experienced greater neurocognitive function decline. Miller *et al*. found that prior WBRT was correlated with inferior HRQoL in a linear mixed model ($\beta = -0.040 \pm 0.017$; P=0.02), which offers support for the association between neurocognitive function decline and QoL detriment (29). To further support the correlation between neurocognition and HRQoL, a study by Li *et al*. observed that a decreasing neurocognitive function scores from prior visits were predictive of future decline in activities of daily living scores and patient self-reported QoL (40).

Soffietti *et al*. (8) compared HRQoL in the two cohorts (WBRT plus SRS *vs*. SRS alone) with other popular metrics, the EORTC Quality of Life Questionnaire C-30 (EORTC QLQ C-30) and the EORTC QLQ-Brain Cancer Module (EORTC QLQ-BN20). Components of HRQoL assessment tools used in selected trials are summarized in *Table 4*. The patients were evaluated every 3 months from baseline for up to three years. The collective score of the test revealed a clinically significant improvement

Table 4 Summary of HRQoL questionnaires in selected trials

HRQoL tools	Description	Scales/components	Used by
FACT-Br	The FACT-Br was designed for primary brain tumours patients. Each question is answered by a rating on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). The FACT-Br consists of 5 subscales, 2 total scales, and 1 index	• Five subscales o Physical well-being o Social/family well-being o Emotional well-being o Functional well-being o Brain cancer subscale (additional concerns specific for patients with brain tumours)	Chang, 2007 (5) Bragstad, 2017 (32) Slotman, 2017 (31) Brown, 2016 (4)
	The FACT-General captures general HRQoL and may be used on diverse patient groups. The FACT-Br combines the FACT-G with a disease-specific subscale score for patients with a brain tumour. Higher scores on each subscale reflect better health-related quality of life	• Two total scales o FACT-general (FACT-G; physical + social + emotional + functional well-being) o FACT-brain (FACT-Br; FACT-G + brain cancer subscale)	
	The FACT-Br has high validity and reliability coefficients thus, it is an appropriate measure for use in patients with brain metastases (34,35)	• One index o Trial outcome index (TOI; physical + functional well-being + brain cancer subscale)	
EORTC-QLQ-C30	The EORTC QLQ-C30 consists of 5 functional scales, 3 symptom scales, 1 global health/quality of life scale and 6 single items. All of the scales and single-item measures range in scores from 0 to 100, severe symptoms are indicated by higher scores.	• Five functional scales o Physical functioning o Role functioning o Cognitive functioning o Emotional functioning o Social functioning	Habets, 2016 (36) Soffietti, 2013 (8) Slotman, 2009 (31)
	In the case of functional scales, higher scores reflect better functioning. The EORTC QLQ-C30 is a reliable and valid measure of the quality of life of patients with cancer (5)	• Three symptom scales o Fatigue o Pain o Nausea and vomiting • One global quality of life scale • Six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties)	
EORTC-QLQ-BN20	The EORTC-QLQ-BN20 was specifically designed for brain cancer patients and to complement the QLQ-C30. The test includes 20 items and four subscales. All items and scale scores are linearly transformed to a 0–100 scale, more severe symptoms are reflected by higher scores	• Four subscales o Future uncertainty o Motor dysfunction o Visual disorder o Communication deficit	Habets, 2016 (36) Soffietti, 2013 (8) Slotman, 2009 (31)
	The BN20 has adequate psychometric properties for assessment of HRQoL of brain cancer patients in international studies (4,37)	• Seven single items (headaches, hair loss, weakness of legs, seizures, itchy skin, bladder control, drowsiness)	

Table 4 (*continued*)

Table 4 (*continued*)

HRQoL tools	Description	Scales/components	Used by
EQ-5D	The EQ-5D is a standardized measure of health state, and in applied in a variety of patient populations. It consists of 5 items representing 5 dimensions. Each item is answered on a 3-point scale; 1 no problems, 2 some problems, and 3 extreme problems. The index score overall health state consists of all 5 items and ranges between 0 (dead) and 1 (best possible health). Self-perceived health state is measured on a 20 cm vertical scale with endpoints 0 (worst imaginable health) and 100 (best imaginable health) (3,38)	• Five subscales o Mobility o Self-care o Usual activities o Pain/discomfort o Anxiety/depression • One index o Overall health state (all 5 subscales) • One vertical visual analogue scale o Self-perceived health state	Kotecha, 2017 (39) Miller, 2017 (29)

FACT-Br, functional assessment of cancer therapy-brain; FACT-G, FACT-General; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-BN20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Brain Cancer Module; EQ-5D, EuroQoL 5 Dimensions.

in HRQoL for patients who received SRS alone at 9 months (8,9). At eight weeks post-treatment, the SRS alone group presented with better mean scores in physical and role functioning (the patient's ability to perform their occupational and social roles). Patients that underwent WBRT plus SRS also experience statistically significant worse scores for independent measures of bladder control, weakness in legs, motor dysfunction, constipation, appetite loss, nausea and vomiting, pain, and social functioning (8,9). To date, several studies have explored HRQoL as their primary outcome measure (29,32,33). A prospective single arm study by Skeie *et al*. (33) used FACT-Br to assess 97 patients with 1–6 brain metastases treated with SRS alone, have found that overall HRQoL remained stable in their cohort up to 12 months. Similarly, Bragstad *et al*. (32) employed FACT-Br to assess 44 lung cancer patients' (non-small cell lung cancer =39; small cell lung cancer =5) HRQoL. The QoL improved in 23 (60.0%) of the 39 patients surviving more than 1 month post SRS, 6 patients reported unchanged QoL (15.4%), and 9 patients experienced reduced QoL (23.1%). As their primary outcome was to determine the impact of SRS on HRQoL, the authors found that mean values for all HRQoL dimensions remained unchanged from baseline to up to 12 months post SRS (32).

Aforementioned study NCCTG N0574, by Brown *et al*. (4) studied HRQoL as their secondary endpoint. The HRQoL of patients with limited [1–3] brain metastases treated with SRS *vs*. SRS plus WBRT was assessed using the FACT-Br, the scores range from 0 to 200 with higher scores indicating a better QoL (4). The authors found that HRQoL was higher at 3 months with SRS alone, which includes overall QoL (mean difference, 11.9; 95% CI, 4.8–19.0 points; P=0.001). A list of selected trials, HRQoL tools used and outcomes are summarized in *Table 3*. Conversely, 2 additional studies have reported a statistically significant decline in patient's overall HRQoL after SRS at the last follow up (29,39). It should be noted that the latter two studies used EORTC-QLD-C30 and EuroQol 5 Dimensions questionnaire (EQ-5D) and reported a decline in physical aspects of HRQoL (29,39) while other studies that used FACT-Br recorded stable scores over time (32,33). This is likely seen because, HRQoL was assessed at periods of progressive disease, as no subsequent follow up assessment could be completed, which is in line with other studies (33,36) showing a decline in HRQoL after progressive disease.

When interpreting results from studies on HRQoL after brain irradiation, it is important to consider a number of factors beyond the intended treatment. Other factors like effect of treatment for the primary tumour (e.g., systemic therapy, immunotherapy, radiotherapy, surgery), pseudo-progression or true disease progression, pre-treatment HRQoL, baseline cognitive function, medication use (e.g., steroids) and survival should be considered. Studies have demonstrated that HRQoL post SRS was associated

with performance status, total tumour volume in the brain, symptomatic brain metastases, interval since SRS and overall disease progression while number of brain metastases and patients' demographics did not seem to influence HRQoL (32,33,36). However, we are unable to draw to a reliable conclusion owing to the differences across these studies in statistical techniques used, and disparity in the predictor factors chosen.

A phase III RCT by Slotman *et al*. (31) randomised patients with extensive stage small cell lung cancer who responded to chemotherapy to PCI or observation. Secondary endpoints of this study were HRQoL and patient-reported symptoms, assessed using EORTC-QLQ-C30 and the EORTC-QLQ-BN20. The key HRQoL results, at 6 weeks and 3 months post random assignment, revealed an eight-point difference in observed mean scores in global health status in favour of the control arm. The PCI arm had 12.5% more patients that experienced severe worsening (>20 points) in global health status from baseline up to 3 months. Prior to dropout at 6 months, average scores of cognitive functions decreased sharply. The rapid deterioration of patients may have caused an informative dropout for components of the HRQoL scores, which led the authors to perform a sensitivity analysis with HRQoL data cut off at 3 months (31).

For a vast majority of patients with brain metastases, survival is measured in months and therefore maintenance of HRQoL is prudent. High attrition rate and low response rates are commonly seen in studies that include patients whose life expectancy is short (3,41). There would be a reduction in compliance and sample size of the study population over time, making study of this kind inadequately powered (42). Unfortunately, the nature of patient-reported outcomes, such as the FACT-Br and EORTC-BN, is limited by a couple of factors. Firstly, patients adapt to the symptom burden over time, which biases their scoring. Secondly, high patient dropout rates as discussed above make it difficult to establish significance of symptoms between treatment modalities (3). Nonetheless, the results are still very encouraging especially in the subgroup of patients who survive longer, and it is imperative to report on reasons for dropout to properly interpret study results.

Discussion

Given the heterogeneity of study designs, patient selection bias and inherent deficits associated with brain metastases, meaningful synthesis of the data from this group can be challenging. This may be resolved by employing thoughtfully designed, randomised clinical trial, with neurocognitive function as a primary end point, and using standardised, rigorous and well established neurocognitive function measures (15,43) (*Table 5*).

The use of tools not designed to detect smaller differences in neurocognitive function, such as the MMSE which is not sensitive and therefore not considered suitable. The International Cognition and Cancer Task Force, has suggested a battery of validated tests that should be used in clinical trials including: the Hopkins Verbal Learning Test Revised (HVLT-R) to assess immediate recall, delayed memory, and recognition; Controlled Oral Word Association test (COWA) for verbal fluency and Trial Making Test Part A (TMT-A) for executive functioning; Part B (TMT-B) for delayed memory. In regard to HRQoL, future studies should consider the results over a longer period of time, this includes after treatment, with incorporation of both individual changes HRQoL and influencing factors (*Table 5*). To obtain accurate assessments of this patient population, brain cancer-specific self-report HRQoL questionnaires should be utilized to capture different aspects of HRQoL (44). It is advised that studies report within-group changes, distinctively describe statistical analyses, and reasons for patients' dropout. In order to mitigate patients' burden and prevent high dropout rates, it is recommended that HRQoL questionnaires and follow up assessments are conducted directly before standard hospital visits after SRS, by designated personnel. (3,42). Lastly, future studies should aim to recruit adequate sample sizes at long-term follow-ups (>6 months) to analyse different aspects of HRQoL and neurocognition, especially since radiation-induced brain injury is progressive and irreversible, which typically emerges >6 months after treatment (45). Implementing the above strategies in future trials is challenging, but this will undoubtedly increase our ability ascertain the effect of the disease and its treatment on the functional health, neurocognitive function, symptom burden, and well-being of our patients. In the clinical context this facilitates patient-physician communication, which improves patients access to the necessary supports to cope with changes to their QoL. This presents a convincing argument for the incorporation of neurocognition function and HRQoL measures as standard part of clinical care in brain metastases patients.

Finally, with advances in novel agents in recent years, there has been an increase role of systemic

Table 5 Summary of recommendations for neurocognitive and QoL assessments

Measure	Tests	Recommendations
Neurocognitive measures	MMSE	MMSE lacks sensitivity and should be replaced by a battery of neurocognitive test
	HVLT-R	As per the International Cognition and Cancer Task Force, a combination of the HVLT-R, COWA & TMT-A&B should be used
	COWA	Long term follow-up is recommended (>6 months)
	TMT-A&B	
	WAIS-III digit symbol	
	Grooved pegboard	
Quality of life measures	EORTC QLQ C30	Site specific HRQoL questionnaires should be used
	EORTC QLQ-BN-20	Conduct HRQoL assessment before patients' hospital visits to decrease burden on the patient
	FACT-Br	Increase transparency of study by reporting in group changes, methods for statistical analysis, and reasons for patient drop out
		Data should be collected over an extended period of time (including after treatment)

MMSE, mini mental state examination; HVLT, Hopkins Verbal learning test; TMT, trial making test; COWA, Controlled Oral Word Association; WAIS-III, Wechsler Adult Intelligence Scale-3; FACT-Br, functional assessment of cancer therapy-brain; FACT-G, FACT-general; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-BN20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Brain Cancer Module; EQ-5D, EuroQoL 5 dimensions.

therapy in management of brain metastases patients and specific patient groups are surviving longer (46-48). Nonetheless, physicians should exercise caution when withholding cranial radiotherapy (SRS or WBRT). As we see a shift to SRS in the treatment of this patient population, the combination of novel agents with SRS, and specifically the order which interventions are administered comes into question. This approach is especially interesting due to the potential for enhanced systemic antitumor immunity following the delivery of SRS to one or more lesions, known as the abscopal effect (49). It is noteworthy that the risk of toxicities might increase with concurrent delivery of novel agents and SRS. Thus, this combination approach should be evaluated for efficacy and safety in a prospective trial, with incorporation of neurocognitive and HRQoL tools, to provide a standard for management of patients with brain metastases.

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