CANCER DIAGNOSIS & PROGNOSIS *6*: 227-235 (2026)
doi: 10.21873/cdp.10522

Patient-reported Symptoms Differ Between Patients With Brain Metastasis Starting Either Focal Stereotactic Radiotherapy or Whole-brain Radiotherapy

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Abstract

Background/Aim: The presence of brain metastasis is often associated with clinical symptoms and reduced quality-of life scores, potentially triggering palliative care needs. Previous studies have employed the Edmonton symptom assessment system (ESAS) to this end. However, contemporary patient-reported ESAS data from cohorts managed with different radiotherapy techniques rather than whole-brain radiotherapy (WBRT) alone are scarce. Therefore, the aim of this study was to compare ESAS symptom severity before WBRT to that before stereotactic radiosurgery or fractionated radiotherapy (SRS/FSRT).

Materials and Methods: This was a retrospective analysis (2013-2024, n=102) of patients with brain metastasis assessed with ESAS in routine clinical practice in Norway. Patients were stratified based on radiotherapy approach (WBRT±boost *versus* SRS/FSRT). ESAS scores of 0 correspond to absence of symptoms (maximum intensity: 10).

Results: For the whole study group, fatigue and overall wellbeing scores were highest (mean 3.9 and 3.4, respectively). The lowest scores were those for nausea and constipation (mean 1.2 and 1.4, respectively). Within the WBRT cohort, no significant differences were observed between ESAS scores of boost *versus* no boost patients. When comparing WBRT to SRS/FSRT, we found that WBRT patients reported significantly higher anxiety scores (mean 2.6 *vs.* 1.1, p=0.03). Similar trends emerged for fatigue (mean 4.1 *vs.* 2.7, p=0.056, *i.e.,* not significant) and overall wellbeing (mean 3.7 *vs.* 2.5, p=0.087). The sum of symptom scores was significantly higher in the WBRT cohort (mean 31.7), compared to the SRS/FSRT cohort (mean 18.5), p=0.03.

Conclusion: When employing ESAS screening to provide additional palliative care services to patients with brain metastasis who start radiotherapy, clinicians should be aware of the fact that patients undergoing WBRT may have worse symptom burden and higher needs than patients undergoing SRS/FSRT. This is particularly evident for anxiety, fatigue and overall wellbeing, and not explained by differences in number of brain metastasis and diagnostic setting (regular imaging surveillance *versus* clinical trigger).

Keywords: Palliative radiation therapy, stereotactic radiotherapy, quality of care, prognosis, metastatic cancer.

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Received December 30, 2025 | Revised January 23, 2026 | Accepted February 4, 2026

Introduction

Diagnosis of brain metastasis in patients with solid tumors often portends unfavorable prognosis, *i.e.*, survival of one year or less, depending on extent of both intra- and extracranial disease (1, 2). Additional prognostic factors also impact on survival expectation, such as primary tumor type and Karnofsky performance status (KPS) (3). Historically, many patients with brain metastasis were treated with whole-brain radiotherapy (WBRT), and the gradual implementation of stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) was restricted to scenarios where limited-volume single metastasis (or up to three lesions) were present in patients with expected survival of more than 3-4 months (4-6). Some institutions assessed health-related quality-of-life (QoL) and/or other patient-reported outcomes (PROs) either before WBRT or longitudinally (7, 8), although the latter strategy was influenced by the often short survival time and continuous KPS decline towards end of life, creating difficulties in collecting these outcome data (9). A wide range of symptoms including but not limited to pain, fatigue, anxiety and sleep disturbance was reported by many patients before they started with WBRT.

Many different instruments have been used to evaluate QoL and PROs. Amongst these, the Edmonton symptom assessment system (ESAS) has sometimes been employed in patients managed with WBRT or palliative care (10-12). ESAS is a short, one-sheet questionnaire covering major symptoms and wellbeing on a numeric scale of 0-10, which can easily be integrated into routine workflow in radiation oncology departments (13, 14). The radiotherapy Unit at Nordland Hospital started screening of all palliatively irradiated patients with the ESAS tool in late 2012/early 2013. The main aim was to refer patients with high symptom burden to the inhouse palliative care team in order to provide specialist support and medication adjustment. In this context, we collected ESAS data from patients with brain metastasis.

Mirroring trends observed in other institutions (15-17), a recent shift towards focal brain metastasis irradiation, in particular by means of SRS and FSRT, has also taken place at the Nordland Hospital, because of favorable toxicity profiles in terms of fatigue and cognitive function. Nevertheless, WBRT has not been abandoned but rather refined towards hippocampal avoidance and/or radiation dose boost (simultaneously integrated (SIB) or sequentially administered) (4). Particularly patients with more than 3-4 lesions were considered for WBRT.

Given that previous ESAS data was derived from cohorts managed with WBRT alone and before 2015, we felt that a comparison to recently treated patients managed with WBRT, SRS or FSRT would provide additional insights. The primary aim was to compare symptom severity before WBRT to that before SRS/FSRT. Secondarily, we evaluated the additional impact of liver, lung or bone metastases on ESAS scores. In theory, pain scores may be higher in the presence of bone metastases, dyspnea scores in the presence of lung metastases *etc.*

Patients and Methods

Patients. This was a retrospective single-institution study based on a continuously maintained quality-of-care database, which also formed the basis of previous research (18). It included 102 consecutive adult patients with solid tumors and brain metastasis managed in routine clinical practice outside of trial protocols (time period 2013-2024). The following exclusion criteria were employed: prior cranial radiotherapy (prophylactic or other), prior surgical resection of brain metastasis, leptomeningeal spread. Thus, local treatment consisted of WBRT (largely 10 fractions of 3 Gy) with or without boost (largely simultaneously integrated), or SRS/FSRT (Figure 1). Failure to complete all fractions of radiotherapy was registered in 5 patients (4 WBRT, 1 FSRT).

Questionnaire. The printed ESAS sheet was administered by a registered oncology nurse immediately before physician consultation and computed tomography imaging for treatment planning approximately one week before radiotherapy. Symptoms included pain, fatigue,

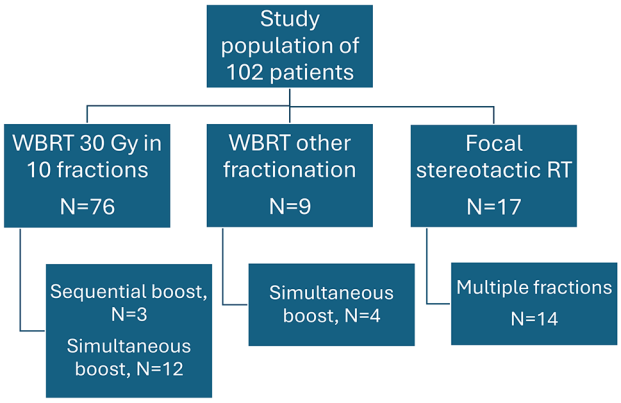

Figure 1. *Radiotherapy strategies employed in 102 study patients.*

nausea, appetite, constipation, dyspnea, depression, anxiety, sleep, dry mouth, and overall wellbeing. Lower scores reflected less severe symptoms.

Outcomes and statistical analyses. All medical records were available in the hospital's electronic patient record (EPR) system. Statistical analysis was performed with IBM SPSS Statistics 29. In addition to all ESAS domains [continuous variables expressed as mean with standard deviations (SD)], we analyzed the ESAS point sum and numerous baseline variables (dichotomized present/absent or categorized by quartiles or treatment groups). ANOVA tables were employed for inter-group comparisons. A p-value ≤0.05 was considered statistically significant. Overall survival was calculated from the first day of radiotherapy and analyzed by comparing actuarial Kaplan-Meier curves with the log-rank test. Nine patients were alive in August 2025 when data was analyzed. The study's median follow-up was 4.4 months [15 months in patients with ongoing follow-up (range=1-78)].

Results

Patients. The study included 59 females and 43 males, and the median age of all 102 patients was 69 years. Non-small cell lung cancer (NSCLC) was the most common primary tumor type (46%), and 84% of the patients had extracranial metastases. In the majority (52%), brain metastases were clinically symptomatic. SRS/FSRT was reserved to patients with fewer brain metastases, and with diagnoses other than small cell lung cancer. The median number of lesions was 6 in the WBRT cohort, compared to 1 in the SRS/FSRT cohort (p<0.001). Age was also significantly different (Table I). The median age was 68 years in the WBRT cohort, compared to 76 years in the SRS/FSRT cohort (p<0.001).

ESAS findings. Patient-reported symptom severity was not uniform. For the whole study group, fatigue and overall wellbeing scores were highest (mean 3.9 and 3.4, respectively). The lowest scores were those for nausea and constipation (mean 1.2 and 1.4, respectively). Within the WBRT cohort, no significant differences were observed between ESAS scores of boost *versus* no boost patients. When comparing WBRT to SRS/FSRT, we found that WBRT patients reported significantly higher anxiety scores (mean 2.6 *vs.* 1.1, p=0.03). Similar trends emerged for fatigue (mean 4.1 *vs.* 2.7, p=0.056, *i.e.,* not significant) and overall wellbeing (mean 3.7 *vs.* 2.5, p=0.087). The differences were less pronounced for all remaining symptoms. The sum of symptom scores was significantly higher in the WBRT cohort (mean 31.7), compared to the SRS/FSRT cohort (mean 18.5), p=0.03 (Table II).

Neither presence of lung, liver or bone metastases showed any significant impact on ESAS scores in any domain. Number of brain metastases, presence of related symptoms, synchronous presentation, presence of extracranial metastases, primary tumor control, age and sex did not significantly impact on ESAS scores, with one notable exception. Females reported poorer overall wellbeing (mean 4.0 *vs.* 2.5 in males, p=0.008). Their sum score was not significantly different but numerically higher (32.0 *vs.* 25.6, p=0.19). Primary tumor type was not analyzed, because most subgroups were very small. The sum of symptom scores was significantly lower in patients with good KPS (mean 17.0 in KPS 90-100, 32.9 in KPS 70-80, and 29.6 in KPS <70, p=0.03).

Table I. *Overview of baseline parameters in 102 patients (Focal RT n=17, WBRT n=85).*

Parameter	All patients	% (all)	WBRT patients	% (WBRT)	Focal RT patients	% (focal RT)
Sex						
Female	59	58	49	58	10	59
Male	43	42	36	42	7	41
Primary tumor type						
Lung, non-small cell	47	46	38	45	9	53
Lung, small cell	11	11	11	13	0	0
Breast	12	12	11	13	1	6
Colorectal	9	9	5	6	4	24
Renal cell	8	8	7	8	1	6
Malignant melanoma	9	9	9	11	0	0
Others	6	6	4	5	2	12
Primary tumor status						
Controlled	58	57	50	59	8	47
Uncontrolled	44	43	35	41	9	53
Extracranial metastases						
None	16	16	14	16	2	12
One organ	32	31	23	27	9	53
Two organs	25	25	21	25	4	24
More than two organs	29	28	27	32	2	12
Liver metastases	31	30	25	29	6	35
Bone metastases	36	35	30	35	6	35
Brain metastases						
Synchronous presentation	67	66	57	67	10	59
Metachronous presentation	35	34	28	33	7	41
Symptomatic	53	52	42	49	11	65
Asymptomatic imaging-detected	25	25	21	25	4	24
Not clearly documented	24	24	22	26	2	12
Treatment						
Incomplete radiotherapy	5	5	4	5	1	6
Sequential systemic therapy*	54	53	45	53	9	53
Further parameters						
Median KPS, range	70, 50-100		70, 50-100		70, 50-100	
Median age, range (years)	69, 46-93		68, 46-90		76, 61-93	
Median number of brain met., range	5.5, 1-50		6, 1-50		1, 1-7	

WBRT: Whole-brain radiotherapy; Focal RT: focal stereotactic radiotherapy; KPS: Karnofsky performance status. *After completion of brain radiotherapy.

Survival. As displayed in Figure 2, patients managed with SRS/FSRT survived non-significantly longer than their counterparts managed with WBRT. The median values were 4.2 (95%CI=3.2-5.2) and 6.0 months (95% CI=2.8-9.2), respectively, p=0.19. After 2 years, 6% of the WBRT patients were alive, compared to 25% of the SRS/FSRT patients.

Discussion

The primary aim of the study was to compare ESAS symptom severity before WBRT to that before SRS/FSRT in real-world patients with brain metastasis. In clinical practice, ESAS screening facilitates referral of patients with high symptom burden causing additional care needs to specialists outside of the radiation oncology team. It has been employed at our site for more than 10 years, also in patients receiving palliative radiotherapy to other areas of the body. In other parts of the world, ESAS has been utilized successfully for more than 20 years (10, 19). Over time, adjustments were made, and certain geographical ESAS variants emerged. Our hospital continued to employ an older Norwegian version (20, 21).

Table II. *ESAS results: mean and standard deviation (Focal RT n=17, WBRT n=85).*

ESAS symptom	All patients	WBRT patients	Focal RT patients	*p*-Value
Pain at rest	1.9, SD 2.5	1.9, SD 2.6	2.0, SD 2.0	0.86
Pain in activity	2.6, SD 2.8	2.6, SD 2.9	2.8, SD 1.9	0.79
Fatigue	3.9, SD 2.8	4.1, SD 2.8	2.7, SD 2.4	0.056
Nausea	1.2, SD 2.3	1.2, SD 2.3	1.2, SD 2.2	0.95
Appetite	2.3, SD 2.9	2.5, SD 3.1	1.2, SD 1.5	0.11
Dyspnea	2.4, SD 2.9	2.6, SD 3.0	1.4, SD 2.2	0.12
Depression	2.5, SD 3.0	2.6, SD 3.1	1.6, SD 2.6	0.20
Anxiety	**2.4, SD 2.8**	**2.6, SD 2.9**	**1.1, SD 1.5**	**0.03**
Dry mouth	2.4, SD 2.7	2.5, SD 2.8	1.5, SD 2.6	0.17
Constipation	1.4, SD 2.5	1.5, SD 2.7	0.8, SD 1.5	0.34
Sleep	2.5, SD 2.9	2.5, SD 2.8	2.4, SD 3.0	0.88
Overall wellbeing	3.4, SD 2.6	3.7, SD 2.5	2.5, SD 2.4	0.087
Sum of symptom scores	29.5, SD 20.4	31.7, SD 20.9	18.5, SD 13.9	0.03

ESAS: Edmonton symptom assessment system; WBRT: Whole-brain radiotherapy; Focal RT: focal stereotactic radiotherapy. Statistically significant *p*-values are shown in bold.

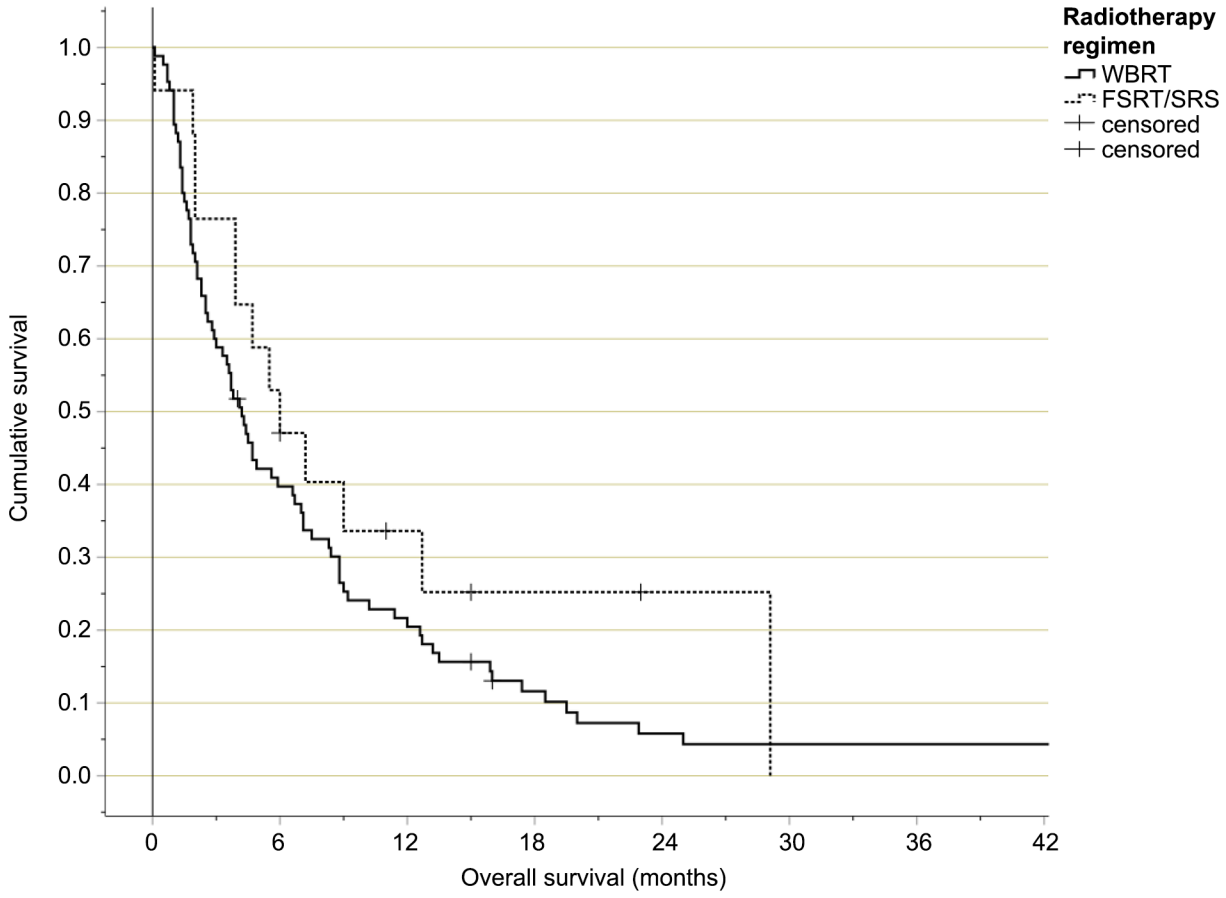

Figure 2. *Actuarial overall survival (Kaplan-Meier estimates) for patients treated with whole-brain radiotherapy or focal stereotactic approaches.*

Our all-comer study population is representative for the case mix clinicians typically face, and included both imaging-surveillance-detected brain metastasis and symptomatic cases over a broad age-range. Most patients had extracranial metastases too, in line with other publications (1, 7, 8). Following intention-to-treat principles, we also included patients who failed to complete all fractions of radiotherapy. Overall survival was comparable to previous experiences in cohorts primarily managed with WBRT (1, 2, 4, 5).

Patient-reported symptom severity varied widely. Several patients reported ESAS sum scores of 1 or 2, while others scored between 70 and 100. The mean sum score was 29.5. For the whole study group, fatigue and overall wellbeing emerged as main issues (mean 3.9 and 3.4, respectively). The lowest scores were those for nausea and constipation (mean 1.2 and 1.4, respectively). Within the WBRT cohort, no significant differences were observed between ESAS scores of boost *versus* no boost patients. When comparing WBRT to SRS/FSRT, we found that WBRT patients reported significantly higher anxiety scores (mean 2.6 *vs.* 1.1, p=0.03). Similar trends emerged for fatigue (mean 4.1 *vs.* 2.7, p=0.056, *i.e.*, not significant) and overall wellbeing (mean 3.7 *vs.* 2.5. p=0.087). The sum of symptom scores was significantly higher in the WBRT cohort (mean 31.7), compared to the SRS/FSRT cohort (mean 18.5), p=0.03. The observed differences were not explained by differences in number of brain metastases and diagnostic setting (regular imaging surveillance *versus* clinically triggered). Besides WBRT, KPS <90 and female sex were associated with certain differences in ESAS scores. However, both KPS and sex were similarly distributed in the WBRT and SRS/FSRT cohorts. Possibly, other factors that were not available in our database and not accounted for could impact on the better ESAS status of SRS/FSRT patients, such as family/caregiver network or comorbidity. Systemic treatment before diagnosis of brain metastasis may also have differed and caused different levels of anxiety and fatigue. In principle, knowledge about the type of brain radiotherapy may cause different types of concern. Patients preparing for WBRT treatment planning may experience more anxiety because they already have information about side effects like hair loss and cognitive impairment, causing higher levels of anxiety and impaired overall wellbeing. Eventually, prospective studies are needed to fully understand these interrelations, also in patients undergoing hippocampal-sparing WBRT (22). Patient interviews may result in particularly detailed information. From our point of view, ESAS information at consultation is desirable regardless of brain radiotherapy strategy. Nevertheless, it is relevant to realize that WBRT patients in general represent a more vulnerable group, and to consider prioritizing them in resource-constrained settings. We were surprised to learn that presence of extracranial metastases in bones or lungs was not associated with different ESAS scores, *e.g.,* for pain or dyspnea. Previous ESAS studies have not focused on these aspects. Harrison *et al.* studied patients with or without brain metastasis referred to palliative care (23). Physical symptom management was the most common reason for referral to supportive care for both patient groups. Patients with brain metastasis had significantly lower pain scores on ESAS. The median survival time from referral was 0.90 years (95% CI=0.7-1.4) for the brain metastasis group, emphasizing the unfavorable prognosis. Table III shows these contemporary ESAS data head-to-head to our own results. As evident from the Table, different ESAS versions were employed. The general impression is that North American scores were higher, likely reflecting the setting of palliative care referral. The proportion of patients referred to palliative care in our study is not known. In contrast to a previous study by our group, the present one did not include patients on advanced/interventional pain therapies such as pump-delivered opioids (24). Other weaknesses include the overall limited study size and resulting challenges with statistical power for comparison of WBRT to SRS/FSRT. We were not able to stratify for primary tumor type. In addition, longitudinal ESAS data was not collected, *e.g.,* at the end of WBRT or during follow-up. Neurological symptoms are not covered by ESAS but may also cause severe symptom burden, not fully described by the

Table III. *ESAS results: median and q1-q3 in 102 patients from Norway and 90 from North America.*

ESAS symptom	North America	Norway
Pain	4, 2-7	2, 0-4
Fatigue	5.5, 4-8	5, 1-6
Nausea	1, 0-4	0, 0-1
Appetite	5, 2-8	1, 0-4
Dyspnea	1, 0-5	1, 0-5
Depression	1, 0-4	1, 0-5
Anxiety	2, 0-5	1, 0-5
Sleep	5, 2-7	2, 0-5
Overall wellbeing	5, 3-7	3, 1-5
Drowsiness	3, 0-5	Not included
Dry mouth	Not included	1.5, 0-4
Constipation	Not included	0, 0-2
Spiritual	0, 0-0	Not included

ESAS: Edmonton symptom assessment system.

Table IV. *ESAS results: mean and standard deviation in 85 patients from Norway and 170 from North America (Toronto, Canada) treated with whole-brain radiotherapy.*

ESAS symptom	North America	Norway
Pain	2.4±2.8	2.6±2.9
Fatigue	5.3±2.8	4.1±2.8
Nausea	1.3±2.2	1.2±2.3
Appetite	3.0±3.2	2.5±3.1
Dyspnea	2.3±2.5	2.6±3.0
Depression	2.8±2.7	2.6±3.1
Anxiety	3.6±3.0	2.6±2.9
Sleep	Not included	2.5±2.8
Overall wellbeing	3.8±2.7	3.7±2.5
Drowsiness	3.5±2.9	Not included
Dry mouth	Not included	2.5±2.8
Constipation	Not included	1.5±2.7

ESAS: Edmonton symptom assessment system.

umbrella domain of overall wellbeing. Chow *et al.* prospectively assessed ESAS in Canadian WBRT patients (1999-2002, n=170) (10). Baseline parameters resembled those in our WBRT subgroup: 60% females (58% at our center), median age 66 years (68 at our center) and median KPS 60 (70 at our center). The most common primary cancer site was lung (58% in both studies). As shown in Table IV, fatigue and overall wellbeing were the highest scored symptoms in both studies. Mean scores were largely comparable for all symptoms. Thus, little has changed in baseline presentation of WBRT patients over the last 15-20 years. Median survival was 8 weeks in Canada and 4.2 months in our study, an increase possibly attributable to higher rates of imaging-detected brain metastases (lead-time bias; uncertain explanation when symptom scores are similar; Chow *et al.* did not report the diagnostic setting) or better options for systemic therapy and boost WBRT, *i.e.,* treatment-related prolongation. After the delivery of WBRT, Chow *et al.* observed statistically significant deteriorations in the mean differences from the baseline for the ESAS domains of fatigue, drowsiness, and appetite. Pulenzas *et al.* performed a comprehensive prospective assessment in patients for up to 3 months post-WBRT by several questionnaires at different times including ESAS, Brain Symptom and Impact Questionnaire (BASIQ), Spitzer Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30; also employed in other brain metastases studies (25-27)], EORTC brain module (EORTC QLQ-BN20+2), EORTC QLQ-C15-PAL, and Functional Assessment of Cancer Therapy-General (FACT-G) (11). However, only 36 patients were interviewed with the ESAS or BASIQ. The median age was 65 years old, and median KPS was 70, similar to our WBRT subgroup. There was a significant correlation between fatigue and overall QoL score at baseline. Both in our, the Chow *et al.* (10) and the North American ESAS study (23), fatigue was the symptom that patients scored highest. Therefore, interventions that improve fatigue could have high clinical impact (28-30).

Conclusion

When employing ESAS screening to provide additional palliative care services to patients with brain metastases who start radiotherapy, clinicians should be aware of the fact that patients undergoing WBRT may have worse symptom burden and higher needs than patients undergoing SRS/FSRT. This is particularly evident for anxiety, fatigue and overall wellbeing, and not explained by differences in number of brain metastases and

diagnostic setting (regular imaging surveillance *versus* clinical trigger).

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

All Authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by C.N. The first draft of the manuscript was written by C.N. and all authors commented on previous versions of the manuscript. All Authors have read and agreed to the published version of the manuscript.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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