Clin Transl Oncol (2018) 20:150–159
https://doi.org/10.1007/s12094-017-1703-5

RESEARCH ARTICLE

Quality of life after whole brain radiotherapy compared with radiosurgery of the tumor bed: results from a randomized trial

L. Kepka[1] · D. Tyc-Szczepaniak[2] · K. Osowiecka[3] · A. Sprawka[4] · B. Trąbska-Kluch[5] · B. Czeremszynska[1]

Received: 13 April 2017 / Accepted: 5 June 2017 / Published online: 14 June 2017

Abstract
Background A recent randomized trial (NCT01535209) demonstrated no difference in neurocognitive function between stereotactic radiotherapy of the tumor bed (SRT-TB) and whole brain radiotherapy (WBRT) in patients with resected single brain metastasis. Patients treated with SRT-TB had lower overall survival compared with the WBRT arm. Here, we compared the health-related quality of life (HRQOL) in patients who received WBRT vs. SRT-TB.
Methods A self-reported questionnaire was used to assess HRQOL (EORTC QLQ-C30 with the QLQ-BN20 module) before RT, 2 months after RT, and every 3 months thereafter. HRQOL results are presented as mean scores and compared between groups.
Results Of 59 randomized patients, 37 (64%) were eligible for HRQOL analysis, 15 received SRT-TB, and 22 had WBRT. There were no differences between groups in global health status and main function scales/symptoms (except for drowsiness and appetite loss, which were worse with WBRT 2 months after RT). Global health status decreased 2 and 5 months after RT, but significantly only for SRT-TB ($p = 0.025$). Physical function decreased significantly 5 months after SRT-TB ($p = 0.008$). Future uncertainty worsened after RT, but significantly only for SRT-TB after 2 months ($p = 0.036$). Patients treated with WBRT had significant worsening of appetite, hair loss, and drowsiness after treatment.
Conclusions Despite higher symptom burden after WBRT attributed to the side effects of RT (such as appetite loss, drowsiness, and hair loss), global health status, physical functioning, and future uncertainty favored WBRT compared with SRT-TB. This may be related to the compromised brain tumor control with omission of WBRT.

Keywords Brain metastasis · Whole brain radiotherapy · Tumor bed · Quality of life · Radiosurgery

Introduction

Whole brain radiotherapy (WBRT) in brain metastases from solid tumors has been a mainstay of management. Randomized trials that compared its use with local treatment (surgery or radiosurgery) that omitted WBRT demonstrated improvement of intracranial control with WBRT without improvement of overall survival [1–4]. Some reports also indicated a negative impact of WBRT on neurocognitive function [4, 5]. For these reasons, the use of WBRT after surgery of brain metastases has been progressively abandoned and a new treatment strategy consisting of stereotactic radiotherapy of the tumor bed (SRT-TB) following surgery of brain metastases with omission of WBRT has emerged. Retrospective series showed that this approach is safe, because despite an excess of relapses in the brain, the local control in the tumor bed was

✉ L. Kepka
lkepka@wim.mil.pl

1 Military Institute of Medicine, Ul. Szaserów 128, 04-141 Warsaw, Poland

2 Maria Sklodowska-Curie Memorial Oncology Center and Institute of Oncology, Warsaw, Poland

3 Independent Public Health Care Facility of the Ministry of the Interior and Warmian & Mazurian Oncology Centre, Olsztyn, Poland

4 Centre of Oncological Diagnostics and Therapy, Tomaszów Mazowiecki, Poland

5 Department of Radiotherapy, Medical University of Lodz, Lodz, Poland

satisfactory and it was claimed that salvage treatment is possible [6]. However, this increased risk of relapse may compromise neurological and cognitive function.

We performed a noninferiority randomized trial to test whether neurological and cognitive functioning in patients with resected single brain metastasis are not different after SRT-TB compared with up-front WBRT. Patients had a baseline and periodical assessment of neurological function according to the Medical Research Council (MRC) scale [7] and cognitive function with the Mini-Mental State Examination (MMSE). Neurological and cognitive functioning were analyzed together and evaluated as cumulative incidence of neurological/cognitive failure (CINCF). Secondary endpoints in this study were overall survival and health-related quality of life (HRQOL) evaluated using the QLQ-C30 and QLQ-BN20 questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC). The main results of the study on the neurocognitive function and overall survival were previously reported [8]. Briefly, 59 patients were included in that study and the difference in the probability of CINCF at 6 months (primary endpoint) was −8% in favor of WBRT (95% confidence interval, +17 to 35%; noninferiority margin, −20%). Two-year overall survival was 10% for SRT-TB and 37% for WBRT ($p = 0.046$); this impairment of overall survival in the SRT-TB arm was related to the excess of neurological deaths. The conclusion from that study was that SRT-TB with omission of up-front WBRT may not be safe [8]. Thus, more data from randomized studies are needed to confirm the safety and value of this new treatment strategy. Recently, the results of a large randomized trial that compared postoperative up-front WBRT with SRT-TB and intact brain metastases with omission of WBRT in patients ($n = 194$) with up to four metastases were presented [9]. No difference was found in overall survival between groups, and neurocognitive function and HRQOL were improved in patients without up-front WBRT.

The relationship between neurocognitive deterioration and QOL decline determined as activities of daily living (ADL) has been demonstrated [10]. In our trial, no statistically significant difference was found in neurological and cognitive functioning between patients allocated to the up-front WBRT arm compared with the SRT-TB-only arm [8]. Because there were no demonstrated differences in neurological and cognitive functioning between both arms, it may be supposed that differences in HRQOL will likewise not be found between patients receiving WBRT and those treated with omission of up-front WBRT. Better intracranial control with WBRT in our trial would compensate for the neurocognitive toxicity of this method. However, there are some areas of functioning that may be compromised by the toxicity of WBRT despite its beneficial effect on improved intracranial control. Thus, in the present study, we aimed to evaluate the results of prospectively collected questionnaires on HRQOL in patients who received up-front WBRT after surgery of single brain metastasis and those who had SRT-TB only.

Methods

The details of materials and methods were reported previously [8]. Briefly, entry criteria included single brain metastasis found by preoperative MRI of the brain, pathologically confirmed metastasis from the solid tumor in the resected brain metastasis, total or subtotal resection in the surgeon's operative report, Karnofsky performance status (KPS) ≥70, life expectancy >6 months, and no obstacle to perform MRI in the follow-up period.

Patients meeting eligibility criteria were randomized after surgery to either WBRT (control arm) or linac-based SRT-TB (experimental arm). At randomization, KPS, neurological status using the MRC scale, MMSE results, and the extent of extracranial disease were recorded. HRQOL was also assessed at that time.

SRT-TB was given at the single dose of 15–18 or 25 Gy in five fractions for large- or irregular-shaped surgical cavities. Patients had post-gadolinium-enhanced T1-weighted MRI (1.5-mm slices) and CT with intravenous contrast performed for planning. The clinical target volume was defined as the contrast-enhancing surgical cavity with exclusion of the surgical tract. A 3-mm margin was added to create the planned target volume. Patients in the WBRT arm had no MRI performed for planning. The WBRT dose was 30 Gy in ten fractions, delivered five times weekly at the linear accelerator.

Two months after RT and every 3 months thereafter, patients had a follow-up visit comprising a brain MRI, physical examination, KPS, neurological status evaluation according to the MRC scale, MMSE, and HRQOL assessment. Treatment of relapses in the brain was left to the discretion of the attending physician.

HRQOL was assessed with the self-administered EORTC QLQ-C30 (version 3.0) and QLQ-BN20 questionnaires. The multi-item scales and single-item measures from both questionnaires were scaled and scored using EORTC recommendations [11, 12]. Briefly, the QLQ-C30 includes five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status scale, and six single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The QLQ-BN20 developed specifically for brain cancer patients includes four symptom scales (visual disorders, motor dysfunction, communication deficit, and future uncertainty)

and seven single-item scales (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control). All of the scales and single-item measures were linearly transformed and scored from 0 to 100. A higher score for a functional scale represents a higher/healthier level of functioning. For the global health status, a higher score represents a higher QOL. For symptom scales and items, a higher score represents a higher level of symptomatology/problems, that is, a poorer QOL.

All QLQ-C30 and QLQ-BN20 scores were prospectively collected into an institutional electronic database. HRQOL measures for respective scales and single items were presented as mean scores and compared between groups at the principle of the treatment actually given (WBRT vs. SRT-TB) using the Mann–Whitney test for independent samples, as well as longitudinally at time points (baseline vs. 2 months after RT and baseline vs. 5 months after RT) for the whole group, and WBRT and SRT-TB separately, using the Wilcoxon rank sum test. Patients were included into the analysis if they had at least two evaluations of HRQOL, that is, at baseline and 2 months after RT.

Results

Between December 2011 and September 2015, 30 patients were allocated to the WBRT group and 30 to the SRT-TB group in this multicenter trial. One patient withdrew consent after randomization, leaving 29 patients in the SRT-TB group for analysis. In the SRT-TB group, 21 patients (72%) were treated as per protocol and in the WBRT group, 29 (97%) received the assigned treatment. In the SRT-TB group, five patients had new asymptomatic brain metastases found on MRI performed for planning. Three patients had received WBRT and two had radiosurgery of the new metastases without WBRT. In two patients with rapid extracranial progression, one had WBRT and one did not receive brain irradiation. One patient from the SRT-TB arm received WBRT for an unknown reason.

HRQOL was compared between patients who received up-front WBRT and those who had SRT-TB. Thus, 24 patients with SRT-TB and 34 patients with WBRT were subject to this analysis. Localizations of primary tumor were: lung (28), colorectal (9), breast (7), melanoma (4), kidney (2), and others (8). From 58 randomized patients who received some form of brain irradiation, we received 51 (88%) filled baseline questionnaires. Compliance with filling QLQ-C30 and QLQ-BN20 questionnaires dropped to 64% (37 patients) 2 months after RT; 15 received SRT-TB and 22 had WBRT. This represented 62.5% and 64.5% of the groups receiving SRT-TB and WBRT, respectively. Among the five patients from the SRT-TB arm with new brain metastases found on MRI performed for planning, there were two patients with up-front WBRT who had completed forms at baseline and at 2 months and these patients were included in the analysis of HRQOL. Thus, 37 patients were eligible for HRQOL analysis (Fig. 1). Among these 37 patients only 3 (WBRT—2, SRT-TB—1) received chemotherapy within the time frame that included evaluation of HRQOL reported in this study.

Compliance with HRQOL measures dropped to 52% [30 patients: 12 (50%) of those receiving SRT-TB and 18 (53%) of those receiving WBRT] at 5 months. We received only 16 (28%) filled QLQ-C30 and QLQ-BN20 questionnaires at 8 months. Thus, with such low compliance we decided to stop our analysis of HRQOL at 5 months of follow-up.

At baseline, no difference was found in HRQOL measures between groups, except for higher cognitive functioning in the SRT-TB group (mean 94.4, SD 17.5) compared with the WBRT group (mean 84.8, SD 16.9) ($p = 0.046$).

At 2 months, there was no difference in global health status measure or in functional scales between the groups. However, two symptom measures appeared worse for WBRT compared with SRT-TB, namely drowsiness and appetite loss, indicating higher symptom burden after WBRT. For drowsiness, the means were 19.9 (SD 27.5) and 36.2 (SD 25.1) for the SRT-TB and WBRT groups, respectively ($p = 0.048$). For appetite loss, the means were 8.9 (SD 27.5) and 30.2 (SD 19.8) for SRT-TB and WBRT groups, respectively ($p = 0.027$). At 5 months, no statistically significant difference was found in any HRQOL measure between the groups. Detailed results of the comparison of the WBRT and SRT-TB groups are presented in Table 1.

When comparing longitudinally HRQOL measures for the whole group, there were no differences in global health status measure or in functional scales, but there was a significant decline in appetite, and increase in hair loss at 2 and 5 months compared with the baseline score. Headaches were marginally more troublesome at 2 months ($p = 0.049$), but not different at 5 months. Constipation had a higher score at 5 months after treatment ($p = 0.005$).

For the SRT-TB group, longitudinal analysis of HRQOL demonstrated a worsening of global health status measures (-11 points, $p = 0.025$) and physical functioning (-14 points, $p = 0.008$) at 5 months compared with baseline. Future uncertainty increased significantly at 2 months ($+4$ points, $p = 0.036$) but not at 5 months. Among single items, only constipation was reported as higher at 5 months ($+19$ points, $p = 0.043$).

For the WBRT group, longitudinal analysis of HRQOL demonstrated no differences in global health status measures or in functional scales after treatment. There was a

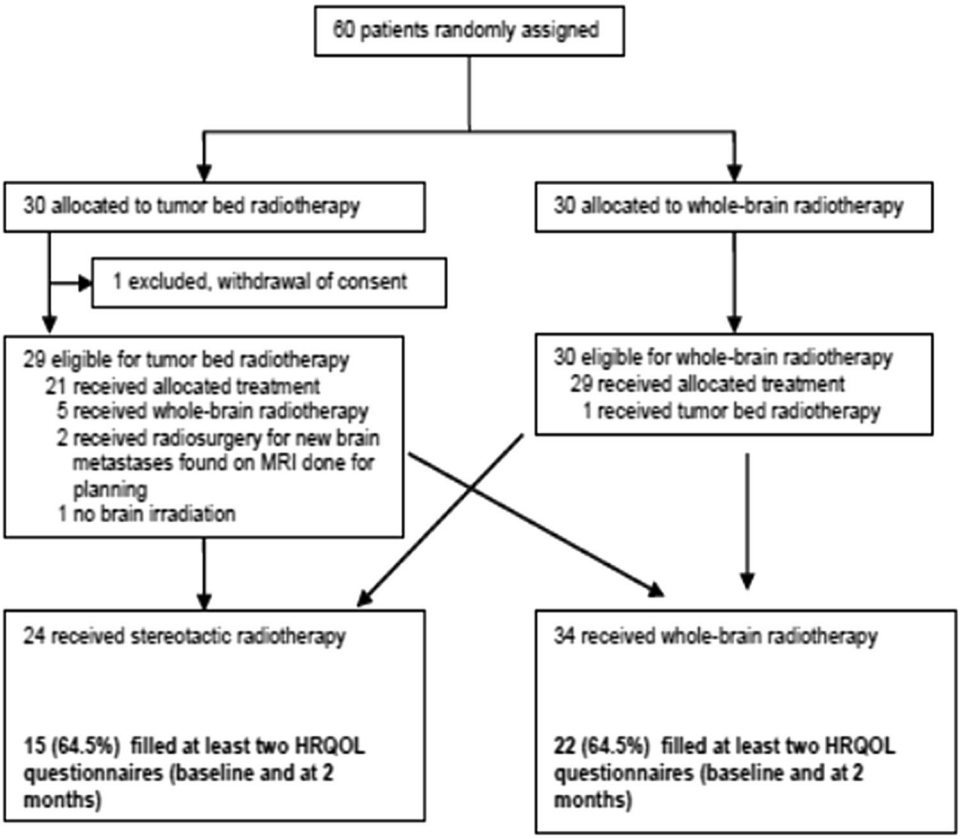

Fig. 1 Consort flow diagram in the study and inclusion of patients into Health-Related Quality Of Life (HRQOL) evaluation

significant decline in appetite at 2 months (+21 points, $p = 0.005$) and 5 months (+17 points, $p = 0.028$), as well as an increase in hair loss at 2 months (+25 points, $p = 0.018$) and 5 months (+28 points, $p = 0.018$). Drowsiness increased significantly at 2 months (+12 points, $p = 0.028$), but was not different at 5 months. Visual disorders improved at 2 months (−7 points, $p = 0.037$) and 5 months (−11 points, $p = 0.008$) after treatment.

Statistically significant changes in HRQOL measures over time for the whole group, the SRT-TB group, and the WBRT group are shown in Figs. 2 and 3.

Discussion

Our prospective self-reported HRQOL evaluation demonstrated a short-term increase in symptom burden attributable to WBRT toxicity, as drowsiness, appetite loss, and hair loss in patients receiving up-front WBRT after surgery of single brain metastasis. Patients who had no up-front WBRT and received SRT-TB had a lower level of WBRT-related symptomatology than patients who received WBRT. However, they experienced a worsening of global health status and physical functioning at 5 months compared with the baseline score. Cognitive functioning as evaluated by patients remained stable in both groups.

It might be expected that if RT is given in the adjuvant setting, at least short-term HRQOL should be affected. Such an effect may be worse for more toxic treatment, which applies to WBRT. Morphological changes that occur in the brain after irradiation are correlated with the volume of irradiated brain [13]. If WBRT is used for intact metastases, we may expect improvement of HRQOL by the alleviation of symptoms of brain metastases. However, this concept has been challenged. Symptoms were evaluated prospectively in 91 patients with poor performance status with brain metastases at baseline and 1 month after WBRT; only 47% of the patients completed symptom checklists at 1 month. The remaining patients died or were not able to respond to 17 questions from the checklist because of deterioration in performance and/or neurological status. Patients who responded had a significantly higher burden of symptoms 1 month after treatment than at baseline, mainly not only due to WBRT toxicity and prolonged consumption of steroids but also due to insufficient symptom alleviation [14]. In a recent randomized trial, WBRT was compared with dexamethasone plus best supportive care without brain irradiation in patients with brain metastases from non-small cell lung cancer who were

Table 1 Mean scores of QLQ-C30 and BN-20 questionnaire measures in the stereotactic radiotherapy of the tumor bed (SRT-TB) and whole brain radiotherapy (WBRT) group at baseline, 2 and 5 months after treatment

HRQOL measure	SRT-TB group Mean (Standard deviation)	WBRT group Mean (Standard deviation)	*p* value
Global health status			
At baseline	66.7 (20.6)	66.7 (17.3)	0.94
At 2 months	65.9 (24.6)	61.4 (25.7)	0.60
At 5 months	55.7 (26.9)	67.1 (23.7)	0.19
Functional scales			
Physical function			
At baseline	79.0 (23.2)	71.6 (24.0)	0.26
At 2 months	75.5 (28.5)	71.0 (19.1)	0.19
At 5 months	64.8 (25.0)	76.8 (17.9)	0.19
Role function			
At baseline	82.2 (33.1)	75.7 (32.4)	0.29
At 2 months	77.7 (32.0)	84.1 (20.2)	0.82
At 5 months	73.5 (33.1)	80.6 (23.8)	0.78
Emotional function			
At baseline	79.5 (17.6)	73.9 (19.2)	0.49
At 2 months	79.5 (26.5)	72.4 (18.4)	0.14
At 5 months	85.4 (12.8)	74.5 (22.1)	0.19
Cognitive function			
At baseline	94.4 (17.5)	84.8 (16.9)	0.046
At 2 months	86.7 (28.3)	85.7 (18.7)	0.55
At 5 months	93.1 (16.6)	86.8 (13.0)	0.13
Social function			
At baseline	75.6 (35.0)	81.1 (20.7)	0.98
At 2 months	66.7 (31.6)	76.5 (25.5)	0.39
At 5 months	74.9 (32.3)	76.9 (22.2)	0.95
Symptom scales/items			
Fatigue			
At baseline	23.5 (22.5)	28.0 (18.6)	0.37
At 2 months	28.0 (29.9)	34.1 (20.3)	0.23
At 5 months	38.2 (27.9)	25.7 (17.3)	0.30
Nausea/vomiting			
At baseline	0.0 (0.0)	4.5 (10.5)	0.36
At 2 months	1.1 (4.4)	11.4 (15.7)	0.07
At 5 months	4.2 (10.3)	9.3 (13.0)	0.33
Pain			
At baseline	11.1 (13.5)	11.3 (16.5)	0.85
At 2 months	14.5 (21.7)	13.0 (17.0)	0.89
At 5 months	19.4 (30.8)	12.1 (17.9)	0.80
Dyspnoea			
At baseline	11.1 (20.6)	12.1 (26.3)	0.90
At 2 months	15.5 (30.5)	6.0 (13.0)	0.59
At 5 months	13.8 (22.3)	9.2 (15.2)	0.74
Insomnia			
At baseline	22.2 (32.6)	30.2 (34.0)	0.42
At 2 months	33.3 (37.9)	21.1 (24.3)	0.47
At 5 months	33.3 (34.9)	24.1 (27.6)	0.54
Appetite loss			
At baseline	4.4 (11.6)	9.0 (15.0)	0.49
At 2 months	8.9 (19.8)	30.2 (30.7)	0.03

Table 1 continued

HRQOL measure	SRT-TB group Mean (Standard deviation)	WBRT group Mean (Standard deviation)	*p* value
At 5 months	25.1 (32.3)	25.8 (33.4)	0.93
Constipation			
At baseline	6.6 (13.7)	12.0 (16.2)	0.41
At 2 months	11.1 (27.2)	13.5 (19.6)	0.47
At 5 months	25.0 (30.0)	25.9 (31.5)	0.98
Diarrhea			
At baseline	4.4 (11.6)	4.5 (11.6)	1.0
At 2 months	2.2 (8.5)	10.5 (18.9)	0.29
At 5 months	8.3 (20.8)	7.3 (14.1)	0.88
Financial difficulties			
At baseline	15.5 (30.5)	24.3 (32.9)	0.46
At 2 months	24.5 (38.8)	24.2 (31.2)	0.78
At 5 months	16.7 (33.4)	20.3 (23.3)	0.41
Visual disorders			
At baseline	9.5 (10.9)	15.2 (18.9)	0.62
At 2 months	11.7 (16.4)	8.5 (12.7)	0.63
At 5 months	10.1 (13.6)	3.7 (9.2)	0.24
Motor dysfunction			
At baseline	11.1 (26.5)	19.5 (26.5)	0.14
At 2 months	14.0 (27.0)	16.2 (19.1)	0.26
At 5 months	14.8 (28.5)	20.2 (20.9)	0.20
Communication deficit			
At baseline	4.4 (10.0)	6.3 (12.8)	0.82
At 2 months	7.4 (25.8)	5.5 (8.8)	0.29
At 5 months	1.8 (6.4)	4.9 (9.4)	0.41
Future uncertainty			
At baseline	31.1 (26.4)	27.0 (18.9)	0.84
At 2 months	27.2 (26.7)	21.2 (15.5)	0.81
At 5 months	24.3 (27.7)	20.7 (18.6)	1.00
Headaches			
At baseline	6.6 (13.7)	14.1 (16.7)	0.26
At 2 months	13.2 (16.7)	19.5 (19.6)	0.41
At 5 months	8.3 (14.9)	18.5 (26.1)	0.42
Seizures			
At baseline	2.2 (8.5)	4.8 (16.0)	0.89
At 2 months	8.9 (26.6)	1.5 (7.0)	0.65
At 5 months	0.0 (0.0)	1.8 (7.8)	0.82
Drowsiness			
At baseline	19.9 (24.6)	23.6 (18.6)	0.51
At 2 months	19.9 (27.5)	36.2 (25.1)	0.048
At 5 months	19.3 (17.0)	29.4 (19.5)	0.24
Hair loss			
At baseline	17.7 (27.7)	4.7 (11.8)	0.18
At 2 months	13.3 (24.6)	30.3 (39.7)	0.26
At 5 months	16.7 (26.7)	33.3 (39.7)	0.32
Itchy skin			
At baseline	11.1 (27.2)	3.1 (9.9)	0.59
At 2 months	13.3 (21.1)	10.6 (21.6)	0.65
At 5 months	2.8 (9.5)	16.7 (26.3)	0.24

Table 1 continued

HRQOL measure	SRT-TB group Mean (Standard deviation)	WBRT group Mean (Standard deviation)	*p* value
Weakness of legs			
At baseline	11.1 (24.2)	12.6 (19.6)	0.63
At 2 months	15.5 (24.8)	15.1 (24.7)	0.96
At 5 months	19.4 (33.2)	14.7 (20.5)	1.00
Bladder control			
At baseline	4.4 (11.6)	11.0 (24.3)	0.59
At 2 months	8.8 (15.1)	9.1 (18.3)	0.99
At 5 months	13.8 (30.0)	5.5 (17.2)	0.54

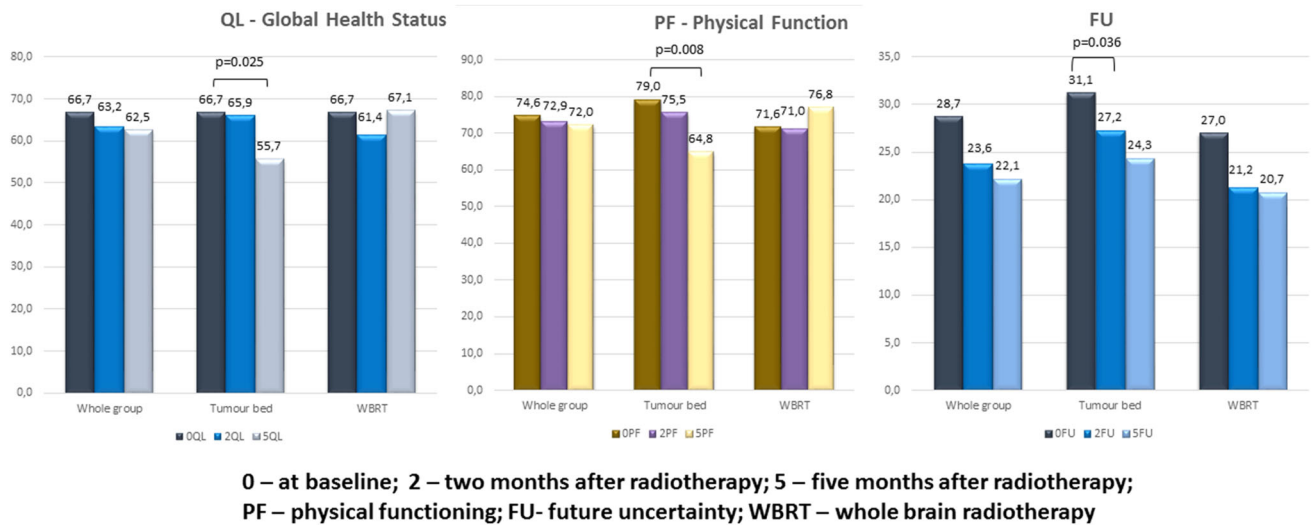

Fig. 2 Changes in global health status, physical functioning, and future uncertainty measures over time for the whole group, the SRT-TB group, and the WBRT group

unsuitable for surgery or radiosurgery. No difference was found between treatments in either overall survival or in QOL assessed using the EQ-5D 3L questionnaire at 4, 8, and 12 weeks and compared with baseline [15]. Wong et al. [16] demonstrated that some symptoms—such as appetite, concentration loss, and insomnia, which are recognized side effects of WBRT—correlate with HRQOL. Thus, the use of WBRT itself may compromise HRQOL.

Two large fully published randomized trials that compared local treatment such as surgery or radiosurgery [4, 17] for one to three brain metastases with the same local treatment but combined with WBRT demonstrated the negative impact of WBRT on HRQOL. The EORTC 22952-26001 trial compared adjuvant WBRT with observation after radiosurgery or surgery of one to three brain metastases. The results showed no difference in overall survival and time to loss of functional independence between arms, despite an increased rate of intracranial progression in the observation arm [3]. This worse control of the disease in the brain did not translate into worse HRQOL in patients without up-front WBRT. On the contrary, when comparing global health status, physical, cognitive, role, emotional functioning, and fatigue evaluated prospectively up to 1 year with QLQ-C30 and QLQ-BN20 questionnaires, patients who received WBRT experienced significantly more fatigue and declared lower physical functioning at 2 months after treatment than patients treated without WBRT. Patients also declared worse global health status at 9 months and worse cognitive functioning at 12 months [17]. Another trial prospectively compared cognitive function with a well-established battery of cognitive tests between patients who received radiosurgery and those who received radiosurgery with up-front WBRT. Better cognitive performance was demonstrated at 3 and 12 months of follow-up for patients treated without WBRT. In that trial, QOL was assessed using the Functional Assessment of Cancer Therapy-Brain (FACT-Br) questionnaire. The results were available only for 3 months

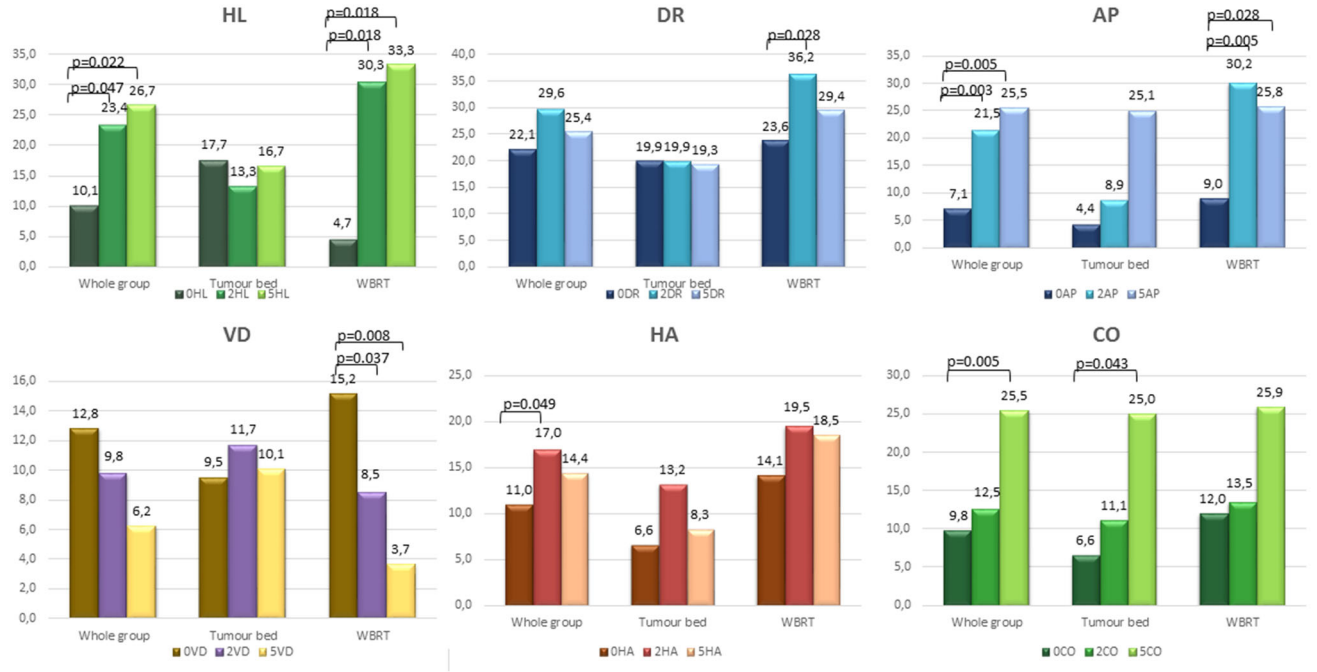

Fig. 3 Changes in hair loss, drowsiness, appetite loss, headache, constipation, and visual disorders over time for the whole group, the SRT-TB group, and the WBRT group

of follow-up, at which point there was worse QOL for patients who received WBRT, including overall score and functional well-being. The Barthel Index of ADL remained high at 3 months without significant differences between the groups [4].

Further studies are required to understand how the toxicity of WBRT impairs some aspects of QOL and to what extent it is transitory. The impairment of some aspects of QOL (physical and role functioning) 3 months after treatment was observed in a small prospective trial of 29 patients with one to four brain metastases who received WBRT with simultaneous boost using volumetric arc therapy to the metastases. No difference was found in HRQOL results at 6 months compared with the pre-WBRT result. However, only five patients returned their forms at that time [18]. Similarly, in the EORTC trial, which demonstrated significant prolongation of overall survival with the use of prophylactic cranial irradiation compared with observation after chemotherapy in extensive-disease small cell lung cancer, HRQOL was impaired 3 months after treatment with the most negative impact of WBRT on hair loss and fatigue and minimal impact on global health status and functional scales. At 6 and 9 months, there was no difference in HRQOL between the groups [19]. Some impairment of QOL related to treatment may be acceptable if it is associated with prolongation of life caused by the treatment. In our trial, patients treated with WBRT had significantly longer overall survival and some adverse effects of WBRT such as drowsiness, appetite, and hair loss were not reflected in their global perception of health status and did not impact physical functioning. On the contrary, patients from the SRT-TB group experienced a significant decrease in global health status and physical functioning. This was likely related to shorter survival and the higher rate of neurological deaths shown in the SRT-TB arm [8]. Patients with disease progression cannot rate highly their health status and physical functioning. Reasons for shortened survival may be complex and may also be due to statistical hazard related to a small sample size. However, we cannot exclude that the omission of up-front WBRT by the increase of intracranial failure is detrimental in group of patients with especially good prognosis related to good performance status and resected single brain metastasis. This result is consistent with a post hoc analysis of the Japanese Radiation Oncology Study Group 99-1 trial, which compared radiosurgery with and without WBRT, in patients with lung cancer and a favorable prognosis as determined by the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA). Patients in whom WBRT had been omitted demonstrated a significantly shorter overall survival (16.7 vs. 10.6 months, $p = 0.04$) [20].

We demonstrated a comparable outcome for neurocognitive function assessed by MMSE and neurological

evaluation according to the MRC scale in our trial for WBRT and SRT-TB. We were aware of the limitations of MMSE used in our study in the assessment of neurocognitive function, because it does not detect the subtle memory and cognition changes and is more suitable for screening of dementia. However, due to its convenience of filling it in a busy department, we were using it similarly as in other studies [2]. Some data indicate a correlation between neurocognitive function and QOL. In the prospective study, in which patients had regular neurocognitive function and QOL (ADL and FACT-Br) testing before and after WBRT, worsening of the score in tests that evaluated neurocognitive function was predictive of deterioration of ADL and FACT-Br [10]. In the phase II study in which patients received hippocampal-avoidance WBRT, the prospective evaluation of memory with the Hopkins Verbal Learning Test-Revised—Delayed Recall and QOL with ADL and FACT-Br tests revealed a preservation of memory and no deterioration of QOL in 42 of 113 patients for whom such an evaluation was performed 4 months after treatment. It was pointed out that prevention of memory decline may represent one potential mechanism for QOL preservation after WBRT [21]. Certainly, there is a relationship between neurocognitive function and HRQOL, but this influence may be reciprocal. Some early side effects of WBRT, measured in QLQ tests as fatigue, may also negatively impact the results of cognitive tests. In our trial, the level of fatigue was insignificantly increased 2 months after WBRT, but not to the point where global perception of health status declined. 5 months after WBRT, the perception of fatigue was reduced, in opposite to that patients who received SRT-TB had an increase in fatigue of 14.7 points in relation to the baseline score. This may be related also to shorter overall survival and worse intracranial control in these patients, as was discussed for physical functioning and global health status.

One limitation of our study is the small size of the group, because this increases the risk of statistical bias. Recently, the results of the prospective trial that compared WBRT with SRT-TB in 194 patients with up to four metastases including at least one resected showed similar overall survival, longer time to cognitive decline, and improvement of QOL evaluated at 3 and 6 months in patients who did not have up-front WBRT [9]. Although the different results in our study may be related to statistical hazard, as noted above, they may be related to differences in patient characteristics (all patients with single brain metastases subject to resection, good performance status). Another limitation of our study is the low compliance for HRQOL evaluation in longer follow-up. This is unfortunate because WBRT is recognized for its late toxicity; indeed, in our trial, four out of 19 cases of neurocognitive failure in the WBRT arm were attributed to treatment toxicity and occurred at 2, 8, and as late as 20 and 45 months of follow-up [8]. If neurocognitive failure precedes deterioration of HRQLQ, this might also decrease QOL of survivors [10]. However, its clinical meaning should be interpreted in the light of improved overall survival.

In conclusion, in this prospective study, we demonstrated a short-term increase of symptoms recognized as side effects of WBRT in patients who received WBRT without impact on global health status and functional scales. Patients treated only with SRT-TB had a significantly lower level of WBRT-related symptomatology. However, at 5 months they had a significant decrease in global health status and physical functioning, which reflects their worsened state of being after the treatment.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Patchell R, Tibbs P, Regine W, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280:1485–9.
2. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs. stereotactic radiosurgery alone for treatment of brain metastases. JAMA. 2006;295:2483–91.
3. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol. 2011;29:134–41.
4. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA. 2016;316:401–9.
5. Chang E, Wefel J, Hess K, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10:1037–44.
6. Roberge D, Parney I, Brown PD. Radiosurgery to the postoperative surgical cavity: who needs evidence? Int J Radiat Oncol Biol Phys. 2012;83:486–93.
7. Van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomized trial. Lancet. 2005;366:985–90.
8. Kepka L, Tyc-Szczepaniak D, Bujko K, Olszyna-Serementa M, Michalski W, Sprawka A, et al. Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: results from a randomized study. Radiother Oncol. 2016;121:217–24.
9. Brown PD, Ballman KV, Cerhan J, Anderson SK, Carrero XW, Whitton AC, et al. A phase III trial of post-operative stereotactic radiosurgery (SRS) compared with whole brain radiotherapy (WBRT) for resected metastatic brain disease. Int J Radiat Oncol Biol Phys. 2016;96:937S.
10. Li J, Bentzen SM, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. Int J Radiat Oncol Biol Phys. 2008;71:64–70.

11. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365–76.
12. Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer. 2010;46:1033–40.
13. Stokes TB, Niranjan A, Kano H, Choi PA, Kondziolka D, Dade Lunsford L, et al. White matter changes in breast cancer metastases patients who undergo radiosurgery alone compared to whole brain radiation therapy plus radiosurgery. J Neurooncol. 2015;121:583–90.
14. Komosinska K, Kepka L, Niwinska A, Pietrzak L, Wierzchowski M, Tyc-Szczepaniak D, et al. Prospective evaluation of the palliative effect of whole-brain radiotherapy in patients with brain metastases and poor performance status. Acta Oncol. 2010;49:382–8.
15. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet. 2016;388:2004–14.
16. Wong E, Zhang L, Rowbottom L, Chiu N, Chiu L, McDonald R, et al. Symptoms and quality of life in patients with brain metastases receiving whole-brain radiation therapy. Support Care Cancer. 2016;24:4747–59.
17. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol. 2013;31:65–72.
18. Weber DC, Caparrotti F, Laouiti M, Malek K. Simultaneous in-field boost for patients with 1 to 4 brain metastasis/es treated with volumetric modulated arc therapy: a prospective study on quality of life. Radiat Oncol. 2011;6:79.
19. Slotman BJ, Mauer ME, Bottomley A, Faivre-Finn C, Kramer GW, Rankin EM, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol. 2009;27:78–84.
20. Aoyama H, Tago M, Shirato H. Japanese Radiation Oncology Study Group 99-1 (JROSG 99-1) Investigators. Stereotactic Radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99-1 randomized clinical trial. JAMA Oncol. 2015;1:457–64.
21. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol. 2014;32:3810–6.