Confirmatory Analysis of QUARTZ Study Results: Survival Prolongation after Whole-brain Radiotherapy

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Abstract. *Background/Aim: The aim of this study was to analyze the survival of patients with brain metastases treated with best supportive care or additional whole-brain radiotherapy (WBRT), in order to confirm results from the prospective randomized QUARTZ study, which suggested prolonged survival after WBRT (5 fractions of 4 Gy) if favorable prognostic factors were present (age younger than 60 years, graded prognostic assessment score 2.5-3 points). Patients and Methods: We performed a retrospective single institution analysis of 76 patients with favorable prognosis. In contrast to the QUARTZ trial, inclusion was not limited to patients with non-small cell lung cancer (NSCLC). Furthermore, a cohort treated with higher total doses of WBRT was included (10 fractions of 3 Gy). Results: All patients were younger than 60 years or had a graded prognostic assessment score of 2.5-3. The median survival was significantly shorter after best supportive care (1.2 months; 3.2 months after WBRT with 5 fractions of 4 Gy and 3.9 months after 10 fractions of 3 Gy). Also, in multivariate analyses, survival was significantly better after WBRT. Further favorable prognostic factors included better performance status, no or limited extracranial metastases and primary tumor other than gastrointestinal. Conclusion: In line with the QUARTZ trial results, WBRT prolonged survival in patients with favorable prognostic features.*

In patients with brain metastases from extracranial primary tumors, such as lung or breast cancer, current treatment options include surgical resection and stereotactic radiotherapy, as well as whole-brain radiotherapy (WBRT) and best supportive care (BSC) without metastases-directed approaches (1-3). Patient selection is not always trivial, especially when it comes to the decision to withhold active, metastases-directed approaches (4-6). The prospective randomized multicenter QUARTZ trial was a pragmatic trial performed between 2007 and 2014 (7). The protocol required uncertainty in the clinicians' or patients' minds about the potential benefit of WBRT and used a non-inferiority design. All patients had non-small cell lung cancer (NSCLC) and were offered BSC including dexamethasone, which a significant majority received. In the WBRT arm, treatment consisted of 5 fractions of 4 Gy each. The primary outcome measure was quality-adjusted life-years (QALYs). Median age was 66 years (range=38-85). The authors concluded that there was no significant difference in QALYs between the two treatment arms (mean= 46.4 QALY days for the WBRT arm *versus* 41.7 QALY days for WBRT and BSC, respectively). There was also no significant difference observed in overall survival (hazard ratio= 1.06, 95% confidence interval= 0.90-1.26) between the two groups. In the WBRT arm, median survival was 9.2 weeks. However, WBRT prolonged survival in patients younger than 60 years of age (hazard ratio= 1.48, 95% confidence interval= 1.01-2.16) and those with graded prognostic assessment (GPA) score of 2.5-3 points (hazard ratio= 1.65, 95% confidence interval= 1.04-2.60). The GPA score is a widely used 4-tiered prognostic model based on different baseline parameters, which differ by primary diagnosis, *e.g*. lung cancer, breast cancer, malignant melanoma and kidney cancer (8). Given that many patients with brain metastases have primary tumors other than NSCLC, we designed a retrospective study of WBRT *versus* BSC that included all patients irrespective of primary tumor, if they had the same favorable prognostic

features that were associated with better survival after WBRT in the QUARTZ trial, *i.e.* age younger than 60 years or diagnosis-specific GPA 2.5-3 points. Furthermore, we included an additional group of patients treated with WBRT who received a higher total dose than in the QUARTZ trial (10 fractions of 3 Gy).

Material and Methods

Patients and treatment

A retrospective study of all patients with parenchymal brain metastases from histologically verified extracranial primary tumors treated with WBRT (5 fractions of 4 Gy or 10 fractions of 3 Gy, no boost) or BSC at our hospital was performed. The patients were treated between January 01, 2007 and December 31, 2018 and identified from a continuously updated database (9, 10). None of the patients had received previous treatment for brain metastases (neither prophylactic cranial irradiation). After WBRT, further systemic and local treatment was individualized. The choice between the two WBRT regimens was at the discretion of the radiation oncologist. BSC was typically pursued if recommended by the multidisciplinary tumor board and agreed by the patients and caregivers. Factors such as old age, poor Karnofsky performance score (KPS) and extensive metastatic spread were common reasons to recommend BSC. The diagnosis-specific GPA was assigned as originally described by Sperduto *et al.* (8). The maximum point sum was 4, minimum 0. A point sum of 2.5-3 indicates a relatively good prognosis. Inclusion was limited to patients with 2.5-3 points or age younger than 60 years.

Statistical methods

Overall survival (time to death) from imaging diagnosis of brain metastases was calculated employing the Kaplan-Meier method, and different groups were compared

using the log-rank test (SPSS 25, IBM Corp., Armonk, NY, USA). Only two patients were censored. Date of death was known in all other patients. A Cox forward conditional regression model was employed for multivariate analysis. The chi-square test was used to compare differences in baseline characteristics between the patient groups. Statistical significance was defined as $p \leq 0.05$ throughout this study.

Results

Patient characteristics

We identified 76 patients from the database. Thirty-two (42%) had NSCLC. The median age was 55.5 years. Twenty patients (26%) were included because of their favorable diagnosis-specific GPA score, meaning that age younger than 60 years was the prevailing reason for inclusion. Further patient characteristics are shown in Table I.

Treatment

Fourteen patients (18%) received BSC, 9 (12%) WBRT with the 5-fraction regimen and 53 (70%) with the 10-fraction regimen. In the latter group, one patient did not complete all 10 fractions of WBRT.

Survival

The median overall survival of the BSC group was 1.2 months. As shown in Figure 1, WBRT was associated with significantly better survival. The difference between the 5- and 10-fraction regimens was not statistically significant. Beyond WBRT, other factors were associated with better survival: female gender (p=0.057), non-gastrointestinal primary tumor (p=0.025), no extracranial metastases or to one organ only (p=0.009),

better KPS (p=0.0001), 1-3 brain metastases (p=0.027), better diagnosis-specific GPA (p=0.001).

Importantly, patients in the 10-fraction WBRT group had significantly better KPS (Table I). However, they also had a significantly larger number of brain metastases. There was also a difference regarding median age (BSC: 57 years, WBRT 5 fractions: 53 years, WBRT 10 fractions: 55 years, p=0.048). Two different multivariate analyses of overall survival were performed to adjust for differences in baseline prognostic parameters. One included only the diagnosis-specific GPA as a surrogate of confounding prognostic imbalance and showed that both GPA (p=0.002) and WBRT (p=0.0001) influenced survival. The other one included all individual prognostic factors rather than GPA and showed that WBRT (p=0.008), KPS (p=0.0001), non-gastrointestinal cancer (p=0.03) and absence of extracranial metastases or involvement of maximum one organ (p=0.02) influenced survival. Female gender and number of brain metastases lost their significance in this model.

Discussion

The large randomized QUARTZ trial has previously shown that WBRT (5 fractions of 4 Gy) prolonged survival in patients with NSCLC who were younger than 60 years of age (hazard ratio= 1.48) and those with GPA score of 2.5-3 points (hazard ratio= 1.65). The subgroup with GPA score of 3.5-4 points was too small for meaningful analyses. Since many patients with brain metastases have primary tumors other than NSCLC additional evidence from mixed cohorts is required. Moreover, WBRT with higher total dose (10 fractions of 3 Gy) may in principle result in even better survival than WBRT with lower total dose. These considerations prompted us to perform the present retrospective study,

which compares three different strategies: BSC, 5-fraction WBRT and 10-fraction WBRT in patients with favorable prognostic characteristics, as defined from the results of the QUARTZ trial.

Limitations of the present study include the limited number of patients, statistical power of subgroup analyses, and retrospective design. Fewer patients than anticipated were managed with BSC and 5-fraction WBRT. Nevertheless, the survival difference between these two groups, which persisted in the multivariate models, is in line with the findings from the QUARTZ trial. Interestingly, 10-fraction WBRT was not significantly better than 5-fraction WBRT. On the other hand, all long-term survivors belonged to the group with 10-fraction WBRT. In the absence of randomization, this finding may still be caused by selection bias and the fact that the WBRT regimens were assigned according to physicians' choice. In order to increase the statistical power, multivariate analyses were stratified by BSC or any WBRT, rather than three different strata. As a result of the patient selection criteria mentioned above, the present cohort was younger than generally observed in the literature (11-16).

Primary WBRT has recently become a rather controversial approach, especially in patients with better prognosis and/or limited number of brain metastases (17, 18). Advanced WBRT techniques with hippocampal sparing and dose escalation on visible brain metastases are under study and may eventually increase the acceptance of WBRT (19). On the other hand, focal stereotactic radiotherapy, which results in superior local control than conventional 10-fraction WBRT, will continue to play an important role. It is likely that improved prognostic models will impact on patient selection, both regarding the decision towards BSC in patients with poor prognostic features and the decision to

recommend effective local treatment in other patients (20-23). The original diagnosis-specific GPA as used in the QUARTZ trial will soon be replaced by its new and refined variants (24, 25).

Conclusion

In line with the QUARTZ trial results, WBRT prolonged survival in patients with favorable prognostic features, defined as age younger than 60 years or diagnosis-specific GPA score 2.5-3 points.

Conflicts of Interest

The Authors declare that they have no competing interests.

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Authors' Contributions

CN participated in the design of the study and performed the statistical analysis. AD and AP collected patient data. CN, and AD conceived the study and drafted the article. All Authors read and approved the final article.

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Figure Legend

Figure 1. Actuarial overall survival after BSC (RT 0, median 1.2 months), 5 fractions of WBRT (RT 20, median 3.2 months) and 10 fractions of WBRT (RT 30, median 3.9 months); log-rank test *p*-values: 0.05 (BSC *versus* 5 fractions), 0.0001 (BSC *versus* 10 fractions) and 0.18 (5 *versus* 10 fractions).

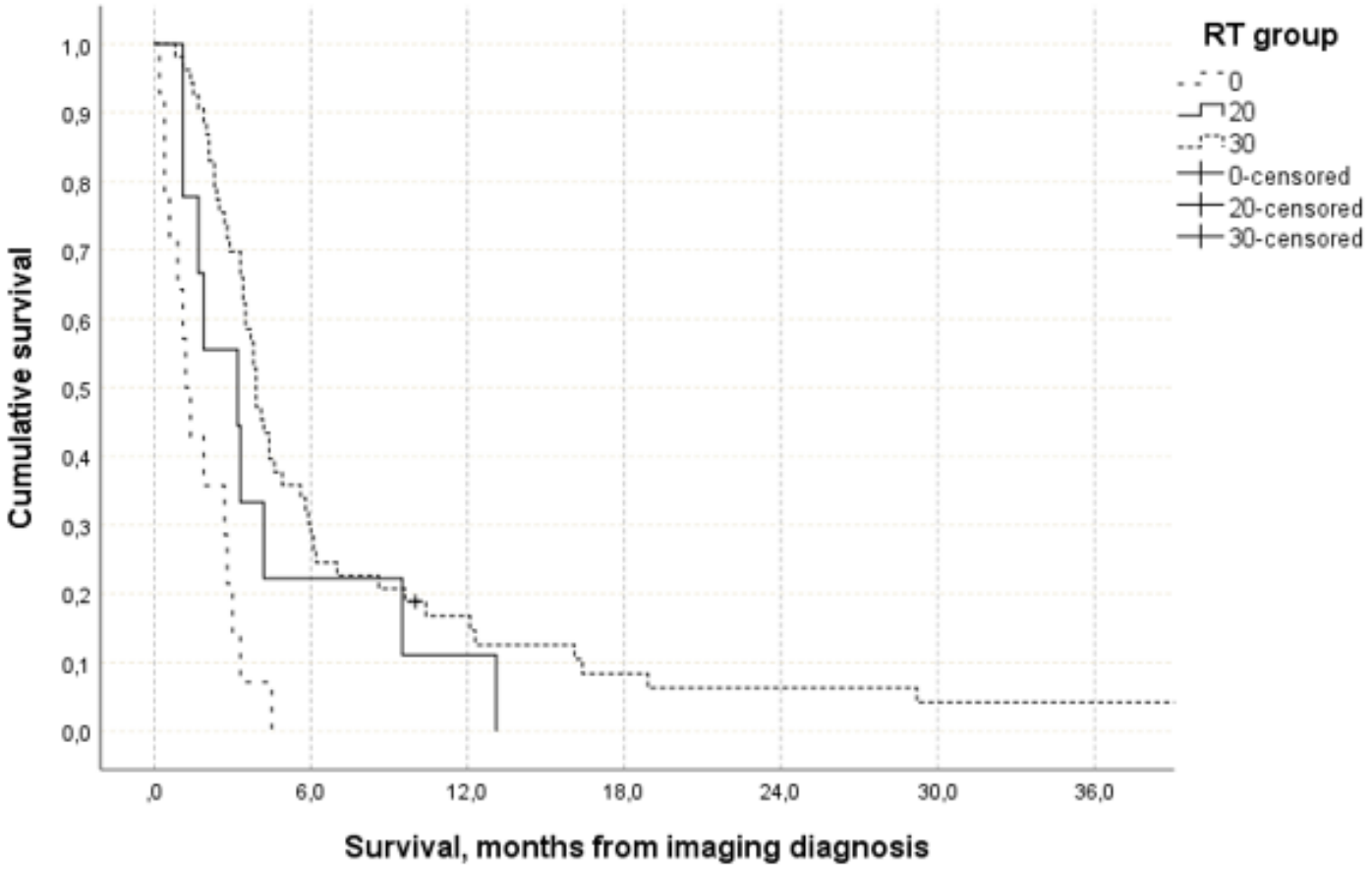
RT group
0
20
30
0-censored
20-censored
30-censored
Cumulative survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
,0
6,0
12,0
18,0
24,0
30,0
36,0
Survival, months from imaging diagnosis

Table I. Patient characteristics.

Baseline parameter	BSC	WBRT 5 fractions	WBRT 10 fractions	Significant differences between the groups
Non-small cell lung cancer	5	5	22	
Small cell lung cancer	1	1	4	
Breast cancer	0	0	9	
Malignant melanoma	2	2	6	
Kidney cancer	2	0	5	
Gastrointestinal cancer	3	1	6	
Other primary	1	0	1	
Synchronous brain metastases*	2	2	10	
No extracranial metastases	2	1	11	
Extracranial metastases, one organ, e.g. bones	1	4	11	
Extracranial metastases, at least two organs	11	4	31	
Controlled primary tumor	9	5	34	
Female gender	5	4	30	
Male gender	9	5	23	
1-3 brain metastases	11	5	20	
More than 3 brain metastases**	3	4	33	p=0.021
KPS >70	0	1	17	
KPS 70	4	3	26	
KPS <70	10	5	10	p=0.001
Poor diagnosis-specific GPA, 0-1	7	5	24	
Intermediate diagnosis-specific GPA, 1.5-2	3	4	11	

Good diagnosis-specific GPA, 2.5-4***	3	0	17	

BSC: Best supportive care; WBRT: whole-brain radiotherapy; KPS: Karnofsky performance score; GPA: graded prognostic assessment.
* Median time interval from first cancer diagnosis 9.5, 6.0 and 9.0 months, *p*=0.65.
** Median number of brain metastases in each group: 1.5, 3.0 and 5.0, *p*=0.05.
***Undefined GPA in two cases. Median GPA in each group: 1.0, 1.0 and 1.5, *p*=0.097.