

IMPLEMENTATION OF QUARTZ TRIAL FINDINGS IN CLINICAL PRACTICE: INSIGHTS FROM A TERTIARY CANCER CENTER

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Abstract

Background: The management of non-small cell lung carcinoma (NSCLC) with multiple brain metastases typically involves whole brain radiotherapy (WBRT). The QUARTZ trial employed a disease-specific grade prognostic assessment (DsGPA) and demonstrated the equivalence of observation with best supportive care (BSC) in comparison to WBRT in patients with poor risk group. **Aim:** This study aims to analyze the overall survival of NSCLC patients with brain metastasis who underwent whole brain radiotherapy and to compare the survival and quality of life (QOL) of poor risk group that received WBRT versus BSC. **Material & Methods:** A retrospective analysis on 50 metastatic non-small cell lung cancer (NSCLC) patients who received whole brain radiotherapy (WBRT) for brain metastasis between January 2016 and December 2019. Patient demographics (age, gender, Karnofsky Performance Status), tumor characteristics (histology, number of brain metastatic lesions, extracranial metastasis), survival, and QOL data were collected from medical records and telephonic interviews with patients' relatives. Each patient given a score based on 4 tier DsGPA system was used to classify patients into risk groups. **Results:** In this study, the mean age of the patient population was 55 years and the majority of patients were male (60%). A high proportion of patients (77%) had a poor performance status (KPS < 70) and the most common histology was adenocarcinoma (95%). The majority of patients (75%) had more than three brain metastatic lesions, with 12.5% having two lesions, 10% having one lesion, and 2.5% having three lesions, The DsGPA for this group was 1. The poor risk group of patients, characterized by KPS < 70, multiple brain lesions, and extra cranial metastasis, experienced a significantly reduced median overall survival of 1.2 months compared to an estimated survival of 3 months from DsGPA. **Conclusion:** These findings align with the results of the QUARTZ trial, supporting the notion that BSC is a reasonable choice for patients with limited survival expectations. This study offers valuable insights into the implementation of QUARTZ trial findings in clinical practice.

INTRODUCTION

Lung cancer is the most common leading cause of cancer related fatalities, contributing to a substantial portion of cancer deaths worldwide. It is noteworthy that a considerable percentage (57%) of non-small cell lung cancer (NSCLC) cases are diagnosed at an advanced stage with metastatic disease, and out of these, approximately 20% develop brain metastasis (BM).^[1,2] Alarming, a significant proportion of NSCLC patients (ranging from 25-50%) will experience the onset of metastatic disease during

course of their illness.^[3] Among the myriad of complications associated with NSCLC, brain metastasis presents a particularly dire scenario, leading to substantial morbidity and mortality among the patients. Brain metastases are categorized into solitary, oligometastatic (<3 metastases) and multiple metastases. Previously, WBRT and steroids has served as the standard of care for all patients presenting with brain metastases. However, the current landscape for managing brain metastasis has evolved, focusing on the radical treatment approach for solitary lesions, which encompasses surgical

resection or radiosurgery followed by WBRT and radiotherapy. In cases of oligometastatic disease, WBRT is generally recommended, with exceptions made for selected cases that may benefit from surgical resection and stereotactic radiosurgery (SRS). For multiple metastases, WBRT remains the conventional treatment choice.^[4,5] Recent studies, however, have cast doubt on the efficacy of WBRT, especially for patients with poor prognosis, as it may not confer significant survival benefits and can potentially lead to cognitive decline. The groundbreaking QUARTZ trial, conducted in 2016, introduced a disease-specific grade prognostic assessment (DsGPA) and demonstrated the equivalence of observation with best supportive care (BSC) in comparison to WBRT for patients in the poor risk group.^[6]

Two widely used risk stratification tools for patients with brain metastases are Disease-specific grade prognostic assessment (DsGPA) and recursive partitioning analysis (RPA). While both tools aim to predict overall survival and to guide treatment decisions, DsGPA distinguishes itself by incorporating disease-specific factors, such as the patient's performance status, extracranial metastases, and number of brain metastases. This nuanced approach allows for a more accurate assessment of overall survival and treatment outcomes. Moreover, DsGPA has demonstrated better predictive accuracy compared to RPA in patients with lung cancer brain metastases. A study published in the *Journal of Clinical Oncology*,^[7] reported DsGPA had an overall accuracy of 72.2% for DsGPA compared to 68.9% for RPA.

In the case of melanoma brain metastases, another study published in *Journal of Clinical Oncology*,^[8] found DsGPA to be more prognostically accurate than RPA with an overall accuracy of 78.4% compared to 75.4% for RPA.

The 4-tier DsGPA, as used in the QUARTZ trial includes age, Karnofsky Performance Status (KPS), extracranial metastasis, and number of brain metastases as prognostic factors. Each factor is assigned a score ranging from 1 to 3, with higher scores indicating a poorer prognosis. The cumulative DsGPA score ranges from 4 to 12, with higher score indicating poorer prognosis and lower scores indicating a better prognosis. This DsGPA system has been developed and validated in various studies.^[9,10]

Aim: The aim of the current study is to compare the survival and quality of life (QOL) of poor risk group that underwent WBRT vs Best supportive care (BSC) as per QUARTZ Trial criteria.

MATERIALS AND METHODS

Ethics statement: This study adhered to ethical guidelines, ensuring the protection of patient confidentiality and informed consent for data collection.

Study design: This retrospective study was conducted to analyze demographic and tumor characteristics, survival, and quality of life outcomes in a cohort of 50 patients diagnosed with metastatic non-small cell lung cancer (NSCLC) who received whole brain radiotherapy (WBRT) for brain metastasis. The study period spanned from January 2016 and December 2019. The specific WBRT regimen administered in this study consisted of a total dose of 30 Gy, delivered in 3 Gy per fraction over 10 fractions.

Data Collection: The patient cohort included individuals diagnosed with metastatic NSCLC with brain metastasis who had undergone WBRT during the specified time frame. The demographic information (age, gender, Karnofsky Performance Status (KPS)), relevant tumor characteristics (Histology of the primary lung cancer, number of brain metastatic lesions and presence of extracranial metastasis) was collected from the patients' medical records. Information regarding the patients' survival outcomes was obtained from medical records, including the date of diagnosis, the date of initiating WBRT, and the date of death or the last follow-up. Survival outcomes were evaluated in terms of overall survival. Quality of life information was obtained through telephone interviews with the patients' relatives. This assessment aimed to gauge the patients' well-being, physical and mental health, and overall QOL. Each patient was assigned a score based on the 4-tier DsGPA system, considering the following prognostic factors: age, Karnofsky Performance Status (KPS), extracranial metastasis and number of brain metastases. A critical aspect of this study involved comparing the survival and QOL outcomes of the poor-risk group that underwent WBRT with those who received Best Supportive Care (BSC) as documented in the QUARTZ Trial.

Data Analysis: Statistical analysis was conducted to assess the impact of WBRT on the survival and QOL outcomes of patients, with a particular focus on the poor-risk group. Comparisons were made between patient groups based on the DsGPA scores, and statistical tests were employed to determine significant differences.

RESULTS

Demographic and tumor characteristics: In this study, the mean age of the patient population was 55 years and the majority of patients were male, constituting 60% of the cohort. A high proportion of patients (77%) had a poor performance status (KPS < 70) and the most common histology was adenocarcinoma (95%). The majority of patients (75%) had more than three brain metastatic lesions, with 12.5% having two lesions, 10% having just one lesion.

DsGPA Score, Risk Group and survival analysis: Among the study cohort, 66% (n=33) fell into poor risk group as per 4-tier DsGPA

The poor risk group patients who received WBRT in this study had a median survival of 7.9 weeks. This median survival in the poor-risk group receiving WBRT closely aligns with the median survival of 8.2 weeks observed in the best supportive care arm of the QUARTZ Trail for the patients with similar risk profiles.

Notably, the poor risk group characterized by KPS score less than 70, multiple brain lesions, and presence of extracranial metastasis, experienced a significantly reduced median overall survival of 2 months. This was in contrast to an estimated survival of 3 months according to the DsGPA. The DsGPA, which considers various prognostic factors such as age, KPS, extracranial metastasis, and the number of brain lesions, stratified patients into different risk groups based on their scores. [Table 1].

Patients of age less than 70 years (score of <70) are associated with a more favorable prognosis, as indicated by a score of 0.5. In contrast, patients aged 70 or older (score of >=70) have a less favorable prognosis with a score of 0. Patients with a KPS score of 90-100 (score of 90-100) have a more optimistic prognosis, evident by a score of 1. The presence of extracranial metastases (score of PRESENT) is associated with a less favorable

prognosis, indicated by a score 0. Patients with 1-4 brain lesions (score of 1-4) have a more favorable prognosis, as indicated by a score of 0.5 while patients with more than four brain lesions (score of >4) are associated with a poorer prognosis, resulting in a score of 0. Patients with positive gene status (score of POSITIVE) have a better prognosis, with a score of 1 and patients with EGFR/ALK-Negative or unknown gene status (score of EGFR/ALK-Neg/UK) have a less favorable prognosis, reflected in a score of 0.

Additionally, a GPA (Grade Point Average) system was used to predict median survival based on the overall score, which was derived from the aforementioned prognostic factors (Table 2). Patients falling within GPA range of 0 to 1, which typically indicates a more severe prognosis, are predicted to have a median survival of 3.0 months. This suggests that patients with lower cumulative scores, influenced by a combination of unfavorable factors, are likely to have a relatively shorter survival time. As the GPA score increases, reflecting more favorable prognostic factors, the predicted median survival also substantially improves. Patients with higher GPA scores are expected to live longer. [Table 2]

Table 1: Prognostic factors present among the study participants

PROGNOSTIC FACTOR	0	0.5	1
AGE	>/-70	<70	
KPS	<70	80	90-100
EXTRACRANIAL METS	PRESENT		ABSENT
NUMBER OF BRAIN LESIONS	>4	1-4	NA
GENE STATUS	EGFR/ALK-Neg/UK		POSITIVE

Table 2: GPA scores among the study participants

GPA	Median Survival(Months)
0-1	3.0
1.5-2	5.5
2.5-3	9.4
3.5-4	14.8

DISCUSSION

The management of non-small cell lung carcinoma (NSCLC) with multiple brain metastases is a formidable challenge for oncologists. Traditionally, whole brain radiotherapy (WBRT) has been the standard of care for these patients. While Advanced Radiation delivery techniques, such as stereotactic radiotherapy, have been explored.^[11,12,13] However, recent studies have raised questions about the efficacy of WBRT in this patient population.^[14]

The QUARTZ trial,^[6] a pivotal phase III, multicenter, randomized controlled trial challenged the status quo by comparing WBRT with best supportive care (BSC) in patients with NSCLC and brain metastases. The trial employed a disease-specific grade prognostic assessment (DsGPA), a risk stratification tool that considers factors such as patient's performance status, extracranial

metastases, and number of brain metastases. Intriguingly, The QUARTZ trial demonstrated the equivalence of observation with BSC to WBRT in terms of overall survival for patients in the poor risk group.

Our study sought to analyze the overall survival of NSCLC patients with brain metastasis who underwent WBRT and to compare the survival and quality of life (QOL) of poor risk group that received WBRT versus BSC. Our findings revealed that the poor risk group characterized by a KPS < 70, multiple brain lesions, and extracranial metastasis, had a significantly reduced median overall survival of 2 months compared to an estimated survival of 3 months. These results corroborate and align with the outcomes of the QUARTZ trial, suggesting that BSC may be a reasonable choice for patients with limited survival expectations.

Moreover, a meta-analysis,^[15] of eight randomized controlled trials involving 1,854 patients with brain metastases from lung cancer showed that WBRT did not improve overall survival in patients with poor prognostic factors, such as poor performance status and multiple brain metastases. Another study that included 1,052 patients with brain metastases from lung cancer had similar findings that WBRT did not improve overall survival in patients with poor prognostic factors, such as poor performance status, multiple brain metastases, and extracranial metastases.

Furthermore, a systematic review and meta-meta-analysis of 17 randomized controlled trials involving 3,045 patients with brain metastases from lung cancer developed a notion that WBRT did not improve overall survival in patients with poor prognostic factors, such as poor performance status, multiple brain metastases, and extracranial metastases. These collective findings align with the QUARTZ trial and our study, collectively advocating that BSC is a viable and reasonable choice in patients with limited survival expectations. One strength of our study is that it substantiates the findings of the QUARTZ trial, which demonstrated the equivalence of observation with best supportive care (BSC) compared to whole brain radiotherapy (WBRT) in patients with poor risk group. The utilization of disease-specific grade prognostic assessment (DsGPA) system in our study also bolsters its validity. DsGPA is a validated risk stratification tool that takes into account the patient's performance status, extracranial metastases, and number of brain metastases. Furthermore, the study's approach of incorporating both medical records and telephone interviews with the patients' relatives to obtain information on survival and quality of life adds depth and comprehensiveness to the data.

However, the study is not without limitations. Its retrospective nature, reliant on data from medical records and telephone interviews with patients' relatives, introduces potential bias and data inaccuracies. Additionally, this study focused solely on poor risk group patients who received WBRT, while the QUARTZ Trial included patients receiving both WBRT and Best supportive care. The relatively small sample size of our study, when compared to the QUARTZ Trial, could affect the generalizability of the findings.

CONCLUSION

In conclusion, despite its limitations, our study, along with the body of previous research advocates the implementation of the QUARTZ trial findings in clinical practice. These findings are instrumental in optimizing the management of NSCLC patients with brain metastases and enhancing their quality of life. It underscores the necessity of individualized treatment decisions for these patients, considering a

holistic assessment of their prognostic profile and the potential benefits of best supportive care in appropriate cases. This approach holds the promise of more compassionate and tailored care for this vulnerable patient population.

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