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Survival benefits of adding palliative whole brain radiotherapy in non-small cell lung cancer with brain metastases unsuitable for resection or radiosurgery: A clinical prediction rule

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INTRODUCTION: The QUARTZ trial demonstrated heterogeneous survival benefits of whole brain radiotherapy (WBRT) in non-small cell lung cancer (NSCLC) patients with brain metastases inappropriate for surgery or stereotactic radiosurgery/radiotherapy (SRS/SRT) which showed a favourable survival outcome with WBRT for those who were younger than 60 years old and potential benefits in patients with good Karnofsky Performance Status (KPS); ≥70%, no extra-cranial metastases and controlled primary NSCLC. The National Institute for Health and Care Excellence (NICE) guideline (NG99) recommends omission of WBRT for NSCLC patients with brain metastases who are not suitable for surgery or SRS/SRT with KPS<70%, while the National Comprehensive Cancer Network guideline (NCCN Version 2.2020) states that it is reasonable to hold on WBRT in selected NSCLC patients with extensive brain metastases if available CNS active agents exist. A question regarding proper selection of these patients to receive WBRT is to be solved. The objective of this study is to evaluate the added survival benefits of WBRT by developing and internal validating the individual survival prediction model for NSCLC patients with brain metastases inappropriate for surgery or SRS/SRT by using WBRT as a main prognostic factor.

METHODS: We retrospectively collected 479 NSCLC patients with brain metastases treated with either WBRT or optimal supportive care (OSC) from January 2004 to December 2019 from Siriraj hospital database using clinical characteristics as potential predictors, previously established elsewhere. The primary outcome was overall survival. By the time of analysis, 452 patients found dead. According to the rule of thumb of 10 events per predictor, 45 predictors were adequately examined in our model. The Cox proportional hazard regression was used for survival analyses. Linearity of continuous variable was checked using Martingale residuals. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement was followed. To handle with missing predictors, multiple imputation by chain equations (MICE) with thirty imputations performing on the complete data set of all participants using identical known information generated primary analysis model. A backward elimination method was used to decide which of the potential predictors should be included in our reduced model based on Akaike information criterion (AIC), keeping predictors with a p-value of less than 0.157. The bootstrap procedure, a random resampling with replacement was performed for optimism-correction model. We combined the estimates across imputed data sets using Rubin's rules to produce final parameter estimates for the final model including baseline survival and slope. The model performance included Harrell's C-index and calibration plot. Finally, the nomogram and web-based individual calculator were generated. All the above analyses were carried out using Stata version 14 and R.

RESULTS: Of 479 patients, 389 (81.2%) received WBRT. There was less female gender in WBRT group, they had better KPS; ≥70% (65.5% vs 38.5%), presented with milder symptoms (39.8% vs 25.3%), had greater number of measurable lesions (87.4% vs 63.8%), were more likely to receive further systemic treatment (35.7% vs 15.2%) and had better prognosis by Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA). Genetic mutation was not tested in three-quarters of the whole cohort. Better survival in WBRT group was observed (5.1 vs 2.3 months). Median follow up time was 4.3 (1.0-8.4) months. Potential predictors included age, gender, KPS, histology, EGFR/ALK status, neurological symptom, extracranial disease, previously received systemic treatment, presence of measurable lesions, received further systemic treatment and WBRT. Extra-cranial disease status and presence of measurable lesions were critical missing values. After MICE and dropping the candidate predictors step wise based on AIC, the following predictors were included in the reduced survival model: gender, KPS, neurological symptom, extra-cranial disease, previously received systemic treatment, received further systemic treatment and WBRT. WBRT exhibits a negative score, a good predictor. The final optimism-correction model was generated using shrinkage factor generated by bootstrapping with a C-index of 70.9% (69.1-73.8%) and an acceptable calibration. A model-transformed nomogram and web-based calculator were generated and available online at https://siriraj.cloud:9001/survival/. To put it simply, there were two characteristics demonstrated greatest benefit of WBRT: (1) patients who had controlled primary NSCLC and no extra-cranial metastases and (2) those who received further systemic treatment.
We also did a separate analysis for 117 patients with known genetic mutation status. The final model included only three predictors: extra-cranial disease, received further systemic treatment and WBRT. The genetic sta-

tus variable was dropped out of the model in the same fashion as we did for the whole cohort. There was only ten percent of the patients received further targeted drug which could obscure the strength of genetic mutation variable. We are planning on updating our model in the modern era database and external validating thereafter.

CONCLUSION: This nomogram is able to help clinicians to make decision making for whole brain radiotherapy in the tough situation. Further external validation is encouraged to be performed.

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