Received: 26 September 2024 | Revised: 25 November 2024 | Accepted: 3 December 2024

DOI: 10.1002/cac2.12641

CANCER COMMUNICATIONS Open Access

LETTER TO THE JOURNAL

# Survival impact of early MRI progression after stereotactic radiotherapy for brain metastases

The management of brain metastases (BMs) has rapidly evolved in recent years [1]. It is estimated that 20%-40% of cancer patients will develop BMs during their disease, while prevalence will probably grow thanks to the increased efficacy of systemic treatments. Whole-brain radiotherapy has long been the first-line treatment for BMs. Large-scale international clinical trials conducted over the past decade have established that stereotactic radiotherapy (SRT) is the treatment of choice for the management of patients harboring up to 3-5 metastases with the compromise of increased distant brain failure (DBF) rates [2]. Selection of patients and appropriate monitoring of patients remain a challenge.

Post-SRT monitoring is crucial to identify DBF and possibly lead to substantial treatment modifications. Indeed, several studies have shown that patients with symptomatic cerebral recurrences have poorer survival rates and generate higher costs for the healthcare system than asymptomatic patients whose recurrences have been detected by routine surveillance imaging [3]. A consensus seems to be emerging on the need for magnetic resonance imaging (MRI) every 3 months after brain SRT [4–6]. In our institution, the first MRI evaluation ($MRI_1$) is performed around 6 weeks after SRT. To our knowledge, no study has evaluated the benefit of early MRI evaluation (before 2 months) nor the survival impact of the MRI delay after SRT. We hypothesize that early MRI can lead to anticipated treatment changes and thus may impact survival. The full methodology is available in Supplementary Materials.

Between January 2014 and July 2022, 678 adult patients with solid cancer were treated with SRT at the Brest University Hospital, corresponding overall to 869 treatment courses and 1,681 lesions. Among these patients, 143 SRT courses did not have an available post-SRT MRI ($MRI_1$) and 41 courses had a histology that did not allow calculation of the Disease Specific-Graded Prognostic Assessment (DS-GPA) score. Of the remaining 685 treatment courses, 80 treatment courses were not considered because $MRI_1$ was performed before 30 days ($n = 17$) or after 90 days ($n = 63$). The final cohort thus consisted of 488 patients, 605 treatment courses and 1,172 treated BMs (mean number of 1.93 BMs per SRT course). A flowchart is available (Supplementary Figure S1). The mean age at the time of SRT was 63.2 years (inter-quartile range [IQR] = 57.3-70.4), and the most common histology was lung (69.9%), particularly pulmonary adenocarcinoma (91.3%). Most patients were male (53.5%), with a maintained performance status: Karnofsky score of 90% (IQR = 80-90) despite a relatively high percentage of symptomatic BMs (44.1%). The clinical status at the time of treatment was most often oligo-progression (61.7%). At the time of SRT, the DS-GPA-score was between 2 and 3 for 44.0% and above or equal to 3 in 34.0% of the population. Median overall survival (OS) was 12.3 months (95% CI = 11.0-14.8) while mean OS was 25.0 months (95% CI = 22.4-27.6). While 20.0% of all SRT courses were given without any concomitant systemic treatment, most patients received a concomitant treatment: chemotherapy (24.1%), immune checkpoint inhibitor (ICI, 20.5%), targeted therapy (19.0%). Associations (chemotherapy + ICI, chemotherapy + targeted therapy or ICI + targeted therapy) were rarer: 9.1%, 6.9%, and 0.4%, respectively.

$MRI_1$ was performed with a mean time of 58.8 days (95% CI = 57.9-59.7) and a median time of 57 days (95% CI = 56-58). $MRI_1$ was realized in 63.3% between 30 and 60 days ($MRI_{30\text{-}60}$) and in 36.7% between 60 and 90 days ($MRI_{60\text{-}90}$). With a median follow-up of 10.8 months (95% CI = 10.0-11.7), early DBF ($DBF_1$) as defined by the presence on $MRI_1$ of new BMs or leptomeningeal enhancement outside the treated region occurred in 22.3% of the treatment courses.

Early DBF had a negative impact on OS as shown in Figure 1 (HR = 2.54; 95% CI = 1.94-3.31; $P < 0.0001$). OS Kaplan Meier curves depending on the timing of $MRI_1$ were not significantly different ($P = 0.87$). To the exception of 6-months restricted mean survival time ($P = 0.04$),

**List of Abbreviations:** BM, brain metastasis; DBF, distant brain failure; DBF1, DBF occurring on MRI1; DS-GPA, Disease Specific-Graded Prognostic Assessment; MRI, magnetic resonance imaging; MRI1, first MRI performed after SRT; OS, overall survival; RSMT, restricted mean survival time; SRT, stereotactic radiotherapy.

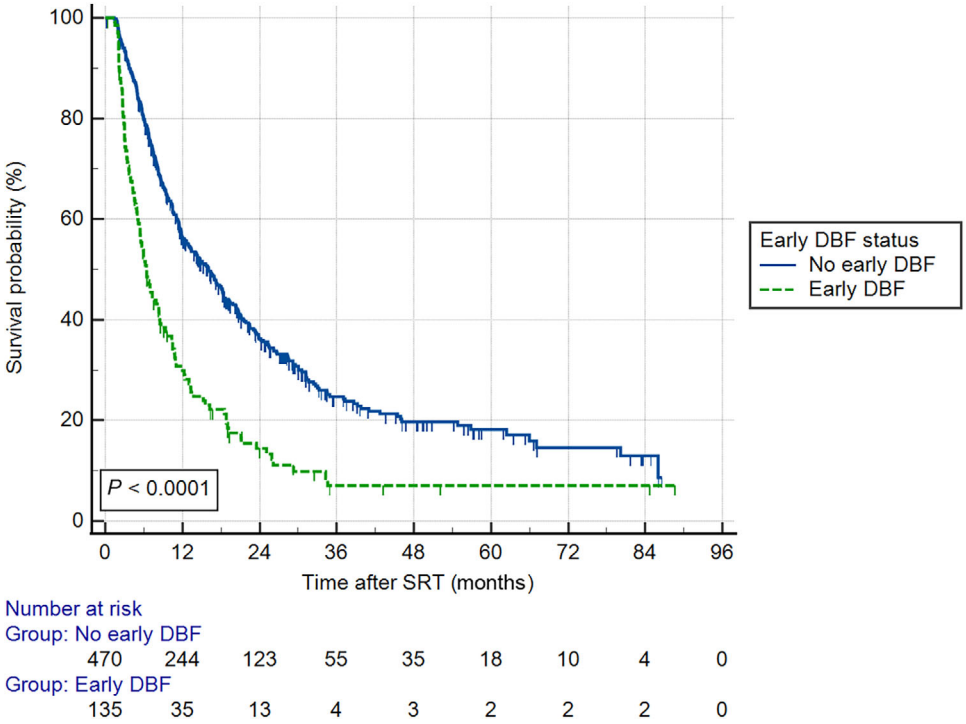


**FIGURE 1** **Kaplan Meier curves of overall survival according to early DBF**.
Abbreviations: SRT: Stereotactic Radiotherapy, DBF: distant brain failure.

comparison of restricted mean survival times (RSMTs) at 12 and 24 months revealed no significant differences either.

In the 135 treatment courses in which early DBF occurred, comparison of 6-months RSMT and 12-months between the two MRI groups achieved statistical significance ($P = 0.0008$ and $P = 0.02$, respectively). The 24-months RSMT comparison was close to significance ($P = 0.08$). Comparison of KMs in this sub-population was not statistically different ($P = 0.11$), Supplementary Figure S2. Patients harboring an early DBF on the $MRI_{30\text{-}60}$ had a decreased OS (HR = 1.35; 95% CI = 0.93-1.96) when compared to patients with early DBF on the $MRI_{60\text{-}90}$.

Among all analyzed potential predictors, the DS-GPA score, the clinical setting at the time of SRT, the number of treated BMs, the type of concomitant treatment at the time of SRT as well as the treatment of all BMs and histology subtype were significantly correlated with the risk of $DBF_1$ on univariate analysis (Supplementary Table S1). On multivariate analysis, the DS-GPA score, the treatment of all BMs and histology subtype (especially melanoma) remained the sole predictors of $DBF_1$ with respective HR of 0.68 (95% CI = 0.52-0.90) and 2.57 (95% CI = 1.34-4.94).

The potential biological mechanisms of the association between early DBF and OS remain to be thoroughly explored. Early DBF might be explained by increased levels of blood circulating and brain infiltrating tumor cells. While not being visible at the time of the first course of SRT, the early appearance of new BMs could thus reflect a more active disease. Based on the theory of the seed and soil approach [7], the greater the metastatic volume is, the greater the risk of developing new BMs is. Early development of new BM thus leads to impaired quality of life due to higher risk of neurological symptoms and/or decreased OS.

To our knowledge, our study is one of the few to focus on early DBF demonstrating the intuitive thought that $DBF_1$ has a negative impact on OS. Timing of the first post-SRT MRI plays a crucial role, but only in high-risk patients. Indeed, our results suggest that early $DBF_1$ is associated with worse OS. Non-personalized monitoring as suggested by current guidelines [8] seem insufficient to counterbalance the poorer prognosis of high-risk patients. It thus seems necessary to predict which patients will tend to present with early regional progression and subsequently propose a personalized monitoring and management. Based on our report and with the inherent limits of a retrospective study, patients with melanoma, uncomplete treatment of all BMs as well as lower DS-GPA score should be considered at higher risk of early DBF and could be proposed with a personalized MRI follow-up.

## AUTHOR CONTRIBUTIONS

Conceptualization: Vincent Bourbonne.

Methodology: Vincent Bourbonne and Gurvan Dissaux.

Validation: all authors.

Formal analysis: Moncef Morjani and Vincent Bourbonne.

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Writing – Review and editing: all authors.

Supervision: Vincent Bourbonne.

All authors read and approved the final manuscript.

## ACKNOWLEDGEMENTS

Not applicable.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest regarding this manuscript.

## FUNDING INFORMATION

Not applicable.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the declaration of Helsinki and has been approved by the local ethics committee of the Brest University Hospital (29BRC23.0143) and registered on ClinicalsTrials.gov (NCT06029140). Written informed consent was obtained from all participants before surgery.

## DATA AVAILABILITY STATEMENT

Data are only available upon request and validation of Vincent Bourbonne.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.