Clinical and Translational Radiation Oncology 48 (2024) 100811

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

Repeated HyperArc radiosurgery for recurrent intracranial metastases and dosimetric analysis of recurrence pattern to account for diffuse dose effect on microscopical disease

Luca Nicosia [a,*], Andrea Gaetano Allegra [a], Niccolò Giaj-Levra [a], Reyhaneh Bayani [b,c], Nima Mousavi Darzikolaee [c], Rosario Mazzola [a], Edoardo Pastorello [a], Paolo Ravelli [a], Francesco Ricchetti [a], Michele Rigo [a], Ruggero Ruggieri [a], Davide Gurrera [a], Riccardo Filippo Borgese [a], Simona Gaito [d,e], Giuseppe Minniti [f,g], Pierina Navarria [h,i], Marta Scorsetti [h,i], Filippo Alongi [a,j]

[a] Advanced Radiation Oncology Department, IRCCS Sacro Cuore Don Calabria Hospital, Cancer Care Center, 37024 Negrar, Italy
[b] Radiation Oncology Department, Hamadan University of Medical Sciences, Hamadan, Iran
[c] Radiation Oncology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
[d] Division of Clinical Cancer Science, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
[e] Department of Proton Beam Therapy, The Christie Proton Beam Therapy Centre, Manchester, UK
[f] Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza University, Rome, Italy
[g] IRCCS Neuromed, Pozzilli, Italy
[h] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele 20090, Milan, Italy
[i] Department of Radiotherapy and Radiosurgery, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano 20089, Milan, Italy
[j] University of Brescia, Brescia, Italy

ARTICLE INFO

Keywords:
Brain metastases
SRS
Radiosurgery
HyperArc
Radiotherapy
Stereotactic radiotherapy
Stereotactic radiosurgery

ABSTRACT

Aims: Evaluate effectiveness and safety of multiple HyperArc courses and patterns of progression in patients affected by BMs with intracranial progression.

Methods: 56 patients were treated for 702 BMs with 197 (range 2–8) HyperArc courses in case of exclusive intracranial progression. Primary end-point was the overall survival (OS), secondary end-points were intracranial progression-free survival (iPFS), toxicity, local control (LC), neurological death (ND), and whole-brain RT (WBRT)-free survival. Site of progression was evaluated against isodoses levels (0, 1, 2, 3, 5, 7, 8, 10, 13, 15, 20, and 24 Gy.).

Results: The 1-year OS was 70 %, and the median was 20.8 months (17–36). At the univariate analysis (UVA) biological equivalent dose (BED) > 51.3 Gy and non-melanoma histology significantly correlated with OS. The median time to iPFS was 4.9 months, and the 1-year iPFS was 15 %. Globally, 538 new BMs occurred after the first HA cycle in patients with extracranial disease controlled. 96.4 % of them occurred within the isodoses range 0–7 Gy as follows: 26.6 % (0 Gy), 16.5 % (1 Gy), 16.5 % (2 Gy), 20.1 % (3 Gy), 13.1 % (5 Gy), 3.4 % (7 Gy) ($p = 0.00$). Radionecrosis occurred in 2 metastases (0.28 %). No clinical toxicity of grade 3 or higher occurred during follow-up. One- and 2-year LC was 90 % and 79 %, respectively. At the UVA BED > 70 Gy and non-melanoma histology were significant predictors of higher LC. The 2-year WBRT-free survival was 70 %. After a median follow-up of 17.4 months, 12 patients deceased by ND.

Conclusion: Intracranical relapses can be safely and effectively treated with repeated HyperArc, with the aim to postpone or avoid WBRT. Diffuse dose by volumetric RT might reduce microscopic disease also at relatively low levels, potentially acting as a *virtual CTV*. Neurological death is not the most common cause of death in this population, which highlights the impact of extracranial disease on overall survival.

* Corresponding author at: Advanced Radiation Oncology Department, IRCCS Sacro Cuore Don Calabria Hospital, Cancer Care Center, via Don Sempreboni 5, 37034, Verona, Negrar, Italy.
E-mail address: lucanicosia.rg@gmail.com (L. Nicosia).

https://doi.org/10.1016/j.ctro.2024.100811
Received 29 November 2023; Received in revised form 9 May 2024; Accepted 22 June 2024
Available online 24 June 2024

Introduction

Stereotactic radiosurgery (SRS)/stereotactic fractionated radiotherapy (SFRT) is the standard of care in the treatment of patients with a limited number of brain metastases (BMs). Prospective data showed that SRS/SFRT is an efficacious treatment to delay whole-brain RT (WBRT) in patients with 1–3 BMs [1]. While several data are showing the effectiveness of SRS/SFRT also in patients with more advanced brain disease (up to 10 lesions), there is no consensus on the best treatment approach in case of intracranial relapse after a first course of SRS/SFRT due to the lack of randomized controlled trials with high level of evidence [2]. International guidelines suggest that repeated SRS/SFRT courses aiming to defer WBRT administration and its side effects, might be beneficial in terms of survival [3]. Nevertheless, the choice between WBRT, repeated SRS/SFRT, or even surgery is actually based on a level C of evidence [3]. Pprevious published series of patients treated with repeated SRS/SFRT courses reported a median overall survival (OS) > 18 months [4,5].

In recent years, monoisocentric techniques like HyperArc (HA) have been introduced in the clinical practice as a linac-based solution for the simultaneous treatment of multiple BMs, reporting local control levels comparable to multiple isocenter approaches, but with a faster treatment administration and a steep dose gradient between lesions [6]. Previous large series demonstrated the ability to spare normal brain tissue, whilst guaranteeing adequate coverage of multiple targets regardless of their distance from the isocenter [7]. These characteristics make SRS/SFRT with monoisocentric technique suitable for the retreatment of multiple intracranial relapses. Additionally, monoisocentric technique might lead to the administration of low radiation dose to wider healthy brain are as more BMs are treated. Actually little is known regarding the effect of low diffuse dose on the normal brain tissue and whether it may eventually have an effect in controlling microscopic disease [8].

In the present analysis, we report clinical outcomes of a series of patients treated with repeated SRS/SFRT HA courses. A dosimetric analysis of the pattern of relapse was also performed.

Material and methods

We reviewed a series of patients affected by multiple BMs treated with HA at our Institution between 2017–2022. Patients were eligible according to the following inclusion criteria: 1) having received at least 2 HA cycles; 2) minimum interval between each HA cycle of 3 months; 3) no evidence of active extracranial progression at the time of HA; 4) no previous WBRT. Salvage WBRT was administered in case of miliary progression or onset of symptomatic brain disease (i.e.: epileptic crisis, motor, sensitivity or coordination impairment). Specific informed consent was obtained from all participants included in the study. The study was conducted in accordance with the Declaration of Helsinki.

HyperArc™ treatment characteristics and planning

Treatment characteristics were described in a previous publication and are hereafter briefly described [6]. Patients underwent a simulation CT without contrast medium (1-mm slice thickness) and immobilized with a thermoplastic mask (QFix®, Avondale, PA–USA). A co-registration of the volumetric planning CT and contrast-enhanced T1-MRI sequences (1-mm slice thickness) no older than 30 days was used to define organs at risk (OARs) and target volumes. OARs, including brain (normal brain minus PTV), eyes, lenses, optic chiasm, optic nerves, brainstem, and spinal cord were delineated. Gross tumor volume (GTV) encompassed the macroscopic contrast-enhancing lesion on T1-MRI and was assumed equal to the clinical target volume (CTV). The planning target volume (PTV) was obtained from the GTV plus an isotropic margin of 0–2 mm in all directions. A PTV margin of 0 mm was applied for BMs adjacent to critical OARs (i.e.: chiasm). A margin of 2 mm was applied in 2017 during the first implementation of HA in our Department. The prescribed total dose and fractionation were chosen based on the size of BMs, proximity to OARs, and previous radiotherapy [9] and ranged from 25 Gy in 1 fraction to 24–27 Gy in 3 fractions. For treatment planning, an SRS/SFRT plan was generated with 5 no-coplanar arcs by HyperArc™ (Varian Medical System Inc., Palo Alto, CA, USA) as previously described [9]. $V_{18\text{-}21Gy}$ to the normal brain tissue was kept < 10 cc [10].

Follow-up

The first follow-up was performed 45–60 days after treatment to evaluate treatment response with MRI and to assess toxicity. Thereafter, patients were followed-up every 3 months for the first 2 years and every 4–6 months for the next 3 years. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) [11]. Toxicities were assessed during radiotherapy and follow-up according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Acute toxicity was defined as an adverse event occurring within 90 days from the beginning of treatment, whereas late toxicity after 90 days.

End-point and statistics

The primary end-point was overall survival (OS). The secondary endpoints were: the pattern of intracranial progression after HA, treatment-related toxicity, intracranial progression-free survival (iPFS), local progression-free survival (LPFS) (evaluated at metastases level), and WBRT-free survival (WFS). OS was considered as the time from the first HA cycle to the death or last follow-up. iPFS was defined as the time from the end of an HA course to the radiological occurrence of new brain metastases. LPFS was defined as the time from HA administration to the radiological progression of a treated lesion. WFS was defined as the time from the first HA course to the date of WBRT or last follow-up/death.

The pattern of intracranial relapse after HA was defined as the occurrence of any new BM within the isodoses of previous HA plan. Brain MRI showing intracranial relapse was fused with the simulation CT of the previous HA cycle. Considering the use of different fractionation and treatment doses in this study, we used the linear-quadratic (LQ) modeling in order to equate the hypofractionated schedules to the normalized total dose (NTD) if delivered in 2 Gy/fractions. Thus, NTD represents the dose given in 2 Gy/fraction that would have an equivalent biologic effect as the new dose:

$$NTD = [Dnew \times (1 + dnew/\alpha/\beta)]/(1 + 2/\alpha/\beta)$$

where Dnew and dnew were the total dose and dose per fraction for a suggested scheme. Therefore, the following isodose level of the corresponding HA plan were delineated: 0 Gy, 1 Gy, 2 Gy, 3 Gy, 5 Gy, 7 Gy, 8 Gy, 10 Gy, 13 Gy, 15 Gy, 20 Gy, and 24 Gy. The pattern of relapse was evaluated as the cumulative number of new metastases per each isodose level, as described in Fig. 1. Furthermore, the number of new BMs per isodose level was adjusted for the isodose volume (n° of new BMs/isodose level volume). The lower isodose level containing 95 % of the new BMs was identified.

Univariate analyses for survival endpoints were performed with the Kaplan-Meier method; the log-rank test was applied to determine differences between the corresponding curves. Multivariate analysis was performed with the Cox proportional hazards model considering all the clinically relevant variables in the univariate analysis ($p < 0.2$). Additionally, primary tumor histology was evaluated for correlation with intracranial pattern of relapse using the Chi-square test in 2x2 contingency table. The Pearson's Rho test was used to correlate brain metastases number adjusted for isodose volume to different isodose threshold.

Statistical analysis was performed using the SPSS statistical software package version 22.0 (SPSS Inc, Chicago, IL). A p-value ≤ 0.05 indicated a significant association.

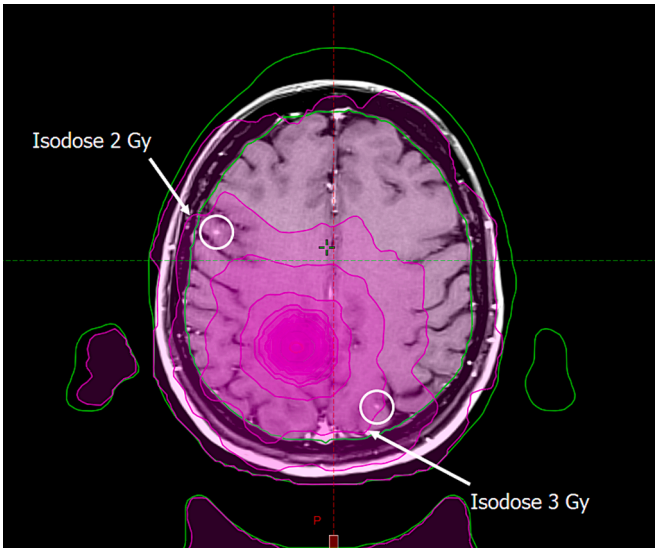

Fig. 1. Analysis of pattern of relapse. Diagnostic MRI showing intracranial relapse was fused with the CT of the corresponding HyperArc plan and treatment isodoses were delineated. New BM position was registered within the corresponding treatment isodose, as shown in the figure.

Results

Patients' characteristics

Fifty-six (56) patients with multiple BMs were treated with 197 HA courses to 702 BMs (median 3, range 2–25). Primary tumour histology was lung (26), breast (18), melanoma (8), other (4). BMs site was: supratentorial in 529 (75 %), infratentorial in 160 (23 %) and brainstem in 13 (2 %). Patients' characteristics are reported in Table 1. The median administered dose was 25 Gy (range 24–27 Gy) in a median of 3 fractions (range 1–3). PTV margins were 0 mm (3 %), 1 mm (83 %), and 2 mm (16.5 %). Lesions and treatment characteristics are reported in Tables 1 and 2.

Overall survival, intracranial progression-free survival, toxicity and local control

The median OS was 20.8 months (range 17–36). The 1-, and 2-year OS was 70 %, and 46.8 %, respectively (Fig. 2). At the univariate analysis (UVA) BED > 51.3 Gy (p = 0.04) and non-melanoma histology (p = 0.00) were significantly correlated with improved OS. In particular,

Table 1
Patients' characteristics (n = 56).

Median age (years) (range)	54 (32–83)
Sex	
Male	23
Female	33
Primary tumor histology	
Lung	26
Breast	18
Melanoma	8
Other	4
Median Karnofsky performance status (range)	95 (80–100)
HyperArc cycles	
2	56
3	11
4	7
5	2
6	1
8	1
Median treated metastases per cycle (range)	3 (2–25)

Table 2
Treatment and lesions' characteristics (n = 702).

Metastases site	
Supratenctorial	529 (75 %)
Infratenctorial	160 (22 %)
Brainstem	13 (3 %)
Median BED (Gy12) (range)	51.3 (43.2–87.5)
Median total dose (Gy) (range)	25 (24–27)
Median dose per fraction (Gy) (range)	9 (8–25)
Median fraction number (range)	3 (1–3)
Median GTV volume (cc)	0.1 (0.08–21.1)
Median cumulative GTV (cc) (per cycle) (range)	2.8 (0.1–26.8)
PTV margin (mm)	
0	3 (0.5 %)
1	647 (92 %)
2	52 (7.5 %)

BED: biological effective dose; GTV: gross tumor volume, PTV: planning treatment volume.

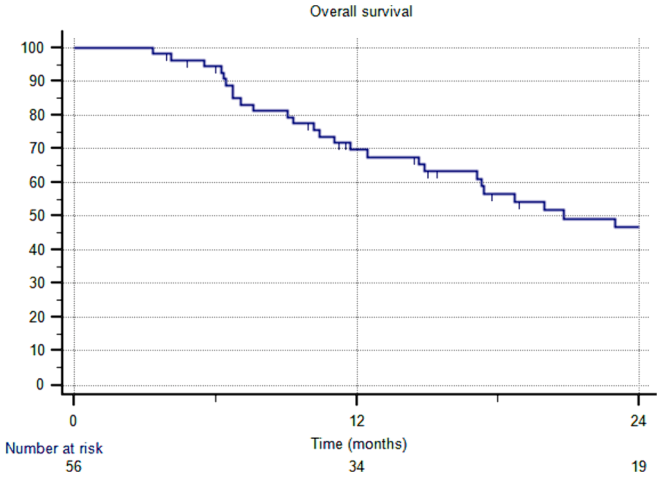

Fig. 2. Kaplan-Meier curve showing overall survival.

the median OS was 14.9 and 31.5 months for patients treated with BED ≤ 51.3 Gy and > 51.3 Gy, respectively. The 1-year OS according to primary tumor histology was 65.2 %, 100 %, 37.5 %, and 66.7 % for lung, breast, melanoma, and other, respectively. On the multivariate analysis, only primary tumor histology remained significantly correlated with OS (p = 0.00;HR 1.96, 95 %CI 1.286–2.989). Detailed uni- and multivariate analyses are reported in Table 3.

The median time to iPFS was 4.9 months, and the 1-year iPFS was 15 % (Fig. 3). Extracranial progression after HA was significantly correlated with iPFS at the UVA (p = 0.00). Also, cumGTV ≤ 2.8 cc per HA cycle was significantly correlated with improved iPFS at the UVA. None of these variables remained significant on multivariate analysis.

One- and 2-year LPFS was 90 % and 79 %, respectively (Fig. 4). At the UVA BED > 70 Gy (p = 0.011), and non-melanoma histology (p = 0.018) were significantly correlated with improved LC. At the MVA the only factors significantly correlated with LPFS remained BED > 70 Gy (p = 0.01;HR 1.98, 95 %CI 1.157 – 3.412; see Fig. 5).

Radionecrosis occurred in 2 metastases (0.28 %). No clinical grade 3 or higher toxicity occurred during follow-up. Salvage WBRT was administered in 13 patients (23.2 %), and the 2-year WBRT-free survival was 70 %. After a median follow up of 17.4 months (range 12–48) 12 patients had deceased.

Pattern of intracranial relapse

The pattern of relapse was analysed in 171 HA courses in 56 patients after the exclusion of 26 HA courses in 31 patients due to extracranial

Table 3
Univariate and multivariate analysis.

	Univariate analysis		
Covariates	OS	iPFS	LPFS
GTV volume ≤ 4.17 cc	–	–	0.30
cumulative GTV volume ≤ 2.8 cc	0.13	*0.035*	–
BED > 51.3 Gy	*0.04*	0.77	0.893
BED > 70 Gy	0.69	0.84	*0.011*
Histology (melanoma vs non-melanoma)	*0.00*	0.89	*0.018*
BM site	0.61	0.08	0.264
PTV margin (mm)	–	–	0.77
Extracranial progression after HA	0.1	*0.00*	–
	Multivariate analysis		
Covariates	OS	iPFS	LPFS
Vol GTV ≤ 4.17 cc	–		–
Vol GTV ≤ 2.8 cc	0.76 (HR1.16, 95 %CI 0.421–3.224)	0.11 (HR 1.67, 95 %CI 0.884–3.172)	–
BED > 51.3 Gy	0.25 (HR 0.58, 95 %CI 0.231–1.460)	–	–
BED > 70 Gy	–	–	*0.01 (HR 1.98, 95 %CI 1.157 – 3.412)*
Histology (melanoma vs non-melanoma)	*0.00 (HR 1.96, 95 %CI 1.286–2.989)*	–	0.31 (HR 1.17, 95 %CI 0.860–1.599)
BM site	–	0.53 (HR 0.81, 95 %CI 0.430–1.549)	–
PTV margin (mm)	–	–	–
Extracranial progression after HA	0.73 (HR 0.866, 95 %CI 0.383–1.962)	0.16 (HR 1.50, 95 %CI 0.843–2.684)	

OS: overall survival, iPFS: intracranial progression-free survival, LPFS: local progression-free survival, GTV: gross tumor volume, BED: biological effective dose, BM: brain metastases, PTV: planning treatment volumer, HA: HyperArc. Italic values indicate a significant correlation

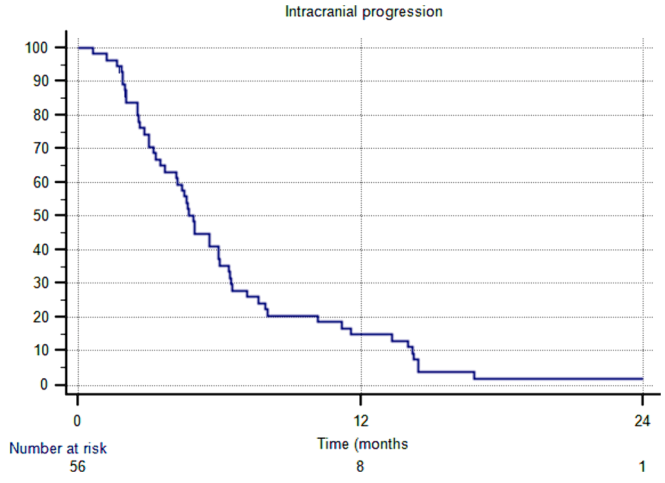

Fig. 3. Kaplan-Meier curve showing intracranial relapse after SRS.

progression before a subsequent SRS cycle or no intracranial progression after the last HA cycle. Therefore, 556 new BMs after HA occurred. The distribution of the new BMs along the isodoses was: 148 (0 Gy), 92 (1 Gy), 92 (2 Gy), 112 (3 Gy), 73 (5 Gy), 19 (7 Gy), 10 (8 Gy), 5 (10 Gy), 2 (13 Gy), 3 (15 Gy), 0 (20 Gy), and 0 (24 Gy). The isodose that covered at least 95 % of the relapse was 7 Gy (96.4 % of the relapses). See Fig. 1. Upon further analysis, the isodose 7 Gy alone covered only 2.7 % of the relapse, while 47 % of them occurred in brain receiving ≤ 1 Gy. The

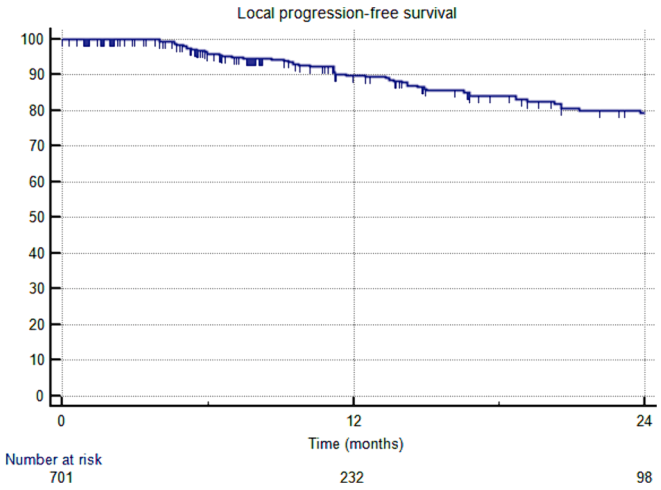

Fig. 4. Kaplan-Meier curve showing local progression-free survival.

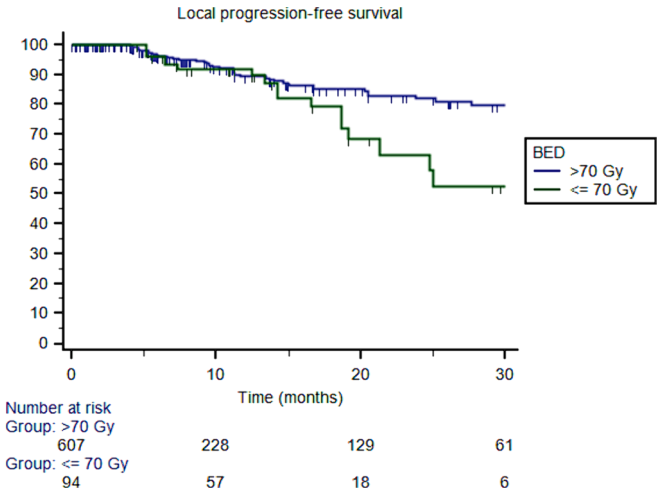

Fig. 5. Kaplan-Meier curve showing local progression-free survival stratified by biological effective dose.

number of new BMs corrected for isodose volume (in cc) showed a statistical significance for 7 Gy threshold (p = 0.024, rho = 0.204).

Discussion

SRS/SFRT is the standard treatment for patients with limited BMs and can be delivered with different systems and techniques (e.g. Gammaknife, Cyberknife, Tomotherapy. Proton therapy still only experimental in this setting) [6,12,13]. SRS/SFRT has been shown to be equal to WBRT in patients with up to 10 metastases, and feasible in selected individuals with > 10 metastases [2,14]. The advantage of SRS/SFRT over WBRT are the higher local control and the reduced neurocognitive impairment [15]. However, SRS/SFRT is related to an increased risk of intracranial progression due to the low radiation dose to the healthy brain [1]. In this clinical scenario, international guidelines suggest as possible treatment options either repeated SRS/SFRT or salvage WBRT, without a consensus on what is the best approach due to the lack of high-level evidence [3]. The choice of treatment might depend on several factors like the number of lesions, size, patients' performance status, extracranial disease status, and time to the intracranial relapse. In the present study, we reported the outcome of a series of patients treated with repeated cycles of SRS/SFRT in case of sequential intracranial progression.

Mizuno et al., reported a median time to intracranial progression of

7.1 months after SRS/SFRT versus 19.1 months after WBRT without statistically significant difference in the cause of death (neurological death versus other causes) and OS [16]. This consideration might suggest that in case of limited intracranial progression a new SRS/SFRT course might be offered. In the present study, the median iPFS was 4.9 months and median OS was 20.8 months. Interestingly, patients with smaller disease burden had a better iPFS, even though the correlation was not confirmed at the MVA.

In a previous retrospective matched-pair analysis, patients with sequential intracranial progression with a maximum of 10 BMs treated with repeated HA courses were compared to patients treated with WBRT alone reporting a significant 1-year OS improvement (77 % versus 34.6 %) (4). Conversely, a recent retrospective study reported no survival benefit between SRS and WBRT (48.2 % versus 35.9 %) (14). Interestingly, the survival rate of the two WBRT cohorts was similar, while the difference in the SRS groups might be attributed to the repeated use of SRS as a salvage treatment in patients with intracranial relapse. This preliminary data suggest that careful patient selection is crucial, as well as a possible survival advantage provided by salvage SRS/SFRT. Several studies reported which clinical factors might be used for selecting patients for salvage SRS/SFRT. Jiang et al. showed that total PTV volume during salvage SRS was a predictor of survival [17]. Kurtz et al. retrospectively analysed data from 106 patients reporting extracranial disease control and interval between initial RT and salvage SRS as predictors of OS [18]. In the present analysis having a non-melanoma histology was the only predictive factor of longer OS.

Other factors to consider are the status of systemic disease (progression versus controlled disease) and the ongoing systemic therapies. In fact, tyrosine-kinase inhibitors, target therapy and immunotherapy are now standard of care in several non-small cell lung cancer and melanoma subtypes. Some of these drugs have also an effect on the central nervous system (CNS) and can contribute to control intracranial progression. For example, some evidence suggest that oncogene-addicted NSCLC with BMs might be considered for systemic treatment alone deferring the use of intracranial RT in case of intracranial relapse, however the consensus is not generalized [19]. For example, Lee et al. treated 76 NSCLC patients, more than 75 % of which with a driver mutation (EGFR, ALK, PD-L1) with $\geq$ 5 gamma-knife cycles reporting an encouraging median OS from the first SRS of 52.3 months [20].

An interesting commentary comes from the analysis of relapse pattern. We showed that $\geq$ 95 % of the relapse occurred to brain receiving $\leq$ 7 Gy from the previous SRS/SFRT treatment. This data comes along with previous evidence in a small population showing that diffuse dose to the healthy brain lower than 4 Gy was associated with an increased risk of developing new BMs [21]. In this context it is conceivable that the diffuse dose provided by VMAT treatments might act as a *virtual CTV* and might contribute to control microscopic disease. This concept was preliminarily documented in an extracranial context. In a study on primary early-stage NSCLC treated with SBRT it was shown that the incidence of mediastinal lymphnode relapse was lower in patients receiving incidental dose to the mediastinum, demonstrating that also relatively low radiation dose might have a cytocidal effect on the microscopic disease [22]. Similarly, in a recent study on non-spinal bone metastases from prostate cancer treated with SBRT to the macroscopic disease only (GTV-PTV concept) it was shown that peripheral relapse was a rare event, as well as intraosseous relapse [8]. This is a relatively new concept, considering the context of spine metastases where the Guidelines by Cox et al. on spinal SRS suggested the use of a CTV (defined by surgical anatomy) to control the intraosseous microscopic disease [23].

In a modern radiotherapy context, we may look at historical data on WBRT dose and critically revise them in the light of new modern biological and technical acquisitions. The first two randomized phase III trials on WBRT dose/fraction were conducted in the early '80 by RTOG, the first [24] using 20 Gy in 1 week, 30 Gy in 2 weeks, 30 Gy in 3 weeks, 40 Gy in 3 weeks, and 40 Gy in 4 weeks, with comparable results in terms of disease progression, survival, and palliative index. In a second trial [25], accelerated schedules of 10 Gy in 1 fraction and 12 Gy in 2 fractions were compared to the longer WBRT courses demonstrating comparable oncological outcomes, even if the improvement duration of symptoms, time to deterioration of neurologic function, and rate of complete disappearance of neurologic symptoms was worse with short schedules in 1 and 2 fractions. A final RTOG trial compared 30 Gy in 2 weeks to 50 Gy in 4 weeks in a favourable patient population and demonstrated no difference in palliation or survival. According to these results, 30 Gy in 10 fraction and 20 Gy in 5 fractions became the standard WBRT regimens [26]. With the increased survival of oncological patients due to therapeutic improvements, the paradigm of microscopic brain disease control might be reviewed in a research scenario considering the concomitant use of ablative dose to the active disease and low radiation dose to the healthy brain as low as capable of ablating the microscopic disease, but not high enough to determine significant neurocognitive deterioration. In particular, the abovementioned standard WBRT dose might be not sufficient to ablate the active brain metastases but also excessive to control the microscopic disease and to determine neurocognitive side effects. In the study of Ni et al. [27] 684 patients were treated with WBRT plus focal RT boost, WBRT or SRS. WBRT-boost patients reported a longer survival compared to WBRT alone or SRS patients. Therefore, future studies might aim to identify the lowest dose able to control the microscopic disease while keeping ablative dose to the active disease (low-dose WBRT plus SRS/SFRT).

This study is not without limitations. First of all, it is a retrospective study, therefore subjected to potential selection bias, and it included patients with different primary tumours. To reduce the impact of confounding factors we used strict selection criteria like the inclusion of patients with controlled extracranial disease, the use of similar fractionation and the same treatment technique, no use of drugs with effect on the CNS. Nevertheless, we cannot exclude all the possible potential confounding factors.

Conclusion

The present study demonstrated the safety and effectiveness of repeated courses of SRS/SFRT with HyperArc in patients with sequential intracranial relapse. HyperArc can be safely administered in selected patients with controlled extracranial disease, deferring or avoiding WBRT. The diffuse dose provided by VMAT technique might act as a *virtual CTV* in controlling the microscopical disease and randomised controlled studies will ultimately clarify the role of SRS/SFRT vs WBRT in the intracranial recurrent setting.

CRediT authorship contribution statement

Luca Nicosia: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Andrea Gaetano Allegra:** Data collection, Writing – original draft. **Niccolò Giaj-Levra:** Validation, Investigation, Writing – review & editing. **Reyhaneh Bayani:** Investigation, Software, Writing – review & editing. **Nima Mousavi Darzikolaee:** Investigation, Software, Writing – review & editing. **Rosario Mazzola:** Data curation, Writing – review & editing. **Edoardo Pastorello:** Data curation, Writing – review & editing. **Paolo Ravelli:** Data curation, Writing – review & editing. **Francesco Ricchetti:** Investigation, Writing – review & editing. **Michele Rigo:** Investigation, Writing – review & editing. **Ruggero Ruggieri:** Visualization, Writing – review & editing. **Davide Gurrera:** Investigation, Visualization, Writing – review & editing. **Riccardo Filippo Borgese:** Investigation, Visualization, Writing – review & editing. **Simona Gaito:** Software, Writing – review & editing. **Giuseppe Minniti:** Supervision, Writing – review & editing. **Pierina Navarria:** Visualization, Writing – original draft. **Marta Scorsetti:** Project administration, Writing – review & editing. **Filippo Alongi:** Supervision, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] 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(2):134–41. https://doi.org/10.1200/JCO.2010.30.1655.

[2] Yamamoto M, Higuchi Y, Sato Y, Aiyama H, Kasuya H, Barfod BE. Stereotactic radiosurgery for patients with 10 or more brain metastases. Prog Neurol Surg 2019;34:110–24. https://doi.org/10.1159/000493056.

[3] Le Rhun E, Guckenberger M, Smits M, Dummer R, Bachelot T, Sahm F, et al. Electronic address: clinicalguidelines@esmo.org. EANO-ESMO clinical practice guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021;32(11):1332–47. https://doi.org/10.1016/j.annonc.2021.07.016.

[4] Nicosia L, Figlia V, Mazzola R, Napoli G, Giaj-Levra N, Ricchetti F, et al. Repeated stereotactic radiosurgery (SRS) using a non-coplanar mono-isocenter (HyperArc™) technique versus upfront whole-brain radiotherapy (WBRT): a matched-pair analysis. Clin Exp Metastasis 2020;37(1):77–83. https://doi.org/10.1007/s10585-019-10004-3.

[5] Shultz DB, Modlin LA, Jayachandran P, et al. Repeat courses of stereotactic radiosurgery (SRS), deferring whole-brain irradiation, for new brain metastases after initial SRS. Int J Radiat Oncol Biol Phys 2015;92(5):993–9. https://doi.org/10.1016/j.ijrobp.2015.04.036.

[6] Alongi F, Nicosia L, Figlia V, Giaj-Levra N, Cuccia F, Mazzola R, et al. Long-term disease outcome and volume-based decision strategy in a large cohort of multiple brain metastases treated with a mono-isocentric linac-based stereotactic radiosurgery technique. Clin Transl Oncol 2021;23(8):1561–70. https://doi.org/10.1007/s12094-020-02550-0.

[7] Kraft J, van Timmeren JE, Mayinger M, Frei S, Borsky K, Stark LS, et al. Distance to isocenter is not associated with an increased risk for local failure in LINAC-based single-isocenter SRS or SRT for multiple brain metastases. Radiother Oncol 2021;159:168–75. https://doi.org/10.1016/j.radonc.2021.03.022.

[8] Pastorello E, Nicosia L, Cuccia F, Olivari L, Fiorini M, Giaj Levra N, et al. PSMA-PET/CT-based stereotactic body radiotherapy (SBRT) in the treatment of uncomplicated non-spinal bone oligometastases from prostate cancer. Cancers (Basel) 2023;15(10):2800. https://doi.org/10.3390/cancers15102800.

[9] Ruggieri R, Naccarato S, Mazzola R, Ricchetti F, Corradini S, Fiorentino A, et al. Linac-based VMAT radiosurgery for multiple brain lesions: comparison between a conventional multi-isocenter approach and a new dedicated mono-isocenter technique. Radiat Oncol 2018;13(1):38. https://doi.org/10.1186/s13014-018-0985-2.

[10] Minniti G, Scaringi C, Paolini S, Clarke E, Cicone F, Esposito V, et al. Repeated stereotactic radiosurgery for patients with progressive brain metastases. J Neurooncol 2016;126(1):91–7. https://doi.org/10.1007/s11060-015-1937-4.

[11] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[12] Bruni A, Gaito S, Ciarmatori A, Lanfranchi B, Mazzeo E, Maffei N, et al. Radiosurgery using tomotherapy for patients with brain oligo-metastasis: a retrospective analysis on feasibility and tolerance. Anticancer Res 2015 Dec;35(12):6805–12.

[13] Gaito S, Marvaso G, Ortiz R, Crellin A, Aznar MC, Indelicato DJ, et al. Proton beam therapy in the oligometastatic/oligorecurrent setting: is there a role? a literature review. Cancers (Basel) 2023;15(9):2489. https://doi.org/10.3390/cancers15092489.

[14] Bodensohn R, Kaempfel AL, Boulesteix AL, Maria Orzelek A, Corradini S, Felix Fleischmann D, et al. Stereotactic radiosurgery versus whole-brain radiotherapy in patients with 4–10 brain metastases: a nonrandomized controlled trial. Radiother Oncol 2023;15:109744. https://doi.org/10.1016/j.radonc.2023.109744.

[15] van Grinsven EE, Nagtegaal SHJ, Verhoeff JJC, van Zandvoort MJE. The impact of stereotactic or whole brain radiotherapy on neurocognitive functioning in adult patients with brain metastases: a systematic review and meta-analysis. Oncol Res Treat 2021;44(11):622–36. https://doi.org/10.1159/000518848.

[16] Mizuno T, Takada K, Hasegawa T, Yoshida T, Murotani K, Kobayashi H, et al. Comparison between stereotactic radiosurgery and whole-brain radiotherapy for 10–20 brain metastases from non-small cell lung cancer. Mol Clin Oncol 2019;10(5):560–6. https://doi.org/10.3892/mco.2019.1830.

[17] Jiang X, Wang H, Song Y, Wang X, Li F, Dong Y, et al. A second course of stereotactic image-guided robotic radiosurgery for patients with cerebral metastasis. World Neurosurg 2019;123:e621–8. https://doi.org/10.1016/j.wneu.2018.11.238.

[18] Kurtz G, Zadeh G, Gingras-Hill G, Millar BA, Laperriere NJ, Bernstein M, et al. Salvage radiosurgery for brain metastases: prognostic factors to consider in patient selection. Int J Radiat Oncol Biol Phys 2014;88(1):137–42. https://doi.org/10.1016/j.ijrobp.2013.10.003.

[19] Thomas NJ, Myall NJ, Sun F, Patil T, Mushtaq R, Yu C, et al. Brain metastases in EGFR- and ALK-positive NSCLC: outcomes of central nervous system-penetrant tyrosine kinase inhibitors alone versus in combination with radiation. J Thorac Oncol 2022;17(1):116–29. https://doi.org/10.1016/j.jtho.2021.08.009.

[20] Lee WJ, Choi JW, Kong DS, Seol HJ, Nam DH, Lee JI. Clinical outcomes of patients with multiple courses of radiosurgery for brain metastases from non-small cell lung cancer. Sci Rep 2022;12(1):10712. https://doi.org/10.1038/s41598-022-13853-3. PMID: 35739135; PMCID: PMC9226031.

[21] Paul S, Ohri N, Velten C, Brodin P, Mynampati D, Tomé W, et al. The effect of low-dose radiation spillage during stereotactic radiosurgery for brain metastases on the development of de novo metastases. Clin Transl Radiat Oncol 2021;29(28):79–84. https://doi.org/10.1016/j.ctro.2021.03.003.

[22] Lao L, Hope AJ, Maganti M, Brade A, Bezjak A, Saibishkumar EP, et al. Incidental prophylactic nodal irradiation and patterns of nodal relapse in inoperable early stage NSCLC patients treated with SBRT: a case-matched analysis. Int J Radiat Oncol Biol Phys 2014;90(1):209–15. https://doi.org/10.1016/j.ijrobp.2014.05.006.

[23] Cox BW, Spratt DE, Lovelock M, Bilsky MH, Lis E, Ryu S, et al. International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2012;83(5):e597–605. https://doi.org/10.1016/j.ijrobp.2012.03.009.

[24] Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. The palliation of brain metastases: final results of the first two studies by the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 1980;6(1):1–9. https://doi.org/10.1016/0360-3016(80)90195-9.

[25] Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 1981;7(12):1633–8. https://doi.org/10.1016/0360-3016(81)90184-x.

[26] Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 1981;7(7):891–5. https://doi.org/10.1016/0360-3016(81)90005-5.

[27] Ni M, Liu W, Jiang A, Wang Y, Sheng Y, Zeng H, et al. Whole brain radiation therapy plus focal radiation boost may generate better survival benefit for brain metastases from non-small cell lung cancer. Front Oncol 2020;20(10):576700. https://doi.org/10.3389/fonc.2020.576700.