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Local control and radionecrosis of brain metastases from non-small-cell lung cancer treated by hypofractionated stereotactic radiotherapy: Evaluation of predictive factors

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ABSTRACT

Background: The objective of our study was to report predictive factors of local control (LC) and radionecrosis (RN) of brain metastases (BM) of non-small cell lung carcinoma (NSCLC) treated by multifractionated stereotactic radiotherapy (MF-SRT) according to French recommendations.

Method: From 2012 to 2020, 87 patients with 101 BM were retrospectively included. The median age was 63 years (37–85). GTV was defined using contrast-enhanced T1w MRI and was isotropically extended by 2 mm to form PTV. Mean maximum BM diameter was 24.5 mm (10–46). Patients were treated with dynamic arctherapy from May 2012 to February 2016 and then with VMAT. The total prescribed dose was 23.1 Gy prescribed to the encompassing 70% isodose, in 3 fractions.

Results: LC rates at 6 months, 1 year and 2 years was 95.7%, 90.7% and 87.9% respectively. In multivariate analysis, high GTV Dmin (HR = 0.822, p = 0.012) was in favor of better LC whereas a large maximum diameter was predictive of poor LC (HR = 1.124, p = 0.02). GTV Dmin of 27.4 Gy was identified as a discriminant threshold of LC. In case of GTV Dmin $\geq$ 27.4 Gy, LC at 1 year was 95.3% versus 75.1% with GTV Dmin $<$ 27.4 Gy. Cumulative incidence of RN at 6 months, 1 year and 2 years was 6.3%, 15.4% and 18.1%, respectively. In multivariate analysis, only dyslipidemia was predictive of RN (HR = 2.69, p = 0.03). No dosimetric predictive factor of RN was found in our study.

Conclusion: MF-SRT (3x7.7 Gy on 70% isodose line, with PTV = GTV + 2 mm; according to French recommendations) of BM from NSCLC gives high LC rates with acceptable RN rate. A GTV Dmin of at least 27.4 Gy could be proposed to optimize dosimetric objectives. No dosimetric predictive factors of RN were found in this study. However, dyslipidemia was identified as a potential predictive factor of RN.

Introduction

Brain metastases are the most common intracranial tumors in adults, accounting for well over half of all brain tumors. They occur in 20–40% of cancer patients during the course of their disease [1,2]. Lung cancer is the leading cause of brain metastases, accounting for 30–50% of cases, and it is associated with a poor prognosis [3–5]. Brain metastases are generally more frequent in adenocarcinomas than in squamous cell carcinomas and are observed in 26.8% of cases [6]. This rate rises to 38%, especially in NSCLC with ALK rearrangement, and is also high in cases of EGFR mutation [7,8].

Whole brain radiotherapy (WBRT), for a long time the reference for

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local control and symptomatic treatment of brain metastases, has been questioned in recent years because of the lack of survival increase and the risk of cognitive impairment [9,10]. Over time, stereotactic radiotherapy, which includes stereotactic radiosurgery (SRS) and multifraction stereotactic radiotherapy (MF-SRT), has become a standard treatment for suitable patients with brain metastases by delivering a lower dose to the healthy brain, with a high rate of local control (LC) and fewer side effects [11].

However, stereotactic radiotherapy can be responsible for inflammatory and necrotic processes resulting in edema with a mass effect that is very difficult to distinguish from a recurrence or a progression of the disease. This can be asymptomatic or affect quality of life. The reported incidence of radionecrosis (RN) varies from 3% to 24% of patients and usually occurs from six weeks up to 15 months after SRT, but can also occur years later [12–15]. Despite the lack of randomized trials, treatment for large brain metastases with MF-SRT regimens (2–5 fractions) may offer a relative reduction of RN compared with SRS, while maintaining high LC [16]. Over the past years, several studies, mainly retrospective, have reported the outcomes of MF-SRT, often including heterogeneous fractionations, and heterogeneous histology [16–20]. French recommendations on the management of brain metastases with stereotactic radiotherapy recommend for MF-SRT a total dose of 23.1 Gy in 3 fractions, on the 70% isodose [5,21]. However, the outcomes of this fractionation have never been clearly published. Thus, the purpose of this study was to assess LC and brain RN rate and identify predictive factors in a retrospective series of 101 unresected brain metastases from NSCLC treated with Linac-based MF-SRT, according to French recommendations [5,21].

Material and methods

Population and metastasis characteristics

Between May 2012 and January 2020, 101 unresected brain metastases from a histologically confirmed NSCLC of 87 patients older than 18 years underwent MF-SRT in our institution and were included in this retrospective study. Previous whole brain radiotherapy (WBRT) was authorized. Patients presenting a tumor other than NSCLC, a tumor size < 1 cm (usually treated with SRS), brainstem metastases, or prior surgery were excluded.

This study was approved by CECIC Rhône-Alpes-Auvergne on 25 September 2020. All characteristics of the 87 patients and the 101 brain metastases from NSCLC are reported in Table 1. Treatment characteristics are reported in Table 2.

The median age was 63.1 (range from 36.5 to 84.8). The population of the study was a majority male (67.8%), most remained in good general state with a performance status ≤ 1 (87.3%), and a majority were treated for a single brain metastasis (62.1%) or two (in 19.5% of cases) with no prior WBRT (75%). Every patient presented a NSCLC, with the most frequent histology adenocarcinoma (82.2%), followed by squamous cell carcinoma (15.8%). Nineteen patients (21.8%) presented a mutation (all patients were tested for), of which the most frequent was KRAS (68.4% of them); other mutations were EGFR (2/19), ALK (2/19), cMET (1/19), and BRCA (1/19).

In 59.8% of patients, systemic therapy was provided at the time of brain MF-SRT. Systemic treatments were mono-chemotherapy in 34.6% of patients (18/52) and chemotherapy in combination with platinum doublet in 29.6% (14/52). One patient received a combination of Paclitaxel and Bevacizumab. In 23% of cases (12/52), systemic treatments were targeted therapies: Erlotinib, a first generation TKI (7/52); Osimertinib, a third-generation TKI (1/52); Alectinib, ALK-inhibitor (1/52), Bevacizumab, anti-VEGF antibody (2/52), which was taken in association with Paclitaxel, and Olaparib, PARP inhibitor (1/52). Seventeen percent of patients (9/52) received immunotherapy such as Pembrolizumab (3/52), Nivolumab (4/52), and Atezolizumab (2/52).

The mean maximum-diameter of brain metastasis was 24.5 mm (min–max: 10–46). Twenty-two percent were smaller than 20 mm, and 13% were larger than 30 mm.

Table 1
Patients and brain metastasis characteristics.

Patients characteristics		
Total		**87**
Gender	Female	28 (32.2%)
	Male	59 (67.8%)
Age – median (min–max)		63.1 (36.5–84.8)
Medical history		
	HTA	33 (37.9%)
	Diabetes	12 (13.8%)
	Dyslipidemia	23 (26.4%)
Systemic treatment		
	yes	52 (60%)
	no	35 (40%)
Ps		
	0	31 (30.7%)
	1	54 (53.5%)
	2	15 (14.9%)
	≥ 3	1 (1%)
Prognostic score - mean (min–max)		
	SIR	6 (2–9)
	RPA	1.9 (1–3)
	GPA	2.5 (0.5–4)
	DS.GPA	2.4 (0–4)
	lung-molGPA	2 (0.5–3.5)
Number of metastases treated per patient		
	1	56 (55.4%)
	2	23 (22.8%)
	≥ 3	22 (21.8%)
Brain metastasis characteristics		
Total		**101**
Tumor volume		
	Maximum diameter	24.5 (10–46)
	GTV (cc)	5.75 (0.2–26.4)
	PTV (cc)	10.2 (0.7–39)
Prior treatment		
	WBRT	26 (26%)
	SRT	1 (1%)
NSCLC histology		
	Adenocarcinoma	83 (82%)
	Epidermoid carcinoma	16 (16%)
	other	2 (2%)
Mutation		
	yes	19 (19%)
	no	82 (81%)
Location		
	cerebellar	21 (21%)
	frontal	32 (32%)
	occipital	15 (15%)
	parietal	17 (17%)
	temporal	14 (14%)
	other	2 (2%)

Abbreviations. PS = performance status; SIR = score index for radiosurgery; RPA = recursive partitioning analysis; DS-GPA; DS.GPA = diagnosis-specific graded prognostic assessment; lung-molGPA = lung-molecular graded prognostic assessment; GTV = gross tumor volume; PTV = planning target volume; WBRT = whole-brain radiotherapy; SRT = stereotactic radiotherapy.

Treatment specifications

Planning-CT images were acquired with a 1.25 mm slice thickness and fused with the dosimetric magnetic resonance imaging (MRI) sequences of interest using Iplan®, version 4.1 (Brainlab). The MRI included 3 sequences: a FLAIR 3D MRI sequence, a T1 3D MPRAGE MRI sequence with contrast agent, and a T1 GE. The maximum delay between dosimetric MRI and first fraction was 7 days.

During the planning-CT and radiotherapy session, patients were

Table 2
Multifractionated stereostactic radiotherapy (MF-SRT; 3x7.7 Gy on the 70% isodose line) characteristics.

Technique		
	Dynarc	59 (58%)
	Vmat	42 (42%)
OTT (days) mean (mean – max)		5.8 (4–10)
GTV doses (Gy)		
	Dmin	27.7 (7.3–31.6)
	D98%	29.2 (9–32)
	Dmean	31.5 (26.6–33.5)
	Dmax	33.2 (27.7–35.9)
PTV doses (Gy)		
	Dmin	21.8 (6.1–27.3)
	D98%	24.9 (7.4–29.5)
	Dmean	29.9 (25–32.1)
	Dmax	33.1 (27.7–35.9)
	V70%	99.3 (73.2–100)
(Brain – GTV) doses (Gy)		
	V23.1	6.4 (1.4–26)
	V21	8 (1.6–31.1)
	V18	10.8 (2.1–39.7)
	V14	16.6 (3.1–61)
	V10	28.3 (5.2–99.4)
	V5	76.9 (15.6–249.4)

immobilized with a noninvasive thermoplastic mask (Brainlab, Munich, Germany) and repositioned daily with an integrated ExacTrac X-ray 6D system (Brainlab, Munich, Germany) which has the ability for pre-treatment positioning.

The target volume was identified on the fused planning-CT and MRI, and the gross tumor volume (GTV) was generated on the post-gadolinium contrast-enhanced T1-weighted MRI sequence. Clinical Target Volume (CTV) definition was identical to the GTV and planning target volume (PTV) was defined as a 2 mm three-dimensional expansion around the GTV. GTV and PTV mean volume were 5.75 cc (min – max: 0.16 – 26.4) and 10.18 cc (min – max: 0.73 – 39.33) respectively. Organs at risk (OARs) delineated were the cranial cavity, healthy brain (entire cranial cavity - GTV), brainstem, optic nerves, chiasma, eyeballs, lenses, and cochlea. For all patients, irradiation was performed with a 6 MV photon beam from a linear accelerator (NovalisTx®), equipped with a high definition MultiLeaf Collimator (HD MLC 120) (Varian Medical Systems, Palo Alto, CA, USA and Brainlab, Munich, Germany).

Two radiotherapy methods were used over two periods. From May 2012 to February 2016, dynamic arc therapy (with 4–5 non coplanar arcs) was used. The dose prescribed was 33 Gy to the isocentre and 23.1 Gy (70%) at the envelope covering the PTV, delivered in 3 fractions. From March 2016 to January 2020, VMAT (volumetric modulated arc therapy), using one full coplanar arc and three partial non-coplanar arcs spaced by 45°, was used. The prescribed dose was 33 Gy for the GTV and 23.1 Gy (70% isodose) for the PTV delivered in 3 fractions, corresponding in practice to a prescribed dose to the 70% isodose line to achieve 99% target coverage of the PTV. Delineation and dose prescription corresponded to French national recommendations [5,21]. MF-SRT was delivered every other day. In case of proximity with OARs, the prescribed dose could be adjusted to meet dose constraints [22]. Concerning Treatment Planning Systems (TPS) for DynArc, final calculations were performed using Iplan® TPS, version 4.1 (Brainlab), using a pencil-beam algorithm with a spatial resolution of 2.5 mm. For VMAT, final calculations were performed using the AAA algorithm on Eclipse® TPS version 13.5 (Varian Medical Systems). The arc optimization algorithm, the Progressive Resolution Optimizer used in Rapidarc®, optimized leaf position, dose rate, and gantry speed.

Before the start of the treatment, patients received oral corticosteroid at an initial dose of 1 mg/kg decreasing on 4 weeks, to prevent brain edema.

Follow-up

Follow-up included MRI (including T1 Gadolinium sequences with dynamic susceptibility-weighted contrast-enhanced [DSC] perfusion), coupled with a clinical examination every 3 months. Treatment related-toxicities such as RN, edema and hemorrhages were recorded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.

Local control failure was defined by a recurrence in the previously irradiated volume using RANO-BM criteria [23], characterized as an increase of at least 20% in sum longest distance relative to nadir, associated with either a relative cerebral blood volume (CBV) > 2.0 at dynamic susceptibility-weighted contrast-enhanced perfusion images (calculated for each lesion by the ratio of the tumor CBV on the mean CBV value of normal white matter) or a maximum lesion to maximum background uptake ratio (SUVLmax/Bkgrmax) > 1.59 at F-DOPA PET-CT (for 2 patients). RN was defined by stable or shrinking lesions over a 6-month period associated with a rCBV < 2.0 in perfusion images, or a SUVLmax/Bkgrmax < 1.59, or on the basis of histologic findings after brain metastasectomy [18,24].

Last follow-up was defined as the date of death or the date of the last consultation with a cerebral IRM, during the period of the study that ended November 2020. Median follow-up was 12 months (range = 1 – 90). Overall survival (OS) was defined as the time between the last session of MF-SRT and the patient's death.

Statistical analysis

RN and LC rates, progression-free survival (PFS), and overall survival (OS) were estimated from the end of MF-SRT using the Kaplan-Meier calculation method. Then the log-rank test was performed to compare survival curves. Predictive factors for LC, OS, and time to RN are investigated using univariate and multivariate Cox regression models. For LC and RN, a competing risk analysis with death as a concurrent risk was performed, as a sensitivity analysis.

Concerning LC, the following factors were assessed in the univariate analysis: histological type, presence or absence of a mutation, presence or absence of a systemic treatment at the time of brain SRS, prior WBRT, GTV volume, PTV volume, largest diameter, location, laterality (right or left), depth (distance from the cranial vault to the surface of the lesion), overall treatment time, doses delivered to GTV and PTV (Dmin, D98%, Dmean, D2%, Dmax), V70% PTV (V70% is the volume of the structure receiving a dose $\geq$ 70% prescribed dose, i.e. prescription isodose), and radiotherapy technique (non-coplanar dynamic arc therapies or VMAT).

For OS, the same factors were analyzed in the univariate analysis, to which were added age, gender, comorbidities (diabetes, dyslipidemia, high blood pressure), performance status, number of brain metastases, and prognostic scoring systems for BM patients including the Score Index For Radiosurgery (SIR), the Recursive Partitioning Analysis (RPA), the Graded Prognostic Assessment (GPA), the disease specific Graded Prognostic Assessment (DS-GPA) and the lung-molGPA which incorporates recently reported gene alteration data, predicting the outcomes of NSCLC.

Concerning RN, the following factors were included: age, gender, comorbidities (diabetes, dyslipidemia, high blood pressure), presence or absence of a systemic treatment at the time of brain SRS, prior WBRT, GTV volume, PTV volume, largest diameter, location, depth, overall treatment time, radiotherapy technique (non-coplanar dynamic arcs therapy or VMAT) and doses delivered to healthy brain parenchyma (brain - GTV): $V_{23.1Gy}$, V_{21Gy}, V_{18Gy}, V_{14Gy}, V_{10Gy}, V_{5Gy} (definition: V_xGy (cc) is the volume of the structure receiving a dose $\geq$ x Gy).

All variables with a p-value < 0.1 in the univariate analysis were and used to build a multivariate regression model, using the LASSO algorithm in order to perform variable selection.

For identifying the optimal GTV Dmin threshold dose, a time-dependent ROC (Receiver Operating Characteristics) curve was

performed to identify the optimal threshold value. Then, a Kaplan-Meier curve of the two populations was estimated and compared using a log-rank test. As a complementary analysis obtaining a p-value adjusted for multiple testing, we performed maximally selected rank statistics threshold analysis using the r-package maxstat with p-value approximation via conditional Monte-Carlo. Intergroup differences were compared using Fisher's exact test for categorical variables and the Wilcoxon-Mann-Whitney for continuous variables. A p-value <0.05 was considered indicative of a statistically significant difference. Statistical analyses were performed using the R software, version 4.1.0 (R-Project, GNU GPL, https://cran.r-project.org/).

Results

Local control

Considering death as competing risk factor, the LC rates were 95.7%, 90.7% and 87.9% at 6, 12, and 24 months respectively (Fig. 1A). No difference in LC was found between DynArc and VMAT techniques. In univariate analysis, predictive factors of better LC were other locations than the cerebellar (HR = 0.282, CI 95% = 0.086 – 0.926, p = 0.047), higher GTV D_{min} (HR = 0.774, CI 95% = 0.676 – 0.887, p = 0.002), higher GTV $D_{98\%}$ (HR = 0.781, CI 95 % = 0.684 – 0.892, p = 0.003), higher GTV D_{mean} (HR = 0.725, CI 95% = 0.540 – 0.973, p = 0.049), higher $V_{70\%}$ PTV (HR = 0.835, CI 95% = 0.750 – 0.929, p = 0.01), no prior WBRT (HR = 3.625, CI 95% = 1.098 – 11.970, p = 0.037), lower PTV volume (HR = 1.073, CI 95% = 1.005 – 1.145, p = 0.045), and lower maximum diameter (HR = 1.100, CI 95% = 1.031 – 1.174, p = 0.006).

In multivariate analysis, higher GTV D_{min} (HR = 0.822, CI 95% = 0.706 – 0.957, p = 0.012) and lower maximum diameter (HR = 1.124, CI 95% = 1.044 – 1.210, p = 0.002) remained significant factors of predictive LC. In the competing risk model considering death as competing event, only higher GTV D_{min} (HR = 0.826, CI 95% = 0.757 – 0.902, p < 0.001), and lower maximum diameter (HR = 1.152, CI 95% = 1.055 – 1.259, p = 0.002) remained significant.

Histology type, the presence of a mutation, and systemic treatment were not predictive factors of LC, whether in univariate analysis or multivariate analysis.

Concerning GTV Dmin, we identified a discriminant threshold-value of 27.4 Gy (AUC = 0.69, CI 95% = 0.49–0.87), using a time dependent ROC curve. The 1-year LC was 97.1% versus 73.1% for GTV Dmin ≥ 27.4 Gy and GTV Dmin < 27.4 Gy respectively (p = 0.002 by logrank test). A complementary analysis, using maximally selected rank statistics with p-value adjustment for multiple testing, provided the same threshold of 27.4 Gy with an adjusted p-value of 0.02 (Fig. 2A and 2B).

Radionecrosis and other toxicities

Considering death as a competing risk factor, the 6-month, 1-year and 2-year actual risks of RN were 6.3%, 15.4%, and 18.1% respectively. Symptomatic RN was described in 5.9% of cases. Predictive factors of RN found in univariate analysis were high blood pressure (HR = 3.126, CI 95% = 1.210 – 8.077, p = 0.017) and dyslipidemia (HR = 3.614, CI 95% = 1.429 – 9.137, p = 0.009). Dyslipidemia was the only significant predictive factor of RN in multivariate analysis (HR = 3.436, CI 95% = 1.140 – 10.355, p = 0.028) and in the competing risk model (HR = 2.69, CI 95% = 1.076 – 6.72, p = 0.03).

We reported the following mean volumes of healthy brain (brain – GTV): $V_{23.1Gy}$, V_{21Gy}, V_{18Gy}, V_{14Gy}, V_{10Gy} and V_{5Gy}, which were 6.43 cc, 8.02 cc, 10.76 cc, 16.64 cc, 28.38 cc, and 76.86 cc respectively. There were no dosimetric predictive factors of RN, whether in univariate analysis or multivariate analysis.

Other symptoms observed during and after MF-SRT were hemorrhage, neurological deficit, intra-cranial hypertension and epilepsy, in 7%, 8%, 4% and 2% of cases, respectively.

Survival

PFS at 6 months, 1 year, and 2 years was 67.9%, 40.9%, and 17.4% respectively. Median PFS was 10 months (Fig. 1B).

OS at 6 months, 1 year, and 2 years was 80.8%, 56.7%, and 34.1% respectively (Fig. 1C). Median OS was 14 months. In univariate analysis, significant prognostic factors of lower OS were higher age (HR = 1.035, CI 95% = 1.004 – 1.066, p = 0.024) and poorer PS status (1.423, CI 95% = 0.805 – 2.515, p = 0.215), whereas higher SIR score (HR = 0.661, CI 95% = 0.537 – 0.813, p < 0.001), higher GPA score (HR = 0.493, CI 95% = 0.333 – 0.731, p = 0.001), higher DS-GPA score (HR = 0.669, CI 95% = 0.507 – 0.883, p = 0.008), higher lung-molGPA (HR = 0.483, CI 95% = 0.315 – 0.743, p = 0.001) and presence of mutation (HR = 0.500, CI 95% = 0.244 – 1.022, p = 0.041) were predictive factors of higher OS. In multivariate analysis, a higher SIR, GPA, and lung-molGPA score remained significant prognostic factors of OS.

Discussion

In our retrospective series, we reported the outcomes of 101 unresected brain metastasis in 87 patients from NSCLC treated with MF-SRT. To our knowledge, this is the first published study to assess the outcomes of MF-SRT, and study predictive factors of LC and RN, in a homogeneous population of patients with intact brain metastases of NSCLC, treated by MF-SRT in 3 fractions according to French recommendations (3x7.7 Gy on the 70% isodose line; PTV = GTV + 2 mm) [21]. In particular, we found that a Dmin < 27.4 Gy to the GTV could be a predictive factor of worse LC; and that dyslipidemia could be a predictive factor of RN.

NSCLC is the main etiology of brain metastasis but in most studies assessing brain RN or LC, the underlying cancers were heterogeneous with various fractionations [16–20]. Only one recent study conducted by Minniti et al. compared the effectiveness of MF-SRT for large brain metastases from NSCLC; however this study included both resected and intact brain metastases [25]. In the group treated for intact brain metastases, 6-month LC was 96% and 12-month LC was 92%, which is quite similar to our results with 6-month and 12-month LC of 95% and 87% respectively [25]. In the study by Minniti et al., patients were treated with 3x9Gy on the 80% isodose line, with PTV = GTV + 1 mm; which is quite similar to our fractionation according to French recommendations with 3x7.7 Gy on the 70% isodose line, with PTV = GTV + 2 mm. Garsa et al reported, in 2014, predictive factors of individual tumor LC after SRS for NSCLC brain metastases in which the estimated local control at 12 months was 74%. However, in this trial all patients were treated by Gamma Knife single-fraction SRS and the median prescription dose was 20 Gy (range 14–24 Gy). Cerebellar tumor location, larger tumor volume, and lower conformity index were significant independent predictors of local failure. The adjusted 1-year local control rate for cerebellar lesions was 60% compared with 77% for supratentorial lesions (controlling for tumor volume and conformality index), which support our results since we found in our study that cerebellar location was a predictive factor of lower rates of local control but only in univariate analysis [26]. However, Vogelbaum et al, in an analysis of 202 patients with multiple types of metastatic malignancies treated with SRS, did not find any difference between infratentorial and supratentorial metastasis [27]. We also reported that maximum diameter (HR = 1.124, CI 95% = 1.044 – 1.210, p = 0.002) was associated with a worse prognosis for LC.

Furthermore, one of the interests of our study was to report dosimetric predictive factors of LC and characterize a minimum dose delivered to the GTV of 27.4 Gy. In our study, the 1-year LC was significantly improved when GTV $D_{min} \geq 27.4$ Gy (97.1% versus 73.1%, p = 0.013). Even if a dose–effect relation is well known in single fraction SRS [28], it is much less studied and reported in MF-SRT. Furthermore, Dmin to the GTV is rarely specified and studied in published MF-SRT series, even if it might be a dosimetric factor of interest since PTV margins vary from 0 to 2 mm in MF-SRT leading to a varying dose in the

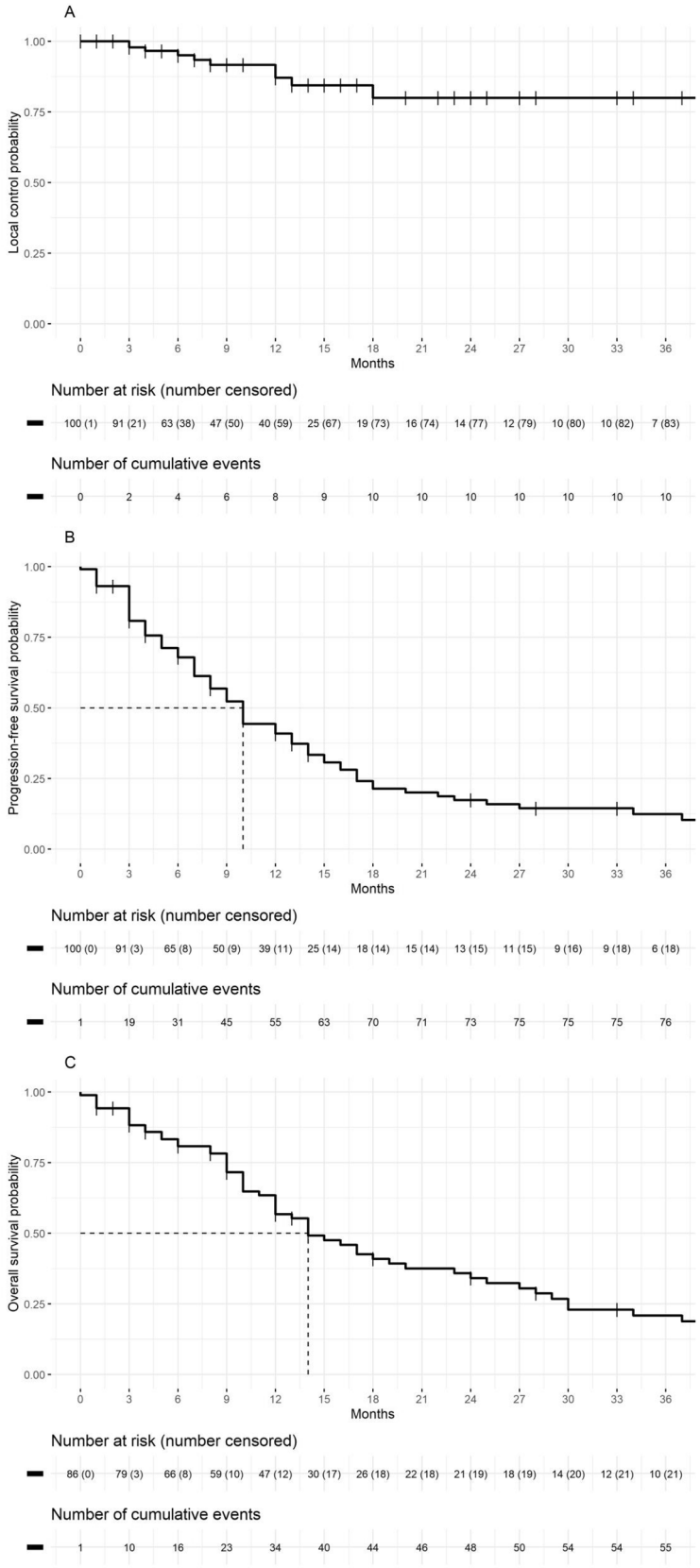

Fig. 1. Probability of local control (1A), progression-free survival (1B) and overall survival (1C) for the 87 patients receiving MF-SRT for 101 brain metastases from NSLC. Abbreviations: MF-SRT, multifractionated stereotactic radiotherapy; NSCLC, non-small-cell lung cancer.

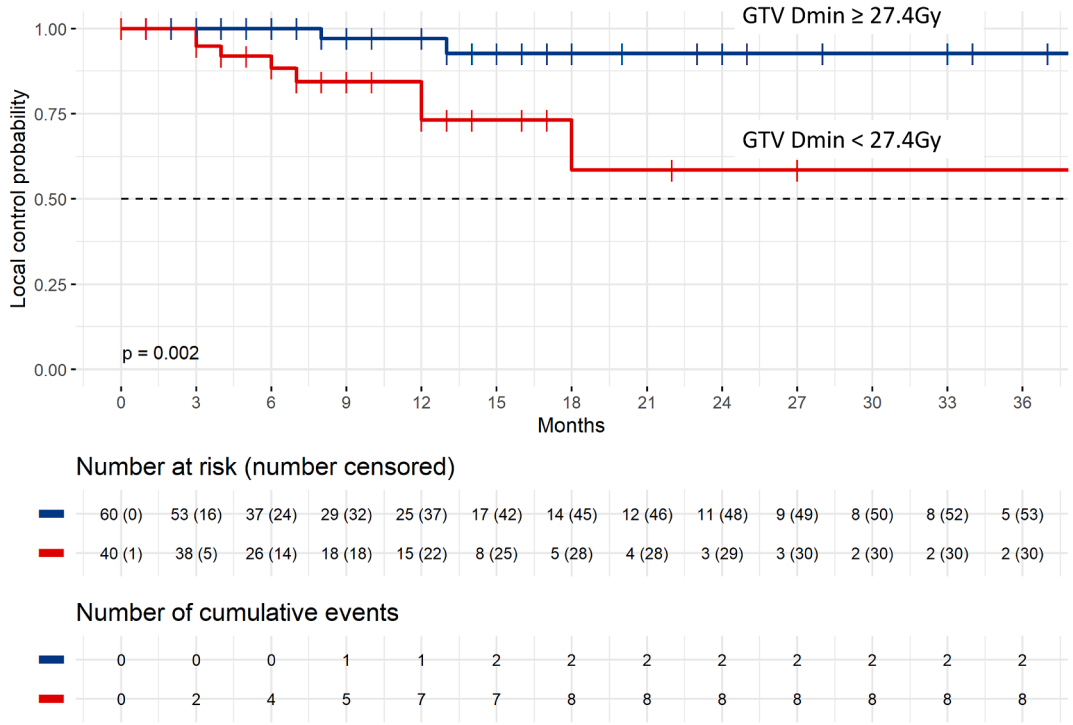

Fig. 2. Comparison of local control curves of all 101 treated brain metastases between those receiving a GTV Dmin < 27.4 Gy in three fractions vs ≥27.4 Gy. Abbreviations: GTV = gross tumor volume; Dmin = minimum dose.

GTV, whereas GTV is always delineated in the same manner. To overcome this limitation, in 2020 Dupic et al published a study which focused on the minimum or near-minimum (D98%) dose delivered to the GTV and not the marginal dose prescribed to the PTV influenced by the use of margins. Therefore, this study demonstrated that a GTV $D_{98\%}$ higher than 29 Gy in 3 fractions was a significant predictive factor of local control in MF-SRT for brain metastases from various histology [19].

Dosimetric data collected for each brain metastasis from NSCLC is not sufficient on its own to explain local control. Another important factor for LC is the choice of systemic treatment. Indeed, the chosen agent must be effective against the primary cancer, but also be able to cross the blood–brain barrier. It is systematically discussed before local treatment. Even if most systemic therapies do not easily pass the blood–brain barrier, the anarchic neo-angiogenesis of brain metastases, responsible for an alteration of the blood–brain barrier, makes the diffusion of some cytotoxic agents possible. For example, platinum-based chemotherapies induce equivalent cerebral and extra-cerebral response rates, usually between 30 and 50% [29]. Tumors with high PDL1 expression (≥50%) are accessible to Pembrolizumab in first-line treatment [30]. Other immunotherapies such as Nivolumab or Atezolizumab may be used with satisfactory safety of use based on brain response rates. Mutations are often present in adenocarcinoma and enable the development of innovative targeted therapies, specifically TKI (Tyrosine Kinase Inhibitor) for EGFR mutations or ALK gene rearrangement. Osimertinib is the preferred drug in the case of EGFR mutations due to a better penetration in the central nervous system compared to 2nd generation TKI, and a better control of brain metastases [31]. A clear decrease in brain progression with Alectinib versus Crizotinib, 12% versus 45% (cause-specific hazard ratio 0.16, $p < 0.001$) associated with an intrabrain response rate of 88% for Alectinib versus 50% for Crizotinib, was observed in ALEX study [7]. In our study, systemic treatment concerned 60% of patients: chemotherapy (63%), Avastin (5.7%), targeted therapies (19.2%): Erlotinib (13.5%), Alectinib (1.9%), Olaparib (1.9%), and immunotherapy (15.3%). Diverse treatments were administered, and do not lead to any conclusions about their association with LC.

RN is the most common adverse event of MF-SRT, but its physiopathology is poorly understood. Several risk factors have been described, including the total dose of radiotherapy delivered, tumor volume, fractionation, healthy brain parenchyma irradiation and previous irradiation. Other factors mentioned include overall treatment time, infratentorial location, and combination with chemotherapy [17,18,20,32–36]. In our study, 1-year actual RN risk rate was 15.4 %. Among RN cases, symptoms were observed in 5.9%. In the series by Minniti et al. [18], retrospectively comparing SRS vs MF-SRT (using more or less the same MF-SRT as in our study) for multiple histology brain metastases, the cumulative 1-year risks of RN were 18% vs 9% ($p = 0.01$), in favor of MF-SRT. The cumulative 2-year risk of RN for MF-SRT was about 18% at two years, as in our study. For lesions > 3 cm, the cumulative 1-year risk was 14% for MF-SRT vs 33% for SRS ($p = 0.01$). Symptomatic RN was 4%. More recently, Minniti et al. [25], using the same MF-SRT schedule, published a series of 241 postoperative or intact NSCLC brain metastases. The 1-year cumulative incidence rates of RN were 15% and 7% after postoperative SRT and SRT alone, respectively. 5.7% of the patients treated with MF-SRT. In a *meta*-analysis conducted in 2018 by Lehrer at al. lower rates of RN were found with 18.2% (95% CI, 9.3%–32.5%) for SRS group and 7.1% (95% CI, 4.4%-11.3%) for MF-SRT group [16]. The RN rates reported in our study might appear slightly higher than in the above cited studies, however symptomatic RN are in the exact same range. Furthermore, the exact diagnosis of RN is difficult as discussed in the RANO-BM working group report [23] and in the recent review from Milano et al. (*American Association of Physicists in Medicine Working Group on Stereotactic Body Radiotherapy*) [37]. In this review, several studies (n = 15) have reported RN risks after MF-SRT (2–5 fractions). Patients selected for MF-SRT often had bulkier disease and/or tumors in critical locations. Toxicity after MF-SRT appears to be relatively lower vs. single-fraction SRS), More recently, a large series of 334 multiple histology intact brain metastases treated in 5 daily fractions of MF-SRT (median dose of 30 Gy in 5 fractions) was published [38]. Fifty-two metastases (15.6%) had an adverse radiation effect, of which 32 (9.5%) were symptomatic RN. In

our study, other symptoms observed during and after MF-SRT were hemorrhage, neurological deficit, intra-cranial hypertension and epilepsy, in 7%, 8%, 4% and 2% of cases, respectively. However, these results are difficult to interpret since these symptoms are not necessarily toxicities related to the irradiated lesion, in patients who may have other intracerebral lesions. In MF-SRT (3 fractions), the most significant prognostic factor reported to date for RN is the brain volume receiving high doses: V23.1 Gy $\geq$ 5 cc [39], V21Gy $\geq$ 20.9 cc [40] and V18Gy $>$ 30.2 cc [18]. In our study, no dosimetric factors were independent predictive factors of RN in univariate or multivariate analysis, probably because of the limitation of healthy brain parenchyma irradiation (mean V23.1 Gy, V21Gy and V18Gy of 6.4 cc, 8.0 cc and 10.8 cc respectively, which are globally lower than the previous published thresholds). Dyslipidemia was the only significant predictive factor of RN in multivariate analysis (HR = 3.436, CI 95% = 1.140 – 10.355, p = 0.028) in our study. To date, no data in the literature have been reported showing an association between dyslipidemia and RN. Although the pathophysiological mechanisms of RN are not yet completely understood, vascular damage is observed a few months to years after the end of SRT, followed by glial and neuronal lesions. Once present, these lesions are usually irreversible and progressive. The vascular phase is characterized by vasogenic edema, followed by hyalinization responsible for a thickening of the vascular wall with parietal thrombi until a fibrinoid necrosis [41,42]. This imbalance could contribute to the secondary cytotoxic edema that leads to tissue necrosis. Oligodendrocytes are very radiosensitive and their destruction is responsible for demyelination. The lesions then mainly affect the white matter, while the cortex is partly spared. Atherosclerosis is an inflammatory response to injury to the arterial wall and lead to necrosis. Actually, the accumulation of LDL cholesterol in the intima will oxidize and be captured by macrophages involving a chronic inflammatory reaction. This endothelial remodeling leads to an increasing endothelial parietal thickness that may be responsible for ischemic necrosis [37]. Disorders of microvascularization caused by dyslipidemia may partially explain our result; nevertheless, high blood pressure and diabetes are also responsible for microangiopathy but did not appear as predictive factors of RN. However, this result remains difficult to interpret, indeed we do not have sufficient data regarding the lipid metabolism disorder which may concern triglycerides or cholesterol. We also have no data on statin intake and the number of patients included seems low to conclude. More investigation is necessary for stronger conclusions about the observed correlation between dislipidemia and increased risk for radiation necrosis.

Conclusion

In conclusion, MF-SRT delivered according to French recommendations (i.e 3x7.7 Gy on the 70% isodose line, with PTV = GTV + 2 mm) for brain metastasis from NSCLC results in high LC rates with acceptable RN rate. The LC, RN and OS rates we reported in this retrospective series of brain metastasis from NSCLC are consistent with results observed in series with heterogeneous primary tumors. GTV D_{min} remained a predictive factor of better LC in NSCLC brain metastasis with a threshold of GTV Dmin $\geq$ 27.4 Gy. No dosimetric predictive factors of RN were found in this study. However, dyslipidemia was identified as a potential predictive factor of RN, which may be explained by microvascular disorders. Further studies are needed to explore this hypothesis.

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.

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