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Significant correlation between gross tumor volume (GTV) D98% and local control in multifraction stereotactic radiotherapy (MF-SRT) for unresected brain metastases

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Running title: GTV D98% and local control in stereotactic radiotherapy

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Abbreviations:

- BBB: Blood Brain Barrier
- BED: Biologically Effective Dose
- CBV: Cerebral Blood Volume
- CI: Conformity Index
- CTV: Clinical Tumor Volume
- DCA: Dynamic Conformal Arcs
- DS-GPA: Diagnosis-Specific Graded Prognostic Assessment
- EGFR: Encoding Epidermal Growth Factor Receptor
- GI: Gradient Index
- GPA: Graded Prognostic Assessment
- GTV: Gross Tumor Volume
- Gy: Gray

- HI: Homogeneity Index
- ICRU: International Commission on Radiation Units and Measurements
- LC: Local Control
- MF: MultiFraction
- MRI: Magnetic Resonance Imaging
- NCI-CTCAE: National Cancer Institute's Common Toxicity Criteria for Adverse Events
- OAR: Organs At Risk
- OS: Overall Survival
- PFS: Progression-Free Survival
- PS: Performance Status
- PTV: Planning Target Volume
- RN: (brain) RadioNecrosis
- RP: Radiation Pneumonitis
- RPA: Recursive Partitioning Analysis
- SIR: Score Index for Radiosurgery
- SRS: Stereotactic RadioSurgery
- SRT: Stereotactic RadioTherapy
- TKI : Tyrosine Kinase Inhibitor
- TPS: Treatment Planning Systems
- VEGF : Vascular Endothelial Growth Factor
- VMAT: Volumetric Modulated Arc Therapy
- WBRT: Whole Brain RadioTherapy

ABSTRACT

Background

Stereotactic radiotherapy (SRT) should be applied with a biologically effective dose with an α/β of 12 (BED_{12}) ≥ 40 Gy to reach a 1-year local control (LC) $\geq 70\%$. The aims of this retrospective study were to report a series of 81 unresected large brain metastases treated with Linac-based multifraction SRT according to the ICRU 91 and to identify predictive factors associated with LC.

Methods

Included in this study were the first 81 brain metastases (BM) consecutively treated with Linac-based volumetric modulated arc therapy (VMAT) multifraction SRT from 2017 to 2019. The prescribed dose was 33 Gy for the GTV and 23.1 Gy (70% isodose line) for the PTV in 3 fractions (3f). Mean BM largest diameter and GTV were 25.1 mm and 7.2 cc respectively. Mean follow-up was 10.2 months.

Results

LC was 79.7% and 69.7% at 1 and 2 years respectively. Significant predictive factors of LC were GTV $D_{98\%}$ (HR = 0.84, CI 95% = 0.75–0.95, $p = 0.004$) and adenocarcinoma as the histological type (HR = 0.29, CI 95% = 0.09–0.96, $p = 0.042$) in univariate and multivariate analysis. A threshold of 29 Gy for GTV $D_{98\%}$ was significantly correlated to LC (1-year LC = 91.9% for GTV $D_{98\%} \geq 29$ Gy vs 69.6% for GTV $D_{98\%} < 29$ Gy ($p = 0.030$)), corresponding to a $BED_{12} = 52.4$ Gy. No tumor progression was observed for a $BED_{12} \geq 53.4$ Gy, corresponding to a GTV $D_{98\%} \geq 20$ Gy /1f and GTV $D_{98\%} \geq 29.4$ Gy 3f. Median OS was 15 months. Symptomatic radionecrosis occurred in 4.9% of cases.

Conclusion

The GTV $D_{98\%}$ is a strong reproducible significant predictive factor of LC for brain SRT. Dose prescription should lead to a GTV $BED_{12\ 98\%} \geq 52.4$ –53.4 Gy to significantly improve LC, corresponding to respectively a GTV $D_{98\%} \geq 19.7$ –20 Gy/1f and 29–29.4 Gy/3f.

Introduction

Stereotactic radiosurgery (SRS) and multifraction stereotactic radiotherapy (MF-SRT) have become increasingly common treatment options for suitable patients with brain metastases [1]. Wiggeraad et al. showed in a systematic review that local control (LC) after single fraction SRS was highly dependent upon dose and was high (> 80%) after 21 Gy or more and low (< 50%) after 15 Gy or less. Using the biologically effective dose of the linear-quadratic model with an α/β of 12 Gy (BED_{12}), they concluded that SRT for brain metastases should preferably be applied with a $BED_{12} \geq 40$ Gy corresponding with a single fraction of 20 Gy (20 Gy/1f) and three fractions of 8.5 Gy (25.5 Gy/3f) [2]. So the largest recorded MF-SRT total prescribed dose to the PTV is 27 Gy in three fractions (range: 23.1–33 Gy) [3]. The clinical tumor volume (CTV) is often a zero-margin expansion of the gross tumor volume (GTV). The planning target volume (PTV) varies in literature and is generally a 1-2-mm geometrical expansion of the CTV [4]. According to published studies, actual 1-year LC varies widely, generally between 79–93% (range: 59–100%), due to various differences in techniques and devices used for delivery of MF-SRT and various differences in definitions of LC and radionecrosis among institutions [3–7].

Very few studies have reported doses delivered to the GTV, yet GTV doses are the most reproducible data among studies where various techniques, devices and definitions of target volumes are used. The International Commission on Radiation Units and Measurements (ICRU) report 91 titled “Prescribing, recording, and reporting of stereotactic treatments with small photon beams” was published in 2017 [8]. ICRU 91 gives recommendations for reporting doses for SRS and MF-SRT (2-12 fractions) with conformal radiotherapy as well as intensity-modulated radiotherapy [9]. Reporting for SRT should contain the following information: delineated volumes, prescription and planning aims, description of the treatment planning system, dose documentation to target volumes and organs at risk (OAR), PTV and GTV $D_{50\%}$, D_{mean} , $D_{2\%}$, $D_{98\%}$ (for volumes ≥ 2 cc), OAR D_{mean} , $D_{2\%}$ and V_{xGy} , dose homogeneity HI (homogeneity index), dose conformity CI (conformity index) and dose gradient GI (gradient index) [9].

The purposes of this retrospective study were to report a series of 81 unresected brain metastases treated with Linac-based multifraction SRT according to the ICRU 91 and to identify predictive factors associated with local control (LC).

Patients and Methods

Patients' selection and characteristics

Included in this study were the first 81 unresected brain metastases consecutively treated in our institution with Linac-based volumetric modulated arc therapy (VMAT) multifraction stereotactic radiotherapy (MF-SRT, 3 fractions) from February 2017 to December 2019. All patients were aged ≥ 18 years with at least a large brain metastasis ≥ 2 cm in diameter derived from a histologically confirmed systemic cancer. They could have received prior SRT or whole brain radiotherapy (WBRT). Exclusion criteria were small field sizes for SRS < 30 mm, brainstem metastases or prior surgery. Study ethics approval was obtained on 25 September 2020 (CECIC Rhône-Alpes-Auvergne, Grenoble, IRB 592).

All pre-treatment characteristics of the 81, including the brain metastases of the 69 patients, are reported in **Table 1**. Mean age was 62 years (range: 33–87 years). Most patients were male (59%), in good general state of health with a performance status ≤ 1 (85%), treated for a single brain metastasis (85%) and with no prior SRT (93%) or WBRT (88%). Primary cancers were mostly lung (59%), breast (15%), digestive (7%), melanoma (7%), ovarian (4%) and renal (3%). Adenocarcinoma was the most frequent histological type (73%) with a mutation in 18 % of cases. The mean brain metastasis' largest diameter was 25.1 mm (8–41 mm). A systemic treatment was provided in 66% of cases (58/88) at the time of brain SRS. Most of these systemic treatments were immunotherapy (22/58, 38%): nivolumab, pembrolizumab, durvalumab and atezolizumab in 24% of cases (14/58), 7% of cases (4/58), 3% of cases (2/58) and 3% of cases (2/58) respectively. Other systemic treatments were targeted therapies in 19% of cases (anti-VEGF antibody bevacizumab (2/58, 3%), EGFR TKI (3/58, 5%) : first generation TKI erlotinib (2/58, 3%) and third-generation TKI osimertinib (1/58, 2%), ALK inhibitor alectinib (1/58, 3), PARP inhibitor olaparib (1/58, 3%) and BRAF inhibitors dabrafenib + trametinib (1/58, 3%), Her2 inhibitor trastuzumab (3/58, 5%)), hormonal therapies (tamoxifen, letrozole, anastrozole) in 12% of cases (7/58) 7/58 and platinum and taxane-based chemotherapy in 33% of cases (12/58 and 7/58 respectively).

Treatment specifications

A planning CT of 1.25-mm thickness was acquired and was matched with the dosimetric magnetic resonance imaging (MRI) sequences of interest using Iplan®, version 4.1 (Brainlab). Three MRI sequences were used: a FLAIR 3D MRI sequence with a

1mm*1mm*1mm voxel size, a T1 3D MPRAGE MRI sequence with contrast agent and a voxel size of 0.8mm*0.8mm*1mm and a T1 EG with a 0.6mm*0.6mm*4mm voxel size. The GTV was defined using post-gadolinium contrast-enhanced T1-weighted MRI sequences. The GTV was then extended symmetrically by 2 mm in all dimensions to create the PTV. Mean GTV and PTV were 7.8 cc (0.5–31.3 cc) and 13.5 cc (1.5–46.2 cc) respectively. The following OAR were contoured: brainstem, eyeballs, lenses, optic nerves, chiasm, cochlea, cranial cavity, and healthy brain (entire cranial cavity - GTV). No margins were added around the OAR to create planning OAR volumes.

All VMAT plans were created with arcs for 6-MV photons. The plans were created with one full coplanar arc and three partial non-coplanar arcs spaced by 45°. The maximum arc rotation amplitude was 160°. The rotation of the collimator was 10°, 350°, 350° and 350° for the first, second, third and fourth arcs respectively. The prescribed dose was 33 Gy for the GTV and 23.1 Gy (70%) for the PTV in three fractions [10]. Doses were prescribed to the 70% isodose line to achieve 99% target coverage of the PTV. Target coverage could be reduced to meet OAR dose constraints [11]. 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. Optimization parameters with *Normal Tissue Objectives* (NTO) were used to spare healthy tissues and were defined as the following: 1) distance from the PTV border (Xstart) = 1 mm, 2) start dose (f0) = target coverage isodose (e.g. 70%), 3) end dose (f∞) = 5% and 4) the fall-off coefficient (k) = 0.3 mm⁻¹. The maximum dose rate was set at 600 MU/min. Couch parameters were also added to the plan to account for attenuation of the mega-voltage beams. VMAT plans followed the recommendations of the ICRU 83 [12]. All treatment characteristics are reported in **Table 1**.

All patients were treated with NovalisTx® equipped with a high definition MultiLeaf Collimator (HD MLC 120) (Varian Medical Systems, Palo Alto, CA, USA and Brainlab, Munich, Germany) using a noninvasive thermoplastic mask plus a localizer box (Brainlab). For the most part, each fraction was delivered every two days (separated by at least 24 hours). Overall treatment time (OTT) should not exceed 10 days. Positioning of the patients was performed using an ExacTrac® stereoscopic X-ray system (Brainlab) and a robotic couch with six degrees of freedom. Treatments were permitted when the setup error was < 0.7 mm in translation and 0.7° in rotation.

Follow-up

Follow-up included a clinical examination and MRI every three months during the first two years post MF-SRT and every six months afterwards. Toxicity was evaluated using the National Cancer Institute's Common Toxicity Criteria for Adverse Events version 4.0 (NCI-CTCAE). Tumor progression was defined as any tumor increase visible on contrast-enhanced T1-weighted images in at least 2 subsequent MRI results associated with either a cerebral blood volume (CBV) ratio > 2.0 at dynamic susceptibility-weighted contrast-enhanced perfusion images (calculated for each lesion by dividing the tumor CBV by the mean CBV value of normal white matter) or a maximum lesion to maximum background uptake ratio ($SUVL_{max}/Bkgr_{max}$) > 1.59 at F-DOPA PET-CT. Stable or shrinking lesions over a 6-month period associated with a CBV ratio < 2.0 or a $SUVL_{max}/Bkgr_{max} < 1.59$ were diagnosed as radionecrosis [4]. Distant failure was defined by the presence of new brain metastases or leptomeningeal enhancement outside the PTV. Overall survival (OS) was defined as the time between the end of MF-SRS and the patient's death. Mean follow-up was 10.2 months (range: 0.5–31.3 months) (*Table 1*).

Statistical analysis

Local control (LC), progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. The Cox proportional hazards model was performed to identify predictive factors of LC and prognostic factors of PFS and OS. A two-sided p-value < 0.05 was considered significant. The following factors were included in the univariate analysis for LC: histological type, presence or absence of a mutation, presence or absence of a systemic treatment at the time of brain SRS, prior surgery, prior SRT, prior WBRT, GTV, PTV, conformity index (CI = inverse Paddick), gradient index (GI = total volume receiving $\geq 50\%$ $D_{coverage}$ / total volume receiving $\geq 100\%$ $D_{coverage}$), overall treatment time, doses delivered to GTV and PTV (D_{min} , $D_{98\%}$, D_{moy} , $D_{2\%}$, D_{max}), $V_{70\%}$ PTV ($V_{70\%}$ is the volume of the structure receiving a dose $\geq 70\%$ prescribed dose, i.e. prescription isodose). Concerning OS, the following factors were included in the univariate analysis in addition to the previously studied LC predictive factors: gender, age, performance status, prognostic classifications (SIR, RPA, GPA, DS-GPA), number of brain metastases, presence or absence of a systemic treatment at the time of brain SRS and presence or absence of a mutation. A logistic regression analysis was performed. Concerning radionecrosis, the following factors were included: age, gender, arterial hypertension, type 2 diabetes, hypercholesterolemia, brain

metastases location, prior surgery, prior SRT, prior WBRT, presence or absence of a systemic treatment at the time of brain SRS, GTV, PTV, conformity index, gradient index, overall treatment time, and doses delivered to healthy brain parenchyma (brain - GTV): $V_{23.1Gy}$, V_{21Gy} , V_{18Gy} , V_{14Gy} , V_{10Gy} , V_{5Gy} (V_{xGy} (cc) is the volume of the structure receiving a dose $\geq x$ Gy).

Factors associated with a p-value < 0.2 in the univariate analysis were included in the multivariate analysis if they were also selected by the LASSO method. The Wald test and the likelihood ratio test were performed to calculate and verify the p-value for each coefficient in multivariate analyses. For each significant linear correlation observed, a ROC (Receiver Operating Characteristics) curve was performed to identify the best threshold-value. Finally, comparison of LC curves with the obtained threshold was conducted using the log-rank test. To compare the two groups of patients obtained with the best threshold-value, Fisher's exact test and the Wilcoxon-Mann-Whitney test were used in the analysis of contingency of these two groups to compare two categorical variables and a categorical variable with a continuous variable, respectively. Statistical analysis was performed using R-Project, version 3.6.1 (R-Project, GNU GPL, <http://cran.r-project.org/>).

Results

Local control (LC) at 6 months, 1 year, and 2 years was 87.5%, 79.7% and 69.7% respectively (**Figure 1**). Significant predictive factors of LC were GTV $D_{98\%}$ (HR = 0.87, CI 95% = 0.78–0.96, $p = 0.046$) and adenocarcinoma as the histological type (HR = 0.25, CI 95% = 0.08–0.83, $p = 0.025$) in univariate analysis. GTV $D_{98\%}$ (HR = 0.84, CI 95% = 0.75–0.95, $p = 0.004$) and adenocarcinoma as the histological type (HR = 0.29, CI 95% = 0.09–0.96, $p = 0.042$) remained significant in multivariate analysis (**Table 2**). Systemic treatment (presence vs absence) and tumor mutation (presence vs absence) were not significant predictive factor of local control in univariate analysis (HR = 0.42, CI 95% = 0.13–0.39, $p = 0.17$ and HR = 0.24, CI 95% = 0.03–1.83, $p = 0.09$ respectively).

The best threshold identified for GTV $D_{98\%}$ using ROC curve was 29 Gy (AUC = 0.73, 95%CI = 0.61–0.84). This threshold of 29 Gy for GTV $D_{98\%}$ was significantly correlated to LC using the log-rank test (**Figure 2**). The 1-year LC was 91.9% for GTV $D_{98\%} \geq 29$ Gy vs 69.6% for GTV $D_{98\%} < 29$ Gy ($p=0.030$). Except for doses received to target volume, the two

groups of patients obtained with this threshold-value did not differ significantly concerning tumor volume (7.2 cc vs 7.2 cc for GTV $D_{98\%} < 29$ Gy and ≥ 29 Gy respectively, $p = 0.99$) or doses received to healthy brain parenchyma (5.4 cc vs 5.5 cc and 7.4 cc vs 7.3 cc respectively for $V_{23.1\text{Gy}}$ and $V_{21\text{Gy}}$) (**Table 1**). They did differ significantly in prior treatment with SBRT or SRT, which was noticeably higher in the group GTV $D_{98\%} < 29$ Gy (18% vs 9%, $p = 0.3$ and 12% vs 4%, $p = 0.2$ respectively) and histological type (18% (6/34) vs 15% (7/47) for the histological type of renal cancer or melanoma, respectively).

Using the linear-quadratic model, the biologically effective dose assuming an α/β of 12 (BED_{12}) for brain metastases at doses of 29 Gy in three fractions was 52.4 Gy, corresponding to a GTV $D_{98\%} \geq 19.7$ Gy in a single fraction. With a mean follow-up of 8.5 months, no tumor progression was observed for the 17 brain metastases treated with GTV $D_{98\%} \geq 29.4$ Gy in three fractions, i.e. for a $BED_{12} \geq 53.4$ Gy, corresponding to a GTV $D_{98\%} \geq 20$ Gy in a single fraction. Progression-free survival (PFS) at 6 months, 1 year, and 2 years was 80.8%, 71.1% and 51.4% respectively (**Figure 1**). Median PFS was not reached.

Overall survival (OS) at 6 months, 1 year, and 2 years was 74.9%, 50.3% and 39.9% respectively (**Figure 1**). Median OS was 15 months. Significant prognostic factors of OS in univariate analysis were male gender (HR = 2.38, 95%CI = 1.07–5.29, $p = 0.02$), performance status (HR = 2.08, CI 95% = 1.40–3.07, $p = 0.001$), SIR (HR = 0.67, CI 95% = 0.53–0.84, $p = 0.001$), RPA classification (HR = 2.38, CI 95% = 1.08–5.3, $p = 0.02$), GPA classification (HR = 0.46, CI 95% = 0.30–0.71, $p = 0.001$), DS-GPA classification (HR = 0.46, CI 95% = 0.31–0.70, $p < 0.001$) and presence of a mutation (HR = 0.25, CI 95% = 0.08–0.81, $p = 0.006$). A prognostic factor of OS that remained significant in multivariate analysis was the presence of a mutation (HR = 0.19, CI 95% = 0.05–0.78, $p = 0.02$).

Brain radionecrosis (RN) was the most significant complication occurring in 12 (14.8%) out of the 81 treated brain metastases. Median time to RN was 6.7 months (range: 2.7–11.1 months). Symptomatic neurological complications occurred in 4 cases (4.9%) (seizure in 2, motor deficit in 1, intracranial hypertension in 3). The 6-month and 1-year actual risk of RN was 9.3% and 27.6% respectively. The 6-month and 1-year actual risk of symptomatic RN was 4.1% and 8.8% respectively.

Mean volumes of normal brain (brain - GTV) that received doses of 23.1 Gy ($V_{23.1\text{Gy}}$), 21 Gy ($V_{21\text{Gy}}$), 18 Gy ($V_{18\text{Gy}}$), 14 Gy ($V_{14\text{Gy}}$), 10 Gy ($V_{10\text{Gy}}$) and 5 Gy ($V_{5\text{Gy}}$) were 5.8cc, 7.9

cc, 11.5 cc, 18.6 cc, 32.8 cc and 88.0 cc respectively. No factors, including age, gender, arterial hypertension, type 2 diabetes, hypercholesterolemia, brain metastases location, prior surgery, prior SRT, prior WBRT, GTV, PTV, conformity index, gradient index, overall treatment time, doses delivered to normal brain ($V_{23.1\text{Gy}}$, $V_{21\text{Gy}}$, $V_{18\text{Gy}}$, $V_{14\text{Gy}}$, $V_{10\text{Gy}}$ and $V_{5\text{Gy}}$) were independent predictive factors of RN in univariate or multivariate analysis, whether for all patients or for patients with a follow-up over 8 months. Other complications observed were headache, seizure and haemorrhage in 1, 1 and 1 patients respectively.

Discussion

To date, the present study is the first to demonstrate a significant threshold of dose delivered to brain metastases correlated to local control. Moreover, this threshold should be reproducible because it concerns the GTV which is always defined in the same way, rather than PTV margins which differ according to the various studies. Furthermore, this study reports a series of 81 unresected large brain metastases treated with Linac-based VMAT multifraction SRT according to the ICRU 91.

In this study, we reported LC for unresected large brain metastases of 80% and 70% at 1 year and 2 years respectively, which are consistent with previous published studies. An international meta-analysis of 24 trials concerning MF-SRT for large brain metastases recently reported in 2019 a 1-year LC of 92.9% and 79.2% (range : 59–100%) respectively for metastases about 2-3 cm in diameter and > 3 cm in diameter [3]. To date, Wiggenraad et al. are the first and only ones to demonstrate a dose-effect relation in SRT for brain metastases and to conclude on a minimum total dose to be prescribed through SRS in a single fraction. They showed that LC was higher (1-year LC $\geq 70\%$) with a $BED_{12} \geq 40$ Gy corresponding with a single fraction of 20 Gy (20 Gy/1f) and three fractions of 8.5 Gy (25.5 Gy/3f) [2]. Limitation of this review was that GTV-PTV margins vary often from 0 to 2 mm among published studies, which may lead to a higher or lower dose in the GTV. Therefore, they could not draw conclusions because they could not determine whether higher LC rates were linked to higher prescribed doses or to the GTV-PTV margins used.

The main interest of our study is to focus on the minimum or near-minimum BED_{12} delivered to the GTV (GTV $D_{98\%}$) and not the marginal BED_{12} prescribed to the PTV, the former of which is more reproducible because it is not influenced by techniques or devices

used for SRT. Dose is always prescribed to the envelope of the tumor whatever the modality employed. What can differ among the teams is the use of margins around GTV to create PTV (0-2 mm), which can make differences for doses received to the GTV. That's why we thought it was important to report received dose to the GTV and not only to the PTV in order to translate these findings to other groups, because GTV is always delineate as the same. What is really important is the dose received to the GTV which corresponds to the tumor and not the dose received to the PTV which depends on the technique employed. Thus, we have demonstrated here that GTV $D_{98\%}$ had to be higher than 29 Gy in three fractions (corresponding to a GTV $BED_{12\ 98\%} \geq 52.4$ Gy) to significantly improve LC (92% vs 70%, $p = 0.030$) and maybe higher than 29.4 Gy (≥ 53.4 Gy for GTV $BED_{12\ 98\%}$) to get closer to a 100% 1-year LC. The threshold-value of 29 Gy enabled the division of the population in our study into two groups with more than 30 brain metastases in each of the groups (34 and 47 for GTV $D_{98\%} < 29$ Gy and ≥ 29 Gy respectively) and a mean follow-up of about 10 months for each group, which enabled us to obtain significant and consistent results. The contingency of these two groups was verified, which enhanced the results of our study. Tumor volume (GTV) did not differ as significantly (7.2 cc vs 7.2 cc for GTV $D_{98\%} < 29$ Gy and ≥ 29 Gy respectively, $p = 0.99$) as prior treatment with SBRT or SRT, which was noticeably higher in the group GTV $D_{98\%} < 29$ Gy (18% vs 9%, $p = 0.3$ and 12% vs 4%, $p = 0.2$ respectively) and histological type (18% (6/34) vs 15% (7/47) for the histological type of renal cancer or melanoma, respectively). Interestingly, differences concerning received doses to target volumes were more significant for received doses to GTV rather than to PTV, which represents another reason why we may have to consider doses received to GTV with greater attention. Finally, higher doses received to GTV were not significantly associated with higher received doses to healthy brain parenchyma (5.4 cc vs 5.5 cc and 7.4 cc vs 7.3 cc respectively for $V_{23.1Gy}$ and V_{21Gy}).

Brain metastases can't be approached as one entity and local control or radiation necrosis can also be dependent on the primary tumor and the administration and timing of systemic treatment. The possible impact of systemic treatment on brain metastases local control has to be considered, even if majority of agents do not have an intracranial response and in this study brain SRS was provided most of time in case of inefficiency of systemic treatments. Traditional systemic chemotherapeutic agents are known to have a limited role in the management of brain metastases, owing to the blood-brain barrier (BBB). However, more and more systemic treatments can be effective on brain metastases. Achrol et al. have reported

the intracranial response rates of systemic treatments used for patients with lung cancers (22-57% for immunotherapy, 50-80% for EGFR (encoding epidermal growth factor receptor) TKI (tyrosine kinase inhibitors), 29-81% for ALK inhibitor) or with melanoma (20-58% for BRAF inhibitors). For patients with ER- or PR-positive breast cancers, hormonal therapies have shown evidence of clinical efficacy, such as cytotoxic agents like platinum or taxane-based chemotherapy [13]. The anti-VEGF antibody bevacizumab has probably a significant clinical benefit in patients with brain metastases but it has not been systematically studied because these patients were generally excluded in the literature to avoid the potential risk of intracranial hemorrhage [14]. In addition, systemic treatments can increase not only local control but also toxicity and brain radionecrosis, and this all the more that patients receive brain SRS concomitantly. This is in fact the case for the Trastuzumab emtansine (T-DM1) antibody drug with a brain radionecrosis after SRS occurring in 39-50% of cases vs 10-15% usually [15,16] and BRAF inhibitors with increase of radionecrosis and hemorrhage. So BRAF inhibitors have to be stopped at least 1 day before brain SRS [17]. We have respected in our study current recommendations, that are a time-lapse of at least 1 week between chemotherapy and brain SRS, at least 1 day for BRAF inhibitors and at least 2 days for crizotinib. The other targeted therapies or immunotherapy could be provided concomitantly, according to the European Federation of Neurological Societies scientific task forces and latest published studies.

In our study, systemic treatments at the time of brain SRS were provided in 66% of cases. These systemic treatments were immunotherapy (38%), platinum or taxane-based chemotherapy (33%), hormonal therapies (12%) and targeted therapies (19%) : anti-VEGF antibody (3%), EGFR TKI (5%), ALK inhibitor (3%), PARP inhibitor (3%), BRAF inhibitor (3%) and Her2 inhibitor (5). So, there were many different treatments and few patients received the same, which makes very difficult to conclude in this study on the role of systemic treatment as predictive factor. In our study, systemic treatment was not a significant predictive factor of local control, overall survival or brain radionecrosis. Anyway, brain SRS was almost provided in case of inefficiency on brain disease control of systemic treatment, which strengthens data in this study concerning impact of brain SRS on local control. Even if the dosimetric analysis probably does not reflect the results on its own, it contributes significantly to them, all the more so when the results can be improved without modifying the prescribed dose or toxicity or systemic treatments.

Distant failure in the brain was observed in our study in 28.9% and 48.6% of cases at 1 year and 2 years respectively, which is in agreement with previous published studies (range: 39–52%) [18–20]. Median OS in our study was 15 months, which was slightly higher than described in literature for patients with ≤ 4 brain metastases [21,22] and allowed for a sufficient follow-up. We confirmed that OS is significantly correlated to the general state of health (performance status), SIR [23], RPA classification [24], GPA classification [25] and DS-GPA classification [26] and directly correlated to systemic treatment, particularly in cases of the presence of a mutation.

Brain radionecrosis (RN) represents the most common late-delayed radiation effect of SRS. Several factors related to RN are reported, such as total radiation dose, fractionation, tumor volume, conformity index, number of isocenters, previous radiotherapy, use of chemotherapy and infratentorial location, but the main factor is the volume of the brain receiving a specific dose [4,27–31]. Therefore, irradiation of healthy brain parenchyma should be reduced as far as possible [32,33]. We have reported in our study concerning large brain metastases a RN rate of 15% at the end of the follow-up (5% symptomatic RN), corresponding to 1-year actual RN risk rate of 27.6% and symptomatic RN rate of 8.8% respectively. That is in agreement with the literature, in particular with the rate of symptomatic RN of about 7.4% (range: 0–16%) reported in the meta-analysis of 24 trials concerning MF-SRT for large brain metastases [3].

Fractionation (3 fractions in general) enables a reduction of the incidence of RN for large brain metastases [34–36], with a 48–68% relative reduction in comparison to single-fraction SRS (SF-SRS) [3]. In MF-SRS (3 fractions), the most significant prognostic factor reported to date for RN is the brain volume receiving high doses: $V_{23.1\text{Gy}}$ (5.7% of symptomatic RN for $V_{23.1\text{Gy}} \geq 5$ cc vs 1.4%; 8.6% of symptomatic RN requiring an operation for $V_{23.1\text{Gy}} \geq 7$ cc vs 0%, $p = 0.04$) [37], $V_{21\text{Gy}}$ (1-year risk of RN was 14% for $V_{23.1\text{Gy}} \geq 20.9$ cc vs 4%, $p = 0.03$) [38] and $V_{18\text{Gy}}$ (14% vs 5% respectively for $V_{18\text{Gy}} > 30.2$ cc and $V_{18\text{Gy}} \leq 30.2$ cc, $p = 0.04$) [4]. No factors in our study were independent predictive factors of RN in univariate or multivariate analysis, probably because of the limitation of healthy brain parenchyma (mean $V_{23.1\text{Gy}}$, $V_{21\text{Gy}}$ and $V_{18\text{Gy}}$ of 5.8 cc, 7.9 cc and 11.5 cc respectively, which are above the previous published thresholds). This can be explained by the use of volumetric modulated arc therapy (VMAT) with non-coplanar arcs in this study. Non-coplanar multiple dynamic conformal arcs (DCA) have often been used in literature to achieve high conformity while sparing healthy tissues [39]. More recently, VMAT has been widely developed [40–42].

Through a dosimetric study, we showed that the use of VMATnc for large brain metastases provided excellent dosimetric results in terms of target coverage, sparing of healthy brain tissue and low-dose delivery ($V_{23.1\text{Gy}}$ and $V_{18\text{Gy}}$ reduced by 36% and 25% respectively for VMATnc vs DCA).

GTV $D_{98\%}$ is a strong reproducible significant predictive factor of local control in stereotactic radiotherapy for brain metastases. Dose prescription should lead to a GTV $BED_{12\ 98\%} \geq 52.4$ Gy to significantly improve LC (92% vs 70%, $p = 0.030$) and maybe ≥ 53.4 Gy to get closer to a 100% 1-year LC, corresponding to respectively a GTV $D_{98\%} \geq 19.7\text{--}20$ Gy in a single fraction and 29–29.4Gy in three fractions. An external validation of these thresholds is necessary. Results will need to be confirmed with larger studies, other teams and other treatment techniques. Whatever, this proposed $D_{98\%}$ is not a real change of the prescribed dose but an optimization of the actual prescribed dose.

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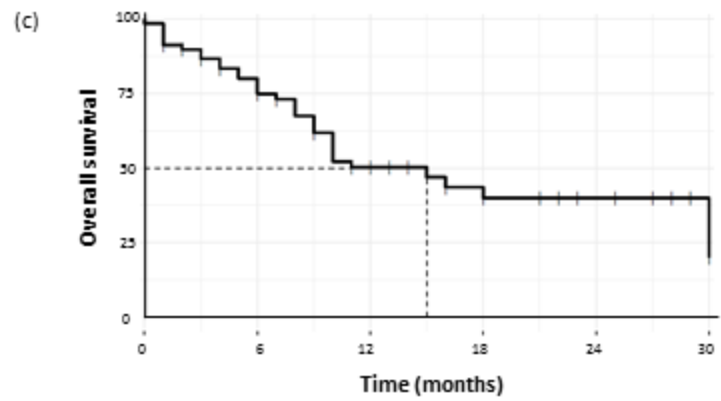
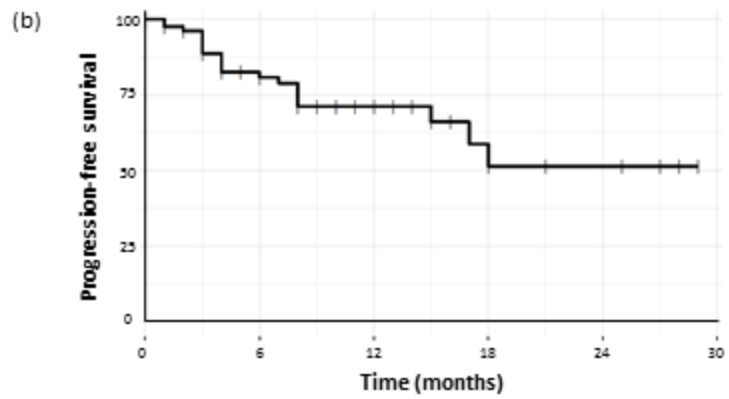
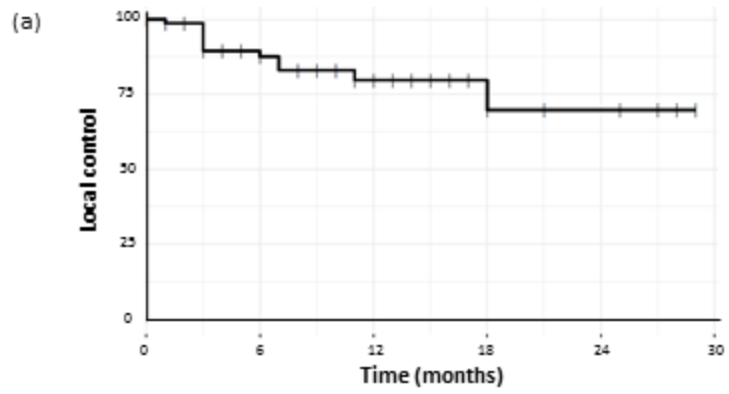
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Figure 1. Probability of local control (a), probability of progression-free survival (b) and overall survival (c) for the 69 patients receiving SRT for brain metastases.

Figure 2. Comparison of local control curves of all 81 treated brain metastases between those receiving a GTV $D_{98\%} < 29$ Gy in three fractions and those ≥ 29 Gy.

Table 1. Patients, brain metastases and SRT characteristics.

Table 2: Results of univariate and multivariate analyses on local control, overall survival and radionecrosis incidence.



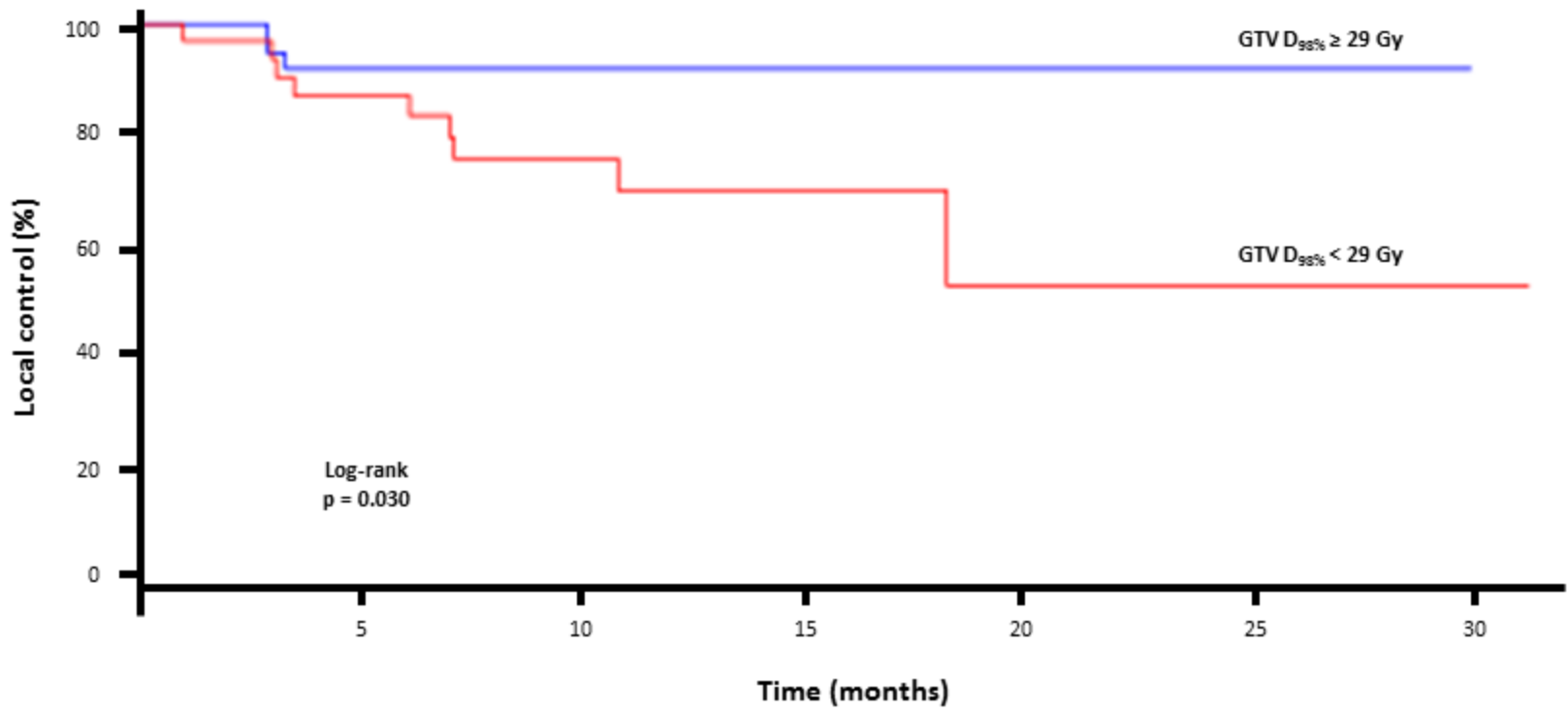


Table 1. Patients, brain metastases and SRT characteristics.

| Characteristics | All | GTV D _{98%} < 29 Gy | GTV D _{98%} ≥ 29 Gy | p |
|--|------------|---------------------------------|---------------------------------|------|
| Patients' characteristics | | | | |
| Total | 69 | 31 | 43 | |
| Gender | | | | |
| Female | 28 (41%) | 13 (42%) | 18 (42%) | 1 |
| Male | 41 (59%) | 18 (58%) | 25 (58%) | |
| Age (years) | 62 (33–89) | 60 (33–81) | 63 (39–87) | 0.39 |
| Performance status | | | | |
| 0 | 28 (41%) | 14 (45%) | 15 (35%) | 0.47 |
| 1 | 31 (45%) | 14 (45%) | 20 (46%) | 1 |
| 2 | 7 (10%) | 3 (10%) | 5 (12%) | 1 |
| ≥ 3 | 3 (4%) | 0 (0%) | 3 (7%) | 0.26 |
| Prognostic score (mean) | | | | |
| SIR | 6 (3–9) | 6 (3–8) | 6 (3–8) | 0.26 |
| RPA | 2 (1–3) | 2 (1–3) | 2 (1–3) | 0.25 |
| GPA | 2.5 (1–4) | 2.5 (1–4) | 2.5 (1–4) | 0.72 |
| DS-GPA | 2.5 (1–4) | 2.5 (1–4) | 2.5 (1–4) | 0.79 |
| Medical history | | | | |
| Arterial hypertension | 25 (36%) | 7 (23%) | 18 (42%) | 0.13 |
| Type 2 diabetes | 11 (16%) | 6 (19%) | 5 (12%) | 0.54 |
| Hypercholesterolemia | 14 (20%) | 6 (19%) | 8 (19%) | 1 |
| Primary cancers | | | | |
| Lung | 41 (60%) | 14 (46%) | 28 (65%) | 0.10 |
| Breast | 10 (14%) | 6 (19%) | 6 (14%) | 0.54 |
| Melanoma | 5 (7%) | 2 (6%) | 5 (12%) | 0.69 |
| Renal | 2 (3%) | 2 (6%) | 0 (0%) | 0.17 |
| Other | 11 (16%) | 7 (23%) | 4 (9%) | 0.18 |
| Number of metastases treated per patient | | | | |
| 1 | 59 (85%) | 26 (84%) | 38 (88%) | 0.56 |
| 2 | 8 (12%) | 4 (13%) | 4 (10%) | 0.49 |
| 3 | 2 (3%) | 1 (3%) | 1 (2%) | 0.24 |
| Systemic treatment | | | | |
| Yes | 49 (71%) | 26 (76%) | 23 (66%) | 0.98 |
| No | 20 (29%) | 8 (24%) | 12 (34%) | |
| Brain metastases' characteristics | | | | |
| Total | 81 | 34 | 47 | |
| Tumor volume | | | | |
| GTV (cc) | 7.2 | 7.2 | 7.2 | 0.99 |
| PTV (cc) | 12.4 | 12.2 | 12.6 | 0.80 |
| Longest diameter (mm) | 25.1 | 25.1 | 25.1 | 0.98 |
| Prior treatment | | | | |
| WBRT | 10 (12%) | 6 (18%) | 4 (9%) | 0.31 |
| SRT | 6 (7%) | 4 (12%) | 2 (4%) | 0.23 |
| Histological type | | | | |
| Adenocarcinoma | 59 (73%) | 26 (76%) | 33 (71%) | 0.62 |
| Melanoma | 11 (14%) | 4 (12%) | 7 (15%) | 0.75 |

| | | | | | |
|-------------------------------|--------------------------|----------|----------|----------|-------|
| | Squamous cell carcinoma | 7 (8%) | 2 (6%) | 5 (10%) | 0.69 |
| | Other | 4 (5%) | 2 (6%) | 2 (4%) | 1 |
| Mutation | | | | | |
| | Yes | 14 (17%) | 8 (24%) | 7 (15%) | 0.39 |
| | No | 67 (83%) | 26 (76%) | 40 (85%) | |
| Location | | | | | |
| | Occipital lobe | 11 (14%) | 4 (12%) | 7 (15%) | 0.75 |
| | Frontal lobe | 29 (36%) | 9 (26%) | 20 (42%) | 0.16 |
| | Parietal lobe | 12 (15%) | 7 (21%) | 5 (11%) | 0.34 |
| | Temporal lobe | 8 (9%) | 3 (9%) | 5 (11%) | 1 |
| | Cerebellum | 21 (26%) | 11 (32%) | 10 (21%) | 0.31 |
| SRT characteristics | | | | | |
| Treatment quality | | | | | |
| | CI | 1.08 | 1.11 | 1.06 | 0.16 |
| | HI | 0.34 | 0.36 | 0.32 | 0.03 |
| | GI | 2.59 | 2.65 | 2.55 | 0.03 |
| | OTT (days) mean | 6 (4–10) | 6 (4–10) | 6 (4–8) | 0.65 |
| Received GTV doses | | | | | |
| | D _{min} (Gy) | 26.5 | 24.7 | 27.8 | <0.01 |
| | D _{98%} (Gy) | 28.5 | 27.2 | 29.4 | <0.01 |
| | D _{moy} (Gy) | 31.8 | 31.4 | 32.1 | <0.01 |
| | D _{2%} (Gy) | 33.4 | 33.3 | 33.5 | 0.12 |
| | D _{max} (Gy) | 33.8 | 33.7 | 33.9 | 0.08 |
| Received PTV doses | | | | | |
| | D _{min} (Gy) | 20.8 | 20.0 | 21.3 | 0.03 |
| | D _{98%} (Gy) | 23.1 | 22.4 | 23.6 | 0.02 |
| | D _{moy} (Gy) | 29.6 | 29.2 | 29.8 | <0.01 |
| | D _{2%} (Gy) | 33.3 | 33.2 | 33.4 | 0.14 |
| | D _{max} (Gy) | 33.8 | 33.7 | 33.9 | 0.08 |
| | V _{70%} (%) | 98.4 | 97.6 | 99.0 | 0.08 |
| Received doses to Brain - GTV | | | | | |
| | V _{23.1Gy} (cc) | 5.5 | 5.4 | 5.5 | 0.84 |
| | V _{21Gy} (cc) | 7.3 | 7.4 | 7.3 | 0.84 |
| | V _{18Gy} (cc) | 10.5 | 10.8 | 10.2 | 0.56 |
| | V _{14Gy} (cc) | 17.0 | 17.8 | 16.4 | 0.40 |
| | V _{10Gy} (cc) | 30.3 | 31.8 | 29.2 | 0.39 |
| | V _{5Gy} (cc) | 84.0 | 90.0 | 79.6 | 0.24 |
| Follow-up (months) | | | | | |
| | Mean | 10.2 | 10.6 | 9.9 | 0.66 |

Table 2: Results of univariate and multivariate analyses on local control, overall survival and radionecrosis incidence

| | Univariate analysis | | | Multivariate analysis | |
|-----------------------------|---------------------|--------|------|-----------------------|------|
| | LC | OS | RN | LC | OS |
| Patients' characteristics | | | | | |
| Gender | - | 0.02 | 0.75 | - | - |
| Age (years) | - | 0.43 | 0.54 | - | - |
| Performance status | - | 0.001 | - | - | 0.15 |
| Prognostic score (mean) | | | | | |
| SIR | - | 0.001 | - | - | 0.50 |
| RPA | - | 0.03 | - | - | - |
| GPA | - | 0.001 | - | - | 0.88 |
| DS-GPA | - | <0.001 | - | - | 0.33 |
| Medical history | | | | | |
| Arterial hypertension | - | 0.80 | 0.20 | - | - |
| Type 2 diabetes | - | 0.06 | 0.99 | - | 0.23 |
| Hypercholesterolemia | - | 0.29 | 0.05 | - | - |
| Primary cancers (Lung vs.) | 0.19 | 0.61 | - | - | - |
| Systemic treatment | 0.17 | 0.95 | 0.20 | - | - |
| Metastases' characteristics | | | | | |
| Tumor volume | | | | | |
| GTV (cc) | 0.77 | 0.81 | 0.46 | - | - |
| PTV (cc) | 0.74 | 0.87 | 0.51 | - | - |
| Longest diameter (mm) | 0.12 | 0.96 | 0.48 | 0.10 | - |
| Prior treatment | | | | | |
| WBRT | 0.84 | 0.82 | 0.76 | - | - |
| SRT | 0.15 | - | 0.23 | - | - |
| Histological type (ADK vs.) | 0.03 | 0.28 | - | 0.04 | - |
| Mutation | 0.09 | 0.006 | - | - | 0.02 |
| Location | 0.06 | - | 0.28 | - | - |

SRT characteristics

Treatment quality

| | | | | | |
|-----------------|------|---|------|---|---|
| CI | 0.12 | - | 0.08 | - | - |
| HI | 0.06 | - | 0.19 | - | - |
| GI | 0.92 | - | 0.51 | - | - |
| OTT (days) mean | 0.87 | - | 0.32 | - | - |

Received GTV doses

| | | | | | |
|-----------------------|------|------|---|-------|---|
| D _{min} (Gy) | 0.07 | 0.69 | - | - | - |
| D _{98%} (Gy) | 0.04 | 0.72 | - | 0.004 | - |
| D _{moy} (Gy) | 0.17 | 0.69 | - | - | - |
| D _{2%} (Gy) | 0.79 | 0.57 | - | - | - |
| D _{max} (Gy) | 0.91 | 0.40 | - | - | - |

Received PTV doses

| | | | | | |
|-----------------------|------|------|---|---|---|
| D _{min} (Gy) | 0.08 | 0.58 | - | - | - |
| D _{98%} (Gy) | 0.09 | 0.50 | - | - | - |
| D _{moy} (Gy) | 0.22 | 0.69 | - | - | - |
| D _{2%} (Gy) | 0.46 | 0.63 | - | - | - |
| D _{max} (Gy) | 0.91 | 0.40 | - | - | - |
| V _{70%} (%) | 0.11 | 0.46 | - | - | - |

Received doses to Brain - GTV

| | | | | | |
|--------------------------|---|---|------|---|---|
| V _{23.1Gy} (cc) | - | - | 0.79 | - | - |
| V _{21Gy} (cc) | - | - | 0.71 | - | - |
| V _{18Gy} (cc) | - | - | 0.66 | - | - |
| V _{14Gy} (cc) | - | - | 0.71 | - | - |
| V _{10Gy} (cc) | - | - | 0.78 | - | - |
| V _{5Gy} (cc) | - | - | 0.99 | - | - |