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Dosimetric comparison of mono-isocentric and multi-isocentric plans for oligobrain metastases: a single institutional experience

Comparaison de plans dosimétriques mono-isocentriques et multi-isocentriques pour les oligo-métastases cérébrales : une expérience institutionnelle

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Abstract

Purpose

To compare dosimetric plans for the treatments of oligobrain metastases (2-6) using mono-isocentric arctherapy and multi-isocentric volumetric modulated arc therapy (VMAT).

Material and Methods

A total of sixteen patients with multiple brain metastases were selected. Prescription dose was between 24 and 15Gy depending on the tumor size. For every patient, arctherapy and VMAT plans were generated respectively, with Elements Multiple Brain Mets SRS version 2.0 (BrainLab) and Eclipse SRS Treatment Planning System version 15.5. The conformity index (CI), homogeneity index (HI), gradient index (GI), dose volume histogram for each organ at risk, total Monitor Units were evaluated.

Results

For coverage of the PTV, mono-isocentric plans showed a better CI and a better GI than multi-isocentric plans, respectively CI of 1.18 ± 0.11 vs 1.41 ± 0.20 ($p < 0.01$), and GI of 3.55 ± 0.59 vs 4.03 ± 1.20 ($p < 0.01$). Homogeneity index was not better with mono-isocentric plans, with respectively HI 24.32 ± 3.87 vs 14.05 ± 4.46 ($p = 1$).

For organs at risk, there were no statistical differences between mono and multi-isocentric plans for both eyes, both lenses, both optic nerves, chiasma, brainstem, and hippocampi. V_{12Gy} and V_{10Gy} of normal brain were statistically lower with mono-isocentric plans than with multi-isocentric plans, respectively V_{12Gy} of 3.06Gy IC95% [2.25;3.86] vs 5.18Gy IC95% [3.43;6.93] ($p < 0.01$) and V_{10Gy} 4.66Gy IC95% [3.33;5.98] vs 7.30Gy IC95% [4.73;9.87] ($p < 0.03$). Total number of MU was significantly lower with mono-isocentric plans than with multi-isocentric plans, respectively 6668 ± 1463 vs 12403 ± 4941 ($p < 0.01$), then treatment time was lower with mono-isocentric plans.

Conclusion

Mono-isocentric plans had a better conformity index and gradient index than multi-isocentric plans for the treatment of multiple brain metastases. Moreover, mono-isocentric techniques gave fewer doses to normal brain and used less monitor units than multi-isocentric techniques.

Key-words:

Brain metastases; stereotactic radiotherapy; VMAT; arctherapy; monoisocenter

Résumé

Objectif del'étude

Comparer les plans dosimétriques pour le traitement des métastases cérébrales multiples (deux à six) en utilisant l'arthérapie mono-isocentrique et l'arthérapie modulée volumétrique multi-isocentrique (VMAT).

Méthodes

Au total, seize patients atteints de métastases cérébrales multiples ont été sélectionnés. La dose prescrite se situait entre 24 et 15 Gy selon la taille de la tumeur. Pour chaque patient, des plans d'arthérapie et de VMAT ont été générés respectivement avec Element System Multiple Mets SRS 2.0 (BrainLab) et Eclipse SRS Treatment Planning Système 15.5. L'indice de conformité (IC), l'indice d'homogénéité (IH), l'indice de gradient (IG), l'histogramme du volume de dose pour chaque organe à risque et le total des unités de surveillance ont été évalués.

Résultats

Pour la couverture du volume cible prévisionnel (PTV), les plans mono-isocentriques ont montré un meilleur IC et un meilleur IG que les plans multi-isocentriques, respectivement, IC de 1.18 ± 0.11 contre 1.41 ± 0.20 ($p < 0.01$), et IG de 3.55 ± 0.59 contre 4.03 ± 1.20 ($p < 0.01$). L'indice d'homogénéité n'était pas meilleur avec les plans mono-isocentriques, avec respectivement 24.32 ± 3.87 contre 14.05 ± 4.46 ($p = 1$). Pour les organes à risque, il n'y avait aucune différence statistique entre les plans mono et multi-isocentriques pour les deux yeux, les deux cristallins, les deux nerfs optiques, le chiasma, le tronc cérébral et les hippocampes. Les V_{12Gy} et V_{10Gy} (volumes revant 10 et 12 Gy) du cerveau normal étaient statistiquement plus faibles avec les plans mono-isocentriques qu'avec les plans multi-isocentriques, respectivement V_{12Gy} de 3.06Gy (intervalle de confiance à 95 % [IC95%] : 2.25-3.86) contre 5.18Gy (IC95% : 3.43-6.93, ; $p < 0,01$) et V_{10Gy} de 4.66 Gy (IC95% : 3.33;5.98) contre 7.30Gy (IC95% :

4.73;9.87 ; $p<0,03$). Le nombre total d'Unités monoiteur était significativement plus faible avec les plans mono-isocentriques qu'avec les plans multi-isocentriques, respectivement 6668 ± 1463 contre 12403 ± 4941 ($p<0.01$), la durée du traitement était donc plus courte avec les plans mono-isocentriques.

Conclusion

Les plans mono-isocentriques avaient un meilleur indice de conformité et un meilleur indice de gradient que les plans multi-isocentriques pour le traitement des métastases cérébrales multiples. De plus, les techniques mono-isocentriques donnaient moins de doses dans le cerveau normal et utilisaient moins d'unités de surveillance que les techniques multi-isocentriques.

Mots-clés :

Métastases cérébrales; radiothérapie stéréotaxique; VMAT; arcthérapie; monoisocentre

Introduction

Among patients with cancer, 10 to 40% will develop one or more brain metastases[1]. Lung cancer is the cancer who provided the most brain metastases, followed by breast cancer and melanoma, nevertheless, all cancers can potentially give brain metastases[2]. The gold standard for the treatment of multiple brain metastases is whole brain radiotherapy (WBRT)[3]. Stereotaxic radiotherapy is a high precision technique. The aim is to deliver a high dose of radiation in a small number of fractions into the tumor using multiple convergent beams or arcs. Thanks to a high dose gradient, adjacent healthy tissues can be spared and doses that could induce complication are lowered[4]. Stereotaxic radiotherapy (SRT) tends to replace WBRT, especially for patients with a life expectancy of more than 3 months, a good performance status, and a small total metastases volume[5]. Traditional SRT with a linear accelerator uses multi-isocentric plan for the treatment of patients with multiple brain metastases. Each lesion had its own isocenter which is approximately in the geometric center of the lesion. The more metastases there are, the longer the treatment will be, especially because of the repositioning of the patient. The total treatment time will last about twenty minutes for single metastasis, but may reach more than one hour when there are several metastases. Single isocenter cranial radiosurgery with dynamic conformal arcs can produce highly conformal dose distribution, and short total treatment times.

Technically, multiple brain metastases SRT using multi-isocenter techniques, is possible, but clinically, the number of metastases is limited to 3 to 5, because of the total treatment time and the dosimetric constraints. During the last decade, several algorithms have been developed using a virtual mono-isocenter.

The aim of this study is to compare dosimetric plans between the Elements Multiple Brain Mets SRS System using a mono-isocentric technique and the Eclipse SRS 15.5 using multi-isocentric technique for sixteen patients treated for multiple brain metastases.

Materials and Methods

Patient population

Sixteen patients were included in this *in silico* study. They were previously treated for multiple brain metastases from solid tumor using SRT between October 2018 and March 2019 in Klinikum Stuttgart (Germany). Patients with tumor bed, primitive brain tumors or hematologic cancer were excluded from this study. Patients with metastases larger than 4cm in diameter were excluded from this study.

All patients had previously magnetic resonance imaging (MRI) scans with MPRAGE (Magnetization Prepared Rapid Gradient Echo imaging) and a brain computed tomography (CT) of one-millimeter slice. The interval between MRI and CT was at maximum seven days. A double thermoformed mask with 5 fixation points immobilized all patients.

Ten patients (63%) were women and 6 patients (38%) were men. Eight patients (50%) had a lung cancer. Median age at SRT was 61 years old (43-82) (min-max). Median number of brain metastases was 3.2 (2-6). The interval between primitive diagnostic and brain metastasis arising was 466 days (16-3615) (min-max). Patients and tumor characteristics were reported in table 1.

Imaging fusion

The fusion between MRI and CT was performed with the BrainLab Element System Multiple Mets SRS 2.0 and the Eclipse SRS 15.5.

GTV and PTV

Gross Tumor Volume (GTV) was manually delineated on the BrainLab Element System Multiple Mets SRS 2.0 using the MPRAGE sequence of MRI, corresponding to the

macroscopic contrast enhancing lesion on T1-MRI. Planning Target Volume (PTV) was defined by adding a 1mm margin to the GTV. PTVs from BrainLab Element System Multiple Mets SRS 2.0 software were imported to Eclipse SRS 15.5 in order to plan on the same structures. The mean volume of the PTV was 2.27mL (0.15-24.74). Table 2 summarized the characteristic of PTV. Dose prescriptions were performed according to the RTOG 90-05 protocol [6]. Forty, nine and two metastases received 24Gy, 18Gy and 15Gy, respectively. Dosimetry plans have been calculated to reach a $V_{98\%}$ of the PTV $> 95\%$. For PTV, the minimum dose, mean dose, maximum dose, $D_{98\%}$, $V_{98\%}$, conformity index [7], homogeneity index [8,9], gradient index [10], and total MU were compared.

A conformity index is a measure of how well the volume of a radiosurgical dose distribution conforms to the size and shape of a target volume. A perfectly conformal plan would have a conformity index equal to 1, and less conformal plans would have a conformity index inferior or superior to 1, depending on whether the target volume was over- or undercovered by the prescription isodose volume. In BrainLab Element System Multiple Mets SRS 2.0 the conformity is evaluated by the Paddick Inverse, given by the following formula:

$$CI = \frac{\text{Target Volume} \times \text{Prescription Isodose Volume}}{\text{Target volume who received the prescribed isodose}^2}$$

The uniformity of the dose distribution inside PTV was estimated using the HI defined based on the dose coverage to 2% ($D2\%$), the dose coverage to 98% of the target volume ($D98\%$), and the prescribed dose. Homogeneity Index is given by the difference between the $D2\%$ and the $D98\%$ divided by the prescribed dose multiplied by 100. A perfect homogenic distributed plan would have a HI equal to 0, whereas the more the plans are heterogeneous the more the HI is high.

$$HI = \frac{D2\% - D98\%}{D_{prescribed}} \times 100$$

The dose falloff evaluation is given by the gradient index. GI is the ratio between the 50% isodose volume and the 100% isodose volume. A GI close to 1 indicates a greater dose falloff and good dose conformity outside the PTV. For single lesion treated by stereotaxic radiosurgery, GI lower than 3 are considered acceptable. There is no consensus for the optimal GI values when there are multiple treated lesions. GI are not available when lesions are too close and the 50% isodose lines of each lesion intersect.

$$GI = \frac{Volume\ Isodose50\%}{Volume\ Isodose100\%}$$

Organs at risk

Organs at risk (OAR) were delineated with the Anatomical Mapping algorithms of the BrainLab Element System Multiple Mets SRS 2.0. The OAR were whole brain, brainstem, both eyes, both lenses, both optic nerves, chiasm, and both hippocampi [11]. OAR from Anatomical Mapping were downloaded to Eclipse SRS 15.5 in order to plan on the same structures. Dosimetric constraints for OAR are shown in the table 3. [12–19]

With regard to the dose to the OARs, healthy brain (i.e. brain minus GTV) dose has been studied in detail considering the probability of complications from radionecrosis as outlined in the QUANTEC report [20,21]. For each organ at risk, minimum dose, mean dose and maximum dose were compared for both techniques. For healthy brain, we calculated and compared $V_{12GyTotal}$ and $V_{10GyTotal}$ for the whole metastases.

Treatment Planning Systems

The VMAT treatment planning was performed for all patients via the Eclipse 15.5 Algorithm stereotactic radiosurgery localization module. One treatment plan was performed for each PTV. The isocenter of the plan corresponded to the center of the PTV. Two coplanar arcs were used with collimator angle of 30° or 330° with blocked portions when an organ at risk was nearby. A sum-plan was performed with an individual plan for each PTV in order to evaluate the dosimetric characteristics.

The arctherapy treatment planning was performed for all patients via BrainLab Element System Multiple Mets SRS 2.0 (BrainLab, Munich). The single isocenter is a virtual isocenter located at the center of all PTVs. Three to five non-coplanar arcs were used by go and return, with collimator angle of 0° to 90°. The algorithm Element Multiple Brain Mets SRS 2.0 calculated the best treatment plan in order to respect the given dose constraints to the OAR and to give an optimal dose to PTVs.

Treatment

Patients were treated in a TrueBeam™STx System equipped with a HD120™Multileaf Collimator (Varian Medical Systems, Palo Alto). Patients were positioned using ExacTrac.

Statistical Analysis

Comparison of the data has been done with the statistic software R v3.3.2. A normality test was performed for each datum using Shapiro-Wilk test. A unilateral paired Student t test was used to compare normally distributed data, whereas a unilateral paired Wilcoxon signed-rank test was used for those data that failed the normality test. The significant threshold was $p < 0.05$.

Results

PTV coverage

Both techniques were not identical in terms of coverage of target volume. $D_{2\%}$ was significantly higher with arctherapy compared to standard VMAT, respectively $27.6\text{Gy} \pm 3.6$ and 26.5 ± 3.6 ($p < 0.01$). Whereas $D_{98\%}$ was lower with arctherapy with respectively $22.1\text{Gy} \pm 2.9$ and $23.4\text{Gy} \pm 3.1$ ($p < 0.01$). Therefore, HI that results from the two values mentioned above was not better with arctherapy, respectively HI $24.3\% \pm 3.9$ and $14.0\% \pm 4.7$. CI and GI was significantly better with arctherapy compared to standard VMAT with respectively CI (IC95%[1.14 ; 1.17] and IC95%[1.34 ; 1.42] ; $p < 0.01$) and GI (IC95%[3.33 ; 3.74] and IC95%[3.57 ; 4.25] ; $p < 0.01$). The results of the PTV coverage and index are shown in the table 4. Figure 1 shows the dose level for both dosimetries.

OAR

The only statistically significant difference was found for the maximum brainstem dose, for all other OAR there was no statistical difference for the D_{\min} , D_{mean} , and D_{\max} between multi and mono-isocenter plans. Table 5 shows reported mean doses and maximum doses of each organ at risk.

Normal Brain

$V_{12\text{GyTotal}}$ and $V_{10\text{GyTotal}}$ of normal brain were statistically lower with mono-isocentric plans than with multi-isocentric plans, respectively $V_{12\text{GyTotal}}$ of 10.26Gy vs 17.07Gy ($p>0.01$) and $V_{10\text{GyTotal}}$ 15.59Gy vs 24.16Gy ($p<0.01$). $V_{12\text{GyTotal}}$ and $V_{10\text{GyTotal}}$ are dependent on the number of irradiated metastases. Subgroup analyses showed that archtherapy give fewer doses to healthy brain, whatever the number of irradiated metastases. Table 6 shows subgroup analyses in function of the number of irradiated metastases.

Metastases close to hippocampus

Nineteen metastases were at less than 2cm of hippocampus (mean of 1.3cm between PTV and the closer hippocampus), with 11 metastases close to the left hippocampus and 8 to the right respectively. For those 19 brain metastases the mean dose for hippocampus were 3.37 CI95% [1.79; 4.95] in multi-isocentric technique vs 2.88 CI95% [1.82; 3.95] in mono-isocentric technique. ($p=0.02$). For the 11 metastases who were at less than 1cm to the hippocampus (mean of 0.8cm between PTV and the closer hippocampus), there was no statistical difference between mean dose to hippocampus ($p=0.2$).

Total MU

Standard VMAT required 12403.31 ± 4941.79 monitor units, whereas archtherapy required 6668.73 ± 1463.83 MU ($p<0.01$). Numbers of MU are growing with the number of irradiated metastases and the total volume of the PTV. Subgroup analyses, among patients with only 2 brain metastases showed that there was a significant trend for the reduction of the needed

Monitor Unit when mono-isocentric technique are used ($p=0.06$). The total needed MU was lower with arctherapy when have 3 or 4 and more 3 metastases, respectively $p=0.02$ and $p=0.03$. Table 6 shows subgroup analyses in function of the number of irradiated metastases.

Discussion

Yamamoto and al. studied SRS without WBRT for patients with multiple brain metastases. His study suggests that SRS alone for patient with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. SRS is a non-invasive treatment with few side effects compared to WBRT [22]. Stereotaxic radiosurgery is a suitable alternative for patients with up to ten brain metastases:-

The best irradiation technique has to be the more efficient (that is to say that the PTV must be well covered) and the less toxic (that is to say that the dose to OAR must be as low as possible). The formula of the CI, HI and GI were either different or not available in the Eclipse SRS 15.5 TPS. We recalculated the Inverse Paddick Conformity index, GI and HI using the following formulas by means of the dosimetry data for all metastases in order to compare them.

At equal coverage (in our study, more than 95% of the PTV was to receive 98% of the dose) arctherapy is more conformational than VMAT. Better CI and GI of the PTV lead to a decrease in low dose and less irradiation of the healthy brain. Kohutek and al. studied radionecrosis after SRS [23]. Radionecrosis is not uncommon. The incidence of radionecrosis was 17% at 12 months, 34% at 24 months. Radionecrosis can occur clinically (two-third of patient), symptoms depend on the area of the brain where the tumor is located. Radionecrosis may not appear clinically and may only be radiological (one third of patient). The larger the tumor is, the greater are the risk of radionecrosis [17,23–25]. Blonigen and al. studied radionecrosis after SRS using a linear accelerator. Their study suggests that V_{10Gy} to normal brain larger than 10.5cm³ or V_{12Gy} larger than 8cm³ are associated with the biggest risk of symptomatic radionecrosis. This patient should better be considered for hypofractionated stereotaxic radiotherapy [17]. In our

study archtherapy minimize V_{12Gy} and V_{10Gy} for normal brain by 70% and could conceptually reduce the risk of symptomatic radionecrosis. Several other studies examined radionecrosis and confirmed that the higher the V_{12Gy} , the higher the risk is. V_{12Gy} superior to 8.5cm³ carries a risk of radionecrosis more than 10% [20,24–26]. In our study V_{12Gy} with archtherapy is equal to 10.26Gy \pm 7.49, probably a portion of the patient would have required hypofractionated irradiation.

We found a statistically significant difference in the maximum brainstem dose in favor of mono-isocentric plans. This positive test can be explained by the multiplication of statistical tests, which increases the alpha risk. Because there were no other difference for the D_{min} , D_{mean} and D_{max} of other OAR.

Hippocampi are central grey nuclei important for cognitive functioning. Their savings have already been attempted for several decades with the WBRT with hippocampal preservation. One of the challenges of brain radiotherapy is the optimal treatment of these metastases close to these critical risk organs. For metastases in the immediate vicinity of hippocampus (distance inferior to one centimeter) the VMAT and archtherapy are not different. For metastases close to hippocampus (less than two centimeters), archtherapy spares hippocampus better than standard VMAT.

One of the advantages of mono-isocentric techniques is that it requires only one repositioning under the treatment table. Radiotherapy session will then last about twenty minutes, while they can last up to an hour when there are 3 or 4 repositioning. Moreover, one unique repositioning reduces the risk of position error and the decrease in the treatment time reduces the risk of intrafraction movement. On the other hand, rotational repositioning errors have a greater impact with the mono-isocentric technique, especially when the isocenter is far from the PTVs. The progress of repositioning techniques, improvement of algorithms for planning allows treating more than ten cerebral metastases simultaneously while respecting dosimetric

constraints. Mono-isocentric planning also reduces the number of MU required from 3 or more metastases and thus reduces the total irradiation time. Our results are comparable with the results of Chea and al. [27]. They compared dosimetry from BrainLab Element System Multiple Mets SRS and Gammaknife for the treatment of multiple brain metastases (2-12). Total treatment time was lower with Mono-isocentric arctherapy.

Conclusion

Mono-isocentric conformational arc therapy is of interest in the treatment of multiple brain metastases. The coverage and dose gradient indices of the target volumes were significantly better in the arctherapy plans than in the standard VMAT plans. The volume of normal brain irradiated was significantly lower with the mono-isocentric techniques.

In addition, mono-isocentric system considerably reduces the duration of the irradiation by reducing the necessary total monitor units and reducing the number of repositioning on the treatment table.

Declaration of Conflicting Interests

The authors declare that they have no conflicts of interest in relation to this article.

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Table 1: Characteristics of tumors and patients

Sex	Male	Number of Patients
	Women	6 (38%) 10 (62%)
Age	40-50	3
	50-60	5
	60-70	6
	>70	2
Primitive cancer	Lung	8
	Breast	2
	Melanoma	2
	Kidney	2
	Head and Neck	1
	Unknown	1
Number of Metastases	2	5
	3	6
	4	4
	6	1

Table 2: Characteristic of the GTV and PTV size

Volume in cm ³	Mean	Min	Max	Standard Deviation	Sum
GTV					
Per patient	5.36	0.48	25.15	6.29	85.83
Per metastases	1.68	0.04	20.84	3.27	
PTV					
Per patient	7.90	0.96	31.60	8.08	118.44
Per metastases	2.28	0.15	24.74	3.88	

Table 3: One fraction treatment Dose constraints per organ

OAR	Maximum Dose (Gy)	Others constraints	[12,13]
Brain		$V_{10Gy} < 10.5mL$ $V_{12Gy} < 8.5mL$	[14,15]
Brainstem	15Gy	$D_{0.5cm^3} < 10Gy$	[16]
Cochlea	9Gy		
Eye	5Gy	$V_{25\%} < 2Gy$	
Lens	10Gy	$V_{25\%} < 0.4Gy$	
Optic Nerve	8Gy	$D_{0.2cm^3} < 8Gy$	[17–19]
Chiasm	10Gy	$D_{0.2cm^3} < 8Gy$	[17,18]

Table 4: Dosimetric characteristic of the PTV with standard VMAT and Arctherapy

	Technic	Mean	Standard Deviation	Min	Max	p
D _{mean}	VMAT	25.32	3.43	16.07	31.57	0.94
	Arctherapy	25.55	3.31	16.50	28.67	
D _{98%}	VMAT	23.39	3.19	15.50	28.90	<0.01
	Arctherapy	22.19	2.91	14.64	24.21	
D _{2%}	VMAT	26.53	3.67	16.66	33.61	<0.01
	Arctherapy	27.64	3.67	17.60	31.65	
CI	VMAT	1.41	0.20	1.10	2.22	<0.01
	Arctherapy	1.18	0.11	1.09	1.68	
GI	VMAT	4.03	1.20	2.42	7.78	<0.01
	Arctherapy	3.55	0.59	2.56	5.17	
HI	VMAT	14.05	4.46	6.8	28.3	1
	Arctherapy	24.32	3.87	16.16	31.52	

Table 5: Dosimetric characteristics of the OAR

		Mean	Standard Deviation	Min	Max	p
MU	VMAT	12403,31	4941,79	7280,00	24717,00	<0,01
	Arctherapy	6668,73	1463,83	4139,00	9849,00	
D _{meanBrainstem}	VMAT	1,44	1,49	0,26	4,83	0,73
	Arctherapy	1,34	0,90	0,18	2,91	
D _{maxBrainstem}	VMAT	4,94	5,33	0,59	18,68	0,03
	Arctherapy	4,24	4,52	1,06	16,27	
D _{meanChiasma}	VMAT	1,64	1,80	0,24	6,09	0,61
	Arctherapy	1,46	1,10	0,17	3,89	
D _{maxChiasma}	VMAT	3,14	3,61	0,35	12,10	0,26
	Arctherapy	2,44	2,24	0,50	8,80	
D _{maxEyeL}	VMAT	1,38	0,92	0,36	3,22	0,1
	Arctherapy	1,08	0,62	0,24	2,54	
D _{maxEyeR}	VMAT	1,17	1,11	0,12	3,38	0,59
	Arctherapy	0,93	0,52	0,23	2,11	
D _{maxLensL}	VMAT	0,70	0,71	0,12	2,37	0,54
	Arctherapy	0,53	0,22	0,09	0,88	
D _{maxLensR}	VMAT	0,47	0,47	0,06	1,56	0,8
	Arctherapy	0,48	0,34	0,08	1,17	
D _{meanOpticL}	VMAT	1,14	1,24	0,19	3,92	0,28

	Arctherapy	1,02	1,34	0,12	3,65	
D ^{max} OpticL	VMAT	1,67	1,77	0,27	5,89	0,39
	Arctherapy	1,55	0,39	0,34	5,78	
D ^{mean} OpticR	VMAT	0,88	1,04	0,13	3,52	0,59
	Arctherapy	0,85	1,47	0,17	2,01	
D ^{max} OpticR	VMAT	1,32	1,47	0,17	4,19	0,72
	Arctherapy	1,23	0,78	0,35	2,55	
D ^{mean} HippoL	VMAT	2,64	2,91	0,24	11,78	0,23
	Arctherapy	2,42	2,20	0,38	9,62	
D ^{mean} HippoR	VMAT	1,79	3,19	0,13	12,93	0,86
	Arctherapy	1,64	1,97	0,34	8,53	
V _{12GyTotal}	VMAT	17,07	13,14	3,26	51,17	<0,01
	Arctherapy	10,26	7,49	2,19	26,58	
V _{10GyTotal}	VMAT	24,16	19,22	4,23	74,65	<0,01
	Arctherapy	15,59	11,73	3,02	40,16	

Table 6: Subgroup analyses in function of the number of irradiated metastases

		Mean VMAT	Mean Arctherapy	p
MU	2 metastases	7461	6208	0.06
	3 metastases	11724	6051	0.02
	4 and more	18160	7739	0.03
V _{12GyTotal}	2 metastases	7.9	5.1	0.03
	3 metastases	18.6	9.6	0.02
	4 and more	24.3	16.2	0.03
V _{10GyTotal}	2 metastases	10.8	7.6	0.03
	3 metastases	26.7	14.9	0.02
	4 and more	34.3	24.4	0.03

Figure 1

Upper figures show a transversal computer tomography section with two metastases
Figures below show a sagittal section with 3 metastases. The green line represents the 100% isodose. The blue line represents the 50% isodose.

A and C: Standard VMAT

B and D: Archtherapy

