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RADIOSURGERY OF BRAIN METASTASES WITH CYBERKNIFE® SYSTEM: ROLE OF IMAGE

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Abstract – *Objective:* *In brain metastases management, radiosurgical treatment with CyberKnife® System (CK) provides, despite a limited number of fractions, high dose to the target volume, with a concomitant reduction of dose to organs at risk (OARs). Volume delineation, a crucial moment in planning process, heavily relies on imaging technologies, such as computed tomography (CT), magnetic resonance imaging (MRI), Positron Emission Tomography (PET) with image fusion.*

Patients and Methods: *From November 2012 to October 2014 we treated 163 patients for brain metastases (311 treatments) with CK, an image-guided frameless robotic SRS/SRT. In the planning of the radiosurgical treatment we used a system of image fusion RM/simul-CT. We enrolled patients, aged ≥ 18 years, with single brain metastases resectable and unresectable size < 4.3 cm or with multiple brain metastases (no more than 3), all dimensions < 3.4 cm with a documented examination RM, with Karnofsky performance status (KPS) ≥ 70, with good prognosis calculated according to functional scoring criteria GPA (graded prognostic assessment). The treatments were performed in 77% with single fraction (range10-24 Gy), in 2% with two fractions (range 18-21 Gy), 18% with three fractions (range 18-24Gy), 3% with five fractions (range 20-25Gy). The dose was prescribed to 80%. All patients were evaluated with clinical and radiological follow-up every two months.*

Results: *Median follow-up was 9 months: overall survival was 14.7 months for patients with Breast Cancer metastases, 10.3 months in Melanoma/RCC e 7.66 months in Lung cancer. Time to Progression of lesions treated with radiosurgery (dose 10- 24 Gy in single fraction), assessed at follow-up according to RECIST criteria, was 23.6 months in Breast Cancer, 11.2 months in Lung cancer, 10.7 months in Melanoma / RCC. Furthermore, we verified the dose constraints and we calculated the median of maximum dose (Dmax) of the OARs. We did not record acute or late treatment-related effects.*

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Conclusions: *The image fusion used for the delineation of target and OARs provided accuracy and uniformity for contouring and planning, ensuring respect of constraints, reduced toxicity, improved quality of life and increased in local control.*

KEYWORDS: *Radiotherapy, Image fusion, Radiosurgery, Brain metastases, CyberKnife.*

INTRODUCTION

Brain metastases occur in 20-40% of patients with primary extracranial cancers: the choice of optimal treatment is based on patients-related factors (age, performance status, comorbidities) and tumor-related factors (extracranial disease status, number, size, location, and histopathology of metastases)[1,2].

Management of brain metastases involves several options: surgery, whole brain radiotherapy (WBRT), radiosurgery (SRS)/stereotactic radiotherapy (SRT), systemic therapy. The SRS/SRT can be performed with dedicated, image-guided systems, such as CyberKnife, which allows millimeter accuracy, high doses to the target, while preserving the critical organs[3-7].

CyberKnife consists of a linear miniaturized accelerator, installed on a movable arm robot, which allows to the system to hit the target tumor from 1200 different positions. Modern systems of treatment planning for the contouring usually rely on the fusion of morphological/functional diagnostic imaging and simul-computed tomography (CT): the planning of radiosurgical treatment typically avails of magnetic resonance imaging (MRI) images and simul-CT centering. The MRI acquired an increasing role not only in the diagnosis of brain metastases, but also in the assessment of treatment response and the delineation of volumes[8].

CT/MRI image fusion improves accuracy in outlining gross tumor volume (GTV), clinical target volume (CTV) and organs at risk (OARs): the aim of our report is to evaluate the role of image fusion in contouring of brain metastases and its impact on the treatment planning in terms of accuracy of contouring, respect of the dose constraints, acute and late toxicity in patients with brain metastases treated with CyberKnife® system[9,10].

PATIENTS AND METHODS

CyberKnife®, 6 MV linear accelerator installed on a robotic arm with 6 degrees of freedom, allows millimeter accuracy in radiation therapy: an image-guided system allows position changes of the robot according to patients moves, while monitoring the movements of target. Patients undergo a thin layer (1 mm), simul-centering, contrast-enhanced computed tomography, after having been immobilized with a customized thermoplastic mask. The identification and delineation of volumes are performed in view of simul-CT images, fused with MR images (T1-T2-FLAIR) (Figure 1A-1B).

Furthermore, all patients undergo a thin layer MRI within one-month prior treatment: "co-registration" and "fusion" of CT/MRI images creates one image with information from both original images. Diagnostic superiority of MRI and geometric superiority of CT provide a better discrimination between tumor tissue with border infiltration and the adjacent normal structures, a better definition of volumes and organs at risk (OARs) (whole brain, eyes, lens, optic nerves, optic chiasm, pituitary gland, brainstem, spinal cord) (Figure 2A-B; Figure 3A-B).

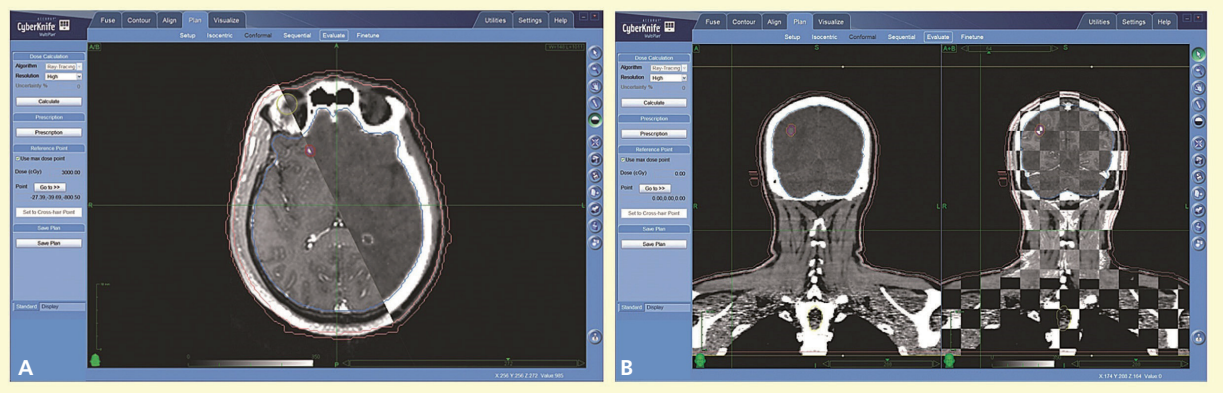

Fig. 1. Fusion CT/MRI in axial images (*A*) and coronal (*B*) in patients with brain metastases.

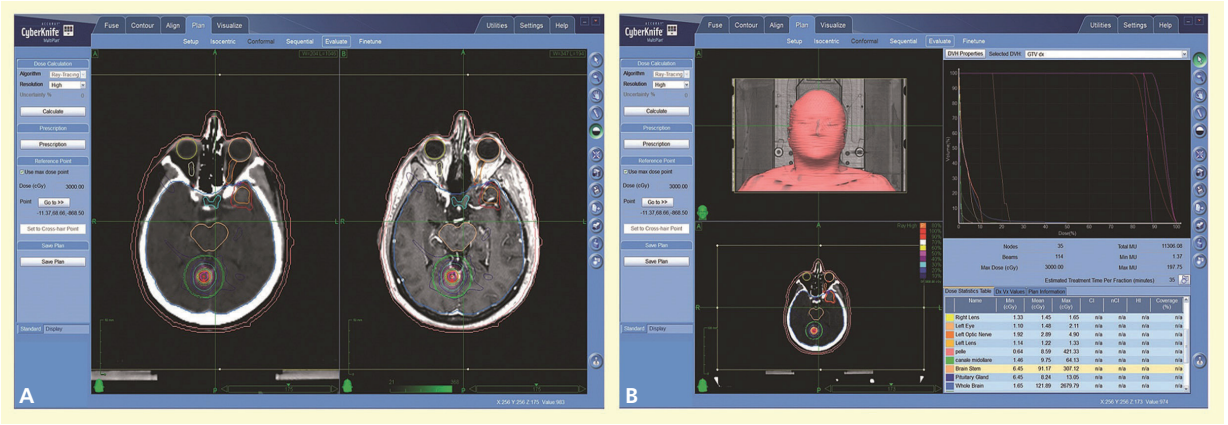

Fig. 2. *A-B*, Contouring and DVH in patients with brain metastases treated with radiosurgery Cyberknife-system.

Decisions about the prescribed dose and fractionation are based on the size of the metastases, on the site of the lesions or previous radiation treatments. Treatment planning was performed by Multiplan Software (Accuray Inc., Sunnyvale, CA, USA). Dose constraints to OARs are assessed according to the Texas South Western University (Georgetown, TX, USA)[11].

In particular, for the planning of radiosurgical treatment for cerebral metastases, used constraints were: Dmax <10 Gy for brainstem, optic chiasm and optic nerve, Dmax <14 Gy for spinal cord.

We evaluated the respect of Dmax (maximum of dose for organs at risk) that allows to control symptoms of acute toxicity (within 90 days of treatment) and late toxicity (after 90 days) assessed for patients with appropriate follow-up, according to RTOG CNS toxicity criteria[12]. Overall survival (OS) and time to progression (TTP) were also calculated.

MR was performed every two months with the evaluation of local control of metastases treated (CL) according to RECIST criteria in full response (CR: full resolution), partial response (PR: diameter reduction of lesion > 30%), progression (PD: increases lesion diameter > 20%), stable disease (SD: all others)[13]. The median maximum dose was calculated for the OARs to see if the correct designation of structures obtained from fusion images succeeded not only to reduce dose to critical structures, but also to significantly lower recommended median Dmax.

RESULTS

Patients main characteristics treated with CyberKnife system from November 2012 to October 2014 are shown in Table 1.

We treated 163 patients and 311 encephalic metastases: 159 patients were evaluated at follow-up. Kaplan-Meier estimated median overall survival (OS) of treated patients was 9.7 months; Figure 4 shows OS in months according to primary tumor site.

238 metastases (77%) were treated with radiosurgery with a dose between 10 and 24 Gy

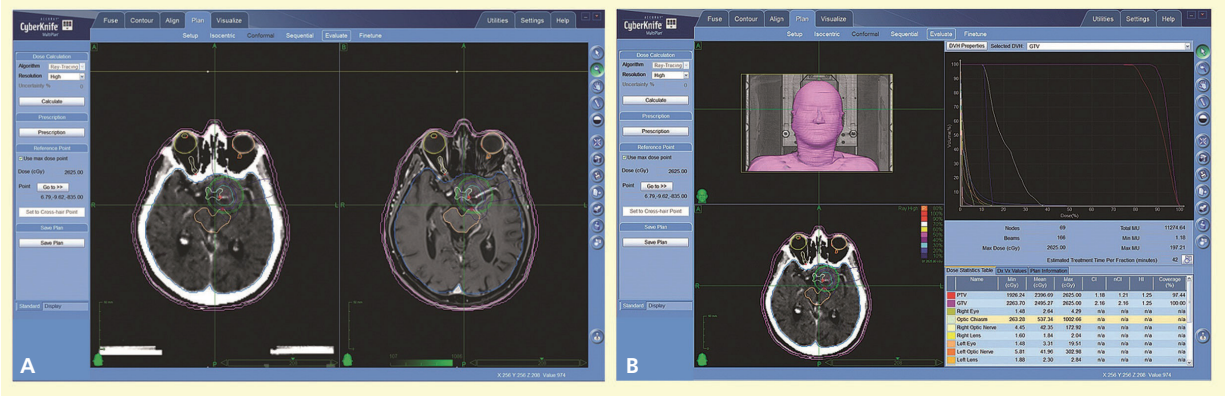

Fig. 3. *A-B*, Contouring and DVH in patients with brain metastases treated with radiosurgery Cyberknife-system.

TABLE 1. Characteristics of patients treated.

	N°	%
N° of patients	163	100%
Sex		
M	86	53%
F	77	47%
Age		
Median (years)	63	
Range	20-87	
KPS		
<70	7	4%
70-80	20	12%
90-100	136	84%
N° of patient with:		
1 lesion	87	53%
2 lesion	33	20%
3 lesion	29	18%
> 3 lesion	14	9%
Primary tumor		
NSCLC/SCLC	69	42%
Melanoma/RCC	32	20%
Breast	30	18%
Other	32	20%

in single session: the local response was evaluated according to RECIST criteria, in particular the percentage of local control as the complete response (CR), partial response (PR) and stable disease (SD), and we calculated the time to progression (TPP) by primary tumor site of lesions treated with radiosurgery (Figure 5).

Time to progression (TTP) was 23.6 months for breast cancer brain metastases, 11.2 months in lung cancer, 10.7 months in melanoma/RCC patients. No treatment-related acute toxicity event was reported. For the assessment of the impact of fusion of images in delineating of volumes and respect for dose limit to critical structures, only patients treated with radiosurgery (single fraction) were considered.

Table 2 shows the value of Dmax considered dose limit and median Dmax registered for critical structures derived from treatment plans with single fraction. The values regarding the median of Dmax relating to OARs were considerably less than those indicated as dose constraints. Furthermore, in the planning phase, in addition to Dmax, the dose constraints referred to cc volumes of organs at risk were evaluated (brain stem V10 (Gy) <1 cc; chiasma V8 (Gy) <0.2 cc; optic nerve V10 (Gy) <0035 cc; spinal cord V10 (Gy) <00:35 cc), but were lower than the reference values of literature. The fusion CT/MR images allow an extremely precise contouring procedure for both the target and organs at risk, thence to deliver a high dose to the target, and to accurately calculate the dose that reaches critical structures.

DISCUSSION

The review of ASTRO 2012, from an analysis of 36 randomized trials, yielded guidelines for management of patients with single or multiple brain metastases[14]. For patients with a single brain metastasis and good prognosis (life expectancy greater than 3 months), WBRT and surgery for single resectable metastases size >3.4 cm are recommended (evidence level 1); alternatively, surgery and postoperative radiosurgery cavity (level of evidence 3). For patients with unresectable metastases of size <3.4 cm, radiosurgery alone or radiosurgery and WBRT, or WBRT and surgery (level of evidence 1) should be considered; alternatively, surgery and radiosurgery on postoperative cavity (level 3). In patients with single unresectable metastasis size <3.4 cm or partially resected, was indicated the WBRT or radiosurgery alone (level of evidence 1). After a surgical resection, in presence of mass effect,

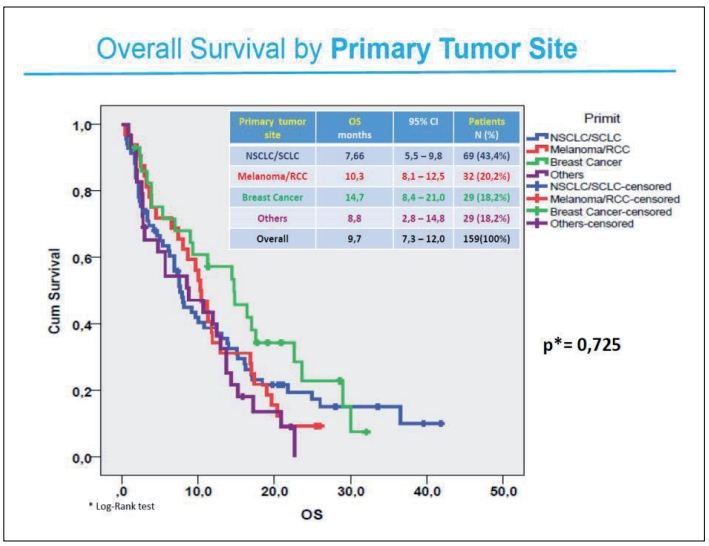

Fig. 4. Overall survival by primary tumor site.

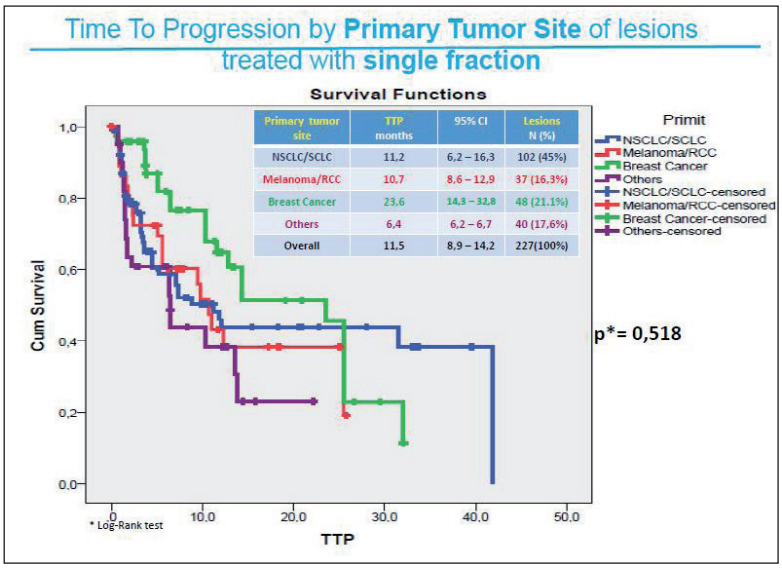

Fig. 5. Time to progression by primary tumor site of lesions treated with radiosurgery.

WBRT can be performed. In patients with single or multiple brain metastases and poor prognosis (life expectancy of less than 3 months), palliative care with or without WBRT should be considered[15-18].

The purpose of the radiation treatment is to kill most cancer cells, with less morbidity possible. Prescribed dose often depends on the tolerance of healthy tissues: modern radiotherapy can deliver higher doses to target volume, and lower dose to healthy tissue. Technological development in the delivery of high-dose treatment requires a greater accuracy in delineation of the target volume (GTV, CTV) and the OARs.

The contouring of volumes of clinical and critical structures has an important role in treatment planning: updating the contouring software allow the fusion of diagnostic images with images of simul-CT. Image fusion, a technique that combines the advantages of the integration of multiple types of images, provides information about the target structures and OARs, with rotation and translation of a second set of images allowing an alignment with the first set of images, including multiple MR sequences (almost always higher for the visualization of the lesion), CT, PET, in the treatment planning[19-24].

TABLE 2. Dmax of OARs and median of Dmax obtained in radiosurgical treatment of brain metastases in patients treated with various doses.

OARs	*Single fraction Constraints Dmax*	*10 Gy*	*12 Gy*	*15 Gy*	*16 Gy*	*17 Gy*	*18 Gy*	*21 Gy*	*24 Gy*
		Maximum Dose							
Brainstem	< 10 Gy	1.94 (0.01-10.73)	1.98 (0.08-3.36)	2.21 (0.56-14.61)	2.66 (2.52-2.81)	14.92	2.24 (0.09-18.94)	2.04 (0.06-17.45)	2.25 (0.14-22.11
Optic Chiasm	< 10 Gy	0.79 (0.00-2.70)	0.81 (0.05-5.65)	1.45 (0.05-9.27)	0.57 (0.11-1.03)	0.20	0.88 (0.02-8.76)	1.24 (0.01-7.60)	0.28 (003-11.15)
Right Optic nerve	< 10 Gy	0.05 (0.00-2.11)	0.10 (0.02-9.31)	0.10 (0.02-0.70)	0.11 (0.07-0.14)	0.06	0.16 (0.01-1.86)	0.11 (0.01-8.13)	0.14 (0.01-13.54)
Left Optic nerve	< 10 Gy	0.07 0.00-2.14)	0.08 (0.02-2.40)	0.11 (0.04-3.74)	0.94 (0.04-1.84)	0.06	0.18 (0.01-17.56)	0.12 (0.00-3.62)	0.13 (0.01-3.56)
Spinal cord	< 14 Gy	0.53 (0.01-6.09)	0.09 (0.04-1.80)	0.92 (0.15-11.63)	1.08 (0.92-1.23)	8.76	0.82 (0.04-5.74)	0.36 (0.02-23.14)	0.38 (0.01-3.45)
Coverage %		98.16 (93.91-100)	98.39 (93.99-100)	99.61 (95.39-100)	98.36 (98.36-98.37)	93.09	98.95 (82.77-100)	99.20 (96.20-100)	99.77 (91.61-100)
CI		1.16 (1.05-1.93)	1.12 (1.05-1.30)	1.08 (1.02-1.54)	1.10 (1.07-1.13)		1.09 (1.00-4.08)	1.11 (1.00-4.03)	1.08 (1.00-2.31)

The radiotherapy planning is usually performed on CT without contrast enhancement, with significant limitations in OARs' delineation, especially of brain structures, which have a similar electron density to adjacent structures. The association to simul-CT of morphological (CT, MRI) and functional images (PET, SPECT, fRM) has a central role in the delineation of clinical volumes and critical structures. In planning is important to evaluate the dose to the target and to OARs with the dose-volume histogram (DVH) to limit side effects[25]. The careful delineation of sensitive structures is critical for proper quantitative evaluation of the dose to normal tissues, and for effects of treatment related to dose, fractionation and volumes. Actually, radiosurgery and stereotactic radiotherapy have improved targeting accuracy, also by using hypofractionated schemes: indeed, radiosurgery involves the delivery of a single high dose of tumoricidal and ablative radiation, with a high probability of local control, as well as surgery, although without the invasivity of the surgery. One of the risks in clinical practice consists in the increase of the dose/fraction ratio, an increased risk of late damage to normal tissues, and in particular with radiosurgery/stereotactic radiotherapy hypofractionated there may be an increased risk of late toxicity, even with the use of techniques which reduce the volume of normal tissues exposed[26-28].

In radiosurgery of brain metastases, most frequent critical structures to evaluate are: brain stem, eyes, optic nerves, chiasm, brain parenchyma, cochlea, and pituitary gland. Toxicity to the optic nerves and chiasm usually consists in decreased visual acuity, visual field defect, and visual impairment, within 3 years after treatment. Recent studies suggest that the maximum dose of 10 Gy to optical apparatus is well tolerated with a low risk (0-3%) of symptomatic optic neuropathy[14-17]. The critical components of the auditory system that are susceptible to toxicity from radiation therapy include the brainstem, the auditory nerves, and the cochlea. A maximum dose exceeding 10 Gy may result in a reduction of auditory function, although it is unclear whether the structure limiting the dose is the auditory nerve, the cochlea or the brainstem. When the exposure dose is much lower than the dose limit, the risk of toxicity from radiation is zero[29].

CONCLUSIONS

Our experience confirms the validity of using the CyberKnife system for the treatment of brain metastases with radiosurgery in terms of local control and low toxicity. Image fusion simul-CT/MRI in radiation treatment of brain metastases allows not only an accurate delineation of target and OARS, but also a consistent coverage of the dose to the tumor, with respect for the constraints of OARs structures related to vital and functional roles.

Conflict of Interests:

All authors declare that they have no conflict of interest.

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Ethical Statement:

The data presented in this document are the results of our clinical practice: when our patients are enrolled to radiotherapy sign an informed consent on the use of images and data relating to the treatment, so it was not necessary to seek a further opinion from the Ethics Committee.

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