

Immediate Side Effects of Cranial Stereotactic Radiosurgery and Radiotherapy (Single Institution Experience)

MOHAMAD ABDULLA, M.D.

The Department of Clinical Oncology and Nuclear Medicine, Kasr El-Aini School of Medicine, Cairo University.

ABSTRACT

Purpose: To examine the incidence and nature of immediate side effects encountered during and within 2 weeks following stereotactic radiosurgery and radiotherapy.

Patients and methods: Between December 1999 and August 2002, 163 patients with benign and malignant cranial lesions were treated by Linac-based stereotactic radiosurgery and radiotherapy (101 and 62 respectively). Inclusion criteria were an upper age limit of 70 years old, adequate performance status ≥ 50 and volume to be treated should not exceed 125 cc. Radiosurgical treatment consisted of a single therapy session of 10-20 Gy depending on lesion volume, while stereotactic radiotherapy treatment consisted of three sessions of 500 cGy each, delivered every other day. Immediate side effects were assessed during and within two weeks of therapy completion and graded according to RTOG system.

Results: Fifty seven (34.9%) patients had developed (69) immediate side effects. Patients had tolerated treatment well without grade III or IV morbid events and no single patient showed deterioration of performance status. The most frequently encountered side effects were; headache in 23 (14%), nausea and vomiting in 39 (23.9%), convulsive fits in 2 (2.9%) and worsening of pretreatment manifestations in 5 patients (3.06%). No specific disease or therapy related factors could be considered to be associated with immediate side effects except for nausea and vomiting which were encountered in patients who received radiation doses greater than 2 Gy to area postrema.

Key Words: Brain - Stereotaxy - Radiosurgery - Radiotherapy - Immediate side effects.

INTRODUCTION

Stereotactic radiosurgery (SRS) was originally defined by Lars Leksell [12] as a closed skull destruction of an intracranial target lesion precisely defined according to a fixed coordinate system (X-Y-Z) with a single dose of ionizing irradiation without surgical intervention. With the availability of relocatable stereotactic frame, the term stereotactic radiotherapy (SRT) was

introduced to denote a fractionated radiosurgical approach [11]. Although several publications reported the results of SRS/SRT, as well as the long term toxicity of treatment [4,7,8,9,19], the incidence and nature of immediate side effects occurring during and within two weeks of treatment completion are not well defined [20].

The neurotoxicity of radiosurgery can be described according to its time course (immediate, acute and chronic) and severity (mild, moderate, severe, life threatening or fatal) based on existing definitions established by the Radiation Therapy Oncology Group (RTOG). The efficacy of radiosurgery and the time course and severity of radiosurgical neurotoxicity are dependent both on the nature of the lesion being treated and the normal tissue milieu in which the lesion resides [18].

Complications following radiosurgery are uncommon and the risk of a permanent deficit arising from an acute neurological event is exceedingly low [6]. Flickinger and associates [10], in 1997 had introduced Post-radiosurgery Injury Expression (PIE) scores for location of arteriovenous malformations; where the risks of symptomatic sequelae of radiosurgery were found to be increased with increasing (PIE) score as shown in Table (1).

It has been customary to divide radiation effects into acute, subacute and chronic. In general, the acute phase is the first 3 months, the subacute occurs from 3 months to 1 year and the late or chronic phase, thereafter [16].

Nausea and vomiting are considered to be among the most commonly encountered immediate side effects of radiation therapy. Alexander

and co-workers [1], had pointed out to the direct correlation between the total dose of stereotactically delivered radiosurgery and radiotherapy to the vomiting center in the floor of the fourth ventricle (area postrema) as shown in Fig. (1), they recommended adequate premedication for patients treated with large fractions of irradiation by SRS or SRT to this area.

PATIENTS AND METHODS

One hundred and sixty three patients with diverse entities of cranial benign and malignant lesions according to NEMROCK protocol were eligible to receive stereotactic radiosurgery or radiotherapy. The immediate side effects encountered during or within 2 weeks of treatment completion were assessed according to RTOG grading system.

All patients had fulfilled the criteria of having pathological and/or radiological evidence of benign or malignant cranial lesion considered to be best treated by stereotactic radiosurgery or radiotherapy according to the decision taken by a combined clinic of Neurosurgery, Neuroradiology and Radiation Oncology specialities. The eligibility criteria were; maximum tumor volume not exceeding 125 cc, age of 70 years or less, performance status (> 50 KPS), ensured adequate organ functions and haemodynamic stability as well as absence of neurological life threatening conditions as massive increased intracranial tension with impending brain stem herniation. Stereotactic radiotherapy was preferred than radiosurgery in higher lesion volume specially those located near the skull base. Previous history of external beam irradiation was reported in 114 patients (69.9%) with dose and fractionation schedule ranging from 30 Gy in 10 fractions over 2 weeks in cases with metastatic disease to brain, to 58 Gy in 29 fractions over 6 weeks to high grade gliomas as adjuvant post-operative adjuvant therapy.

Treatment procedure:

Patients were fixed using stereotactic head ring or frame via artifact free carbon fiber pins with ceramic tips in case stereotactic radiosurgery or by using relocatable mask system for stereotactic radiotherapy schedule.

All patients were pre-medicated with antiemetics, anti-allergics, sedatives and analgesics just before ring or frame application and contin-

ued thereafter for 14 days. Post-treatment-steroid administration was recommended for patients except those expected to develop more radiation induced oedema as those with large lesions or lesions related to anatomical regions known to have vomiting center as area postrema located at the floor of the 4th ventricle.

Magnetic Resonant Imaging Scanning and Computerized Tomographic Scanning of the brain with sections every 2 mm through the target were carried out with the frame fixed to the head in case of CT imaging.

Delineation of target volume and surrounding risk structures as lenses of the eyes, optic nerves, optic chiasma, brain stem and other relevant structures or regions as brain stem or floor of 4th ventricle at the level of the medulla (area postrema) was done in conjunction with a neuroradiologist, followed by dose computation regarding applied dose, dose distribution, number of isocenters, number of arcs per each isocenter, as well as dose to all risk structures. The planning was carried out via BrainScan System® version 4.03.

At the end of the treatment plan, dose distribution through risk and target structures were carefully evaluated via:

- 1- Dose display and isodose lines and dose wash-out on each CT and/or MRI slice separately.
- 2- Dose volume histograms.
- 3- 3D Dose representation.
- 4- RTOG radiosurgery quality assurance guidelines regarding conformity, dose homogeneity and gradient [17], as shown in Table (2).

Treatment was delivered to all patients using Linear Accelerator (Varian – 600 series) with single photon energy of 6MV integrated with BrainScan System and set of circular collimators with diameter ranging from 7.5-35 mm. Pretreatment quality assurance “Winston-Lutz” was performed for verification of laser and isocenter accuracy of gantry and Table.

For Stereotactic radiosurgery (SRS), a single fraction of 10-20 Gy was delivered, whereas for stereotactic radiotherapy (SRT); 15 Gy was delivered in 3 fractions over 5 days. Doses were prescribed at 80% isodose surface.

Patients were closely monitored and scored according to RTOG System [15] during the first

two weeks after completion of treatment with special emphasis upon symptoms of headache, convulsive fits, nausea and vomiting and manifestations of worsening of pretreatment neurological deficits.

RESULTS

One hundred and sixty three patients with 167 intracranial lesions were treated by stereotactic radiosurgery and/or radiotherapy. Table (3) Lists the diagnosis of 163 patients treated by stereotactic radiosurgery and radiotherapy.

Eighty patients were males (49.1%) and 83 were females (50.9%), their age ranged between 5-70 years with median age of 37.8 ± 15.46 years.

Table (4) shows redistribution of cases according to their pre-treatment performance status. The majority had performance status between 60-90. The target volume ranged between 0.21-65.31cc with a median volume of 12.5 ± 13.68 cc. One hundred and sixty patients had one treatment target, 2 patients had two targets and only 1 patient had three distinct lesions. One hundred and one patients (61.9%) had received single treatment session (radiosurgery) whereas the remaining sixty two (38.1%) patients had stereotactic radiotherapy (fractionated schedule) as shown in Table (5).

Among those treated by stereotactic radiosurgery, prescribed dose to target volume had ranged from 10 to 20 Gy, depending on lesion size measurement in 3 dimensions. For those less than 1 cc, a dose of 20 Gy was prescribed, while for those more than 1 cc but less than 5 cc and those with lesions more than 5 cc but less than 125 cc, the prescribed doses were 15 Gy and 10 Gy respectively, as shown in Table (6). For patients treated with fractionated schedule, a dose of 5 Gy for a total of three sessions at every other day schedule was adopted.

As stereotactic radiosurgery and radiotherapy are high precision procedures aiming at delivery of high dose of ionizing irradiation to a limited volume with as minimal as possible contribution to the surrounding normal dose limiting structures, all treated lesions were covered by a dose gradient of 80-130% without affection of risk structures as eyes, optic chiasma and brain stem, keeping the maximum dose received within these structures to less than 1% of their volumes as

evidenced by their dose-volume histograms as shown in Figs. (2,3,4 & 5) and conformity index approaching value (1) whenever possible as shown in Table (7).

Patients were followed up carefully during and within 2 weeks after completion of their prescribed treatment to assess the immediate side effects. All in all, stereotactic radiosurgery and radiotherapy were well tolerated by patients with neither severe side effects (grade III or IV) nor life threatening morbid events. Fifty seven patients (35.4%) had one or more (69) manifestations considered to be immediate side effects. Headache, convulsive fits, nausea and vomiting and worsening of pretreatment deficits were encountered in 23, 2, 39 and 5 patients respectively as shown in Table (8). None of the studied patients had shown deterioration of the performance status during the first 2 weeks after treatment completion. The encountered immediate side effects were mild to moderate in severity and well controlled by conventional medications including steroids and anti-convulsive therapy.

Moreover, high grade gliomas and metastatic brain lesions had a high propensity to develop more immediate side effects rather than low grade or purely benign lesions treated by stereotactic radiosurgery and radiotherapy and astonishingly none of the patients with initial diagnosis of pituitary adenoma had experienced any of the immediate side effects, as seen in Tables (9) and (10).

Apart from nausea and vomiting, none of the reported side effects were found to be affected by disease entity, lesion volume, lesion location, dose of irradiation received, previous history of radiation treatment or any of treatment related physical parameters as number of isocenters needed for adequate coverage of the lesion volume, number of arcs per each isocenter, cone diameter or percentage dose gradient within lesion volume.

Nausea and vomiting were found to be closely related to the radiation dose to a region at the floor of the 4th ventricle at the level of the medulla known anatomically to contain the vomiting center (area postrema). Among all patients treated by stereotactic radiosurgery or radiotherapy, dose computation at this region revealed a range of 0-8.1 Gy with a mean dose of 1.21 Gy ($SD \pm 1.77$). Among the thirty nine patients who

experienced nausea and vomiting as immediate side effects of cranial stereotactic irradiation, a highly significant positive correlation with the dose delivered to the region harboring area potrema (Vomiting Center) with cut off point at 2 Gy was found. After 2 Gy dose, all patients

Table (1): Post-radiosurgery injury expression (PIE) scores for location of arteriovenous malformation (Flickinger et al., 1997) [10].

PIE score	Location
1 (Low risk)	Frontal lobe
2	Cerebellum, temporal lobe, parietal lobe
3	Occipital lobe or basal ganglia
4 (High risk)	Medulla, thalamus, intraventricular, pons or corpus callosum

Table (2): Radiation therapy oncology group (RTOG) radiosurgery quality assurance guidelines [15].

	Conformity	Dose homogeneity	Dose gradient
Per protocol	≤ 2	1-2	≥ 0.3
Minor (acceptable deviation)	> 2 & < 2.5	> 0.9 & < 1 or > 2 & < 2.5	–
Major (unacceptable)	> 2.5	< 0.9 & > 2.5	–

Conformity: Prescription Isodose Surface Volume to Target Volume (TV) Ratio.
Dose homogeneity: Maximum Dose (MD) to Prescription Dose (PD) Ratio.
Dose gradient: Target Volume (TV) to Volume Enclosed by 50% (V50%) Ratio.

Table (3): Initial diagnosis among 163 patients treated by stereotactic radiosurgery and radiotherapy (NEMROCK 1999-2002).

Category	Diagnosis	Number	%
Benign Diseases	Meningiomas	29	19
	Arteriovenous Malformations	22	13
	Acoustic Neuromas	21	13
	Low grade Gliomas	39	28
Tumors	High grade Gliomas	20	12.5
	Pituitary Adenomas	8	5
	Metastatic Brain disease	5	3
	Others*	19	9.5
	Total		163

*Others include; haemangiopericytoma in 2 patients (1%), chordoma of skull base in 4 patients (2%), ependymoma in 4 patients (2%), pineal body tumor in 3 patients (1.5%), glomus jugulare in 3 patients (1.5%) and medulloblastoma in 3 patients (1.5%).

developed nausea and vomiting (Pearson's Chi Square) (p value < 0.0001) [3] as shown in Table (11). Poor correlation data were obtained on analyzing other encountered immediate side effects in relation to any of the disease or therapy related parameters.

Table (4): Karnofsky performance scale among 163 patients treated by stereotactic radiosurgery and radiotherapy (NEMROCK 1999-2002).

Performance status	Number	%
100-90	65	39.8
80-70	71	43.6
60-50	27	16.6
Total	163	100

Table (5): Lesion volume, multiplicity and treatment schedule among 163 patients treated by stereotactic radiosurgery and radiotherapy (NEMROCK 1999-2002).

Item	Values
Volume:	
Range (cc)	0.21-65.31
Median volume (cc)	12.5
Standard deviation	±13.6
Multiplicity:	
One lesion	160 patients
Two lesions	2 patients
Three lesions	1 patient
Treatment schedule:	
SRS	101 (61.9%)
SRT	62 (38.1%)

Table (6): Dose scheme adopted among (101) patients treated by stereotactic radiosurgery (NEMROCK 1999-2002).

Volume	N	%	Dose (Gy)
< 1 cc	11	10.9	20
1-5 cc	33	32.7	15
> 5-125 cc	57	56.4	10

Table (7): Dose contribution to risk structures and conformity index among 163 patients treated by stereotactic radiosurgery and radiotherapy (NEMROCK 1999-2002).

Risk structure	Dose range (Gy)	Mean dose (Gy)	Standard deviation
Left eye	0-4.4	0.47	±0.75
Right eye	0-3.6	0.42	±0.59
Brain stem	0-19.4	4.60	±4.84
Chiasma	0-17.2	1.30	±4.08
Conformity Index	Range	Mean value	Standard Deviation
	1-2.95	1.44	±0.39

Table (8): Incidence of immediate side effects “of mild & moderate severity” reported among 163 patients treated by stereotactic radiosurgery and radiotherapy (NEMROCK 1999-2002).

Immediate side effects	Number of patients with side effects	% of total
Naudea and vomiting	39	23.9
Headache	23	14
Worsening of pretreat. Deficits	5	3.06
Convulsive fits	2	1.2

Table (9): Incidence of immediate side effects according to initial diagnosis among 163 patients treated by stereotactic radiosurgery and radiotherapy (NEMROCK 1999-2002).

Diagnosis	Number	%
Acuostic neuroma	10/21	43
Low grade glioma	13/39	33
High grade glioma	14/20	70
Arteriovenous malformation	4/22	20
Meningioma	9/29	31
Metastatic brain disease	3/5	60
Pituitary adenoma	0/8	0
Others	4/19	21.1

Table (10): Distribution of immediate side effects (I.S.E.) within different disease entities among 163 patients treated by stereotactic radiosurgery and radiotherapy (EMROCK 1999-2002).

	Headache	Nausea & vomiting	Worsening of pretreatment deficits	Fits
Acuostic Neuroma	4	7	0	0
Low G. Glioma	5	8	1	0
High G. Glioma	5	10	2	1
AVM	3	1	0	0
Meningioma	3	6	2	0
Metastases	2	3	0	1
Others	1	4	0	0

Table (11): Incidence to develop nausea and vomiting according to radiation dose delivered to area postrema among 163 patients treated by stereotactic radiosurgery and radiotherapy (NEMROCK 1999-2002).

Dose	0 ≤ 2 Gy		> 2 Gy		p-value
	No.	%	No.	%	
N/V					
No	124	95.4	0	0	< 0.0001
Ye	6	4.6	33	100	
Total	130	100	33	100	

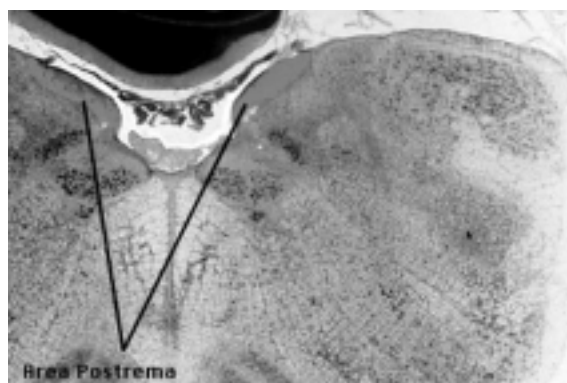
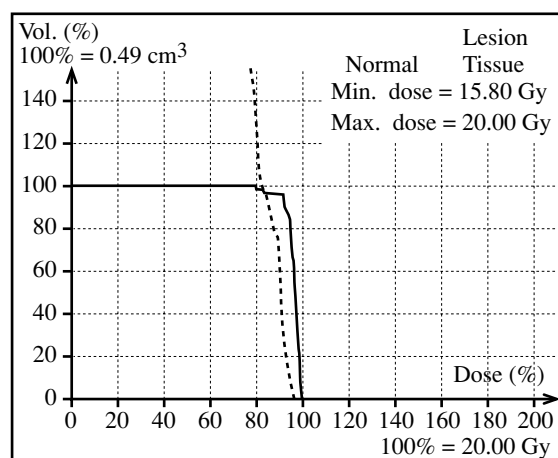


Fig. (1): Cut section in human brain showing area postrema “vomiting center”.



No dose delivery for:
Rt eye mri (12.64 cm³) Lt eye mri (11.94 cm³)

Fig. (2): Dose volume histogram showing adequate lesion volume coverage without dose contribution to surrounding normal structures and conformity index approaching value 1.

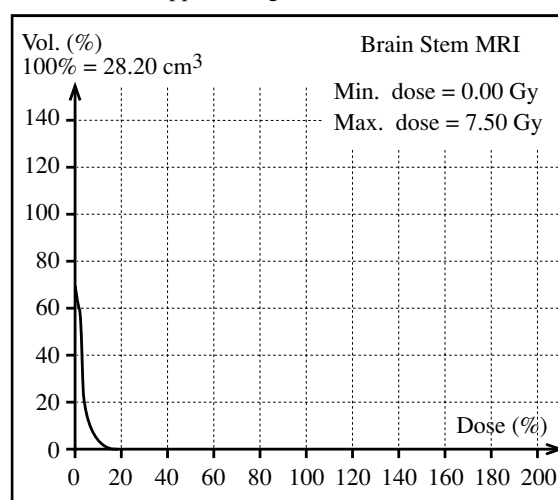


Fig. (3): Dose volume histogram of brain stem denoting sparing of the major part of its volume, keeping the maximum dose (7.50 Gy) to less than 1% of brain stem volume. The treated lesion is located at the cerebello-pontine angle.

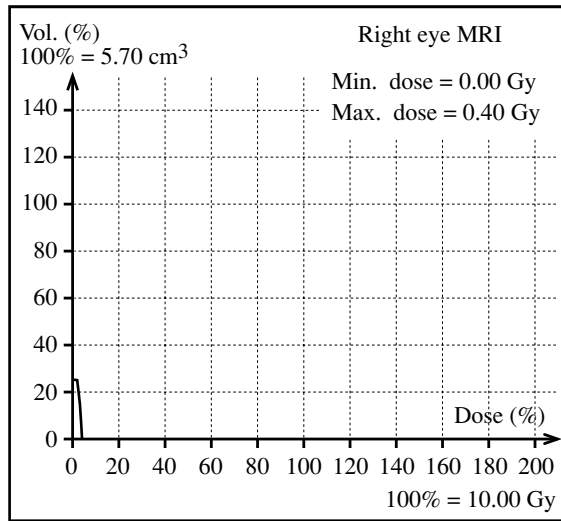


Fig. (4): Dose volume histogram denoting nearly complete sparing of the right eye. The treated lesion is located at para-sellar region.

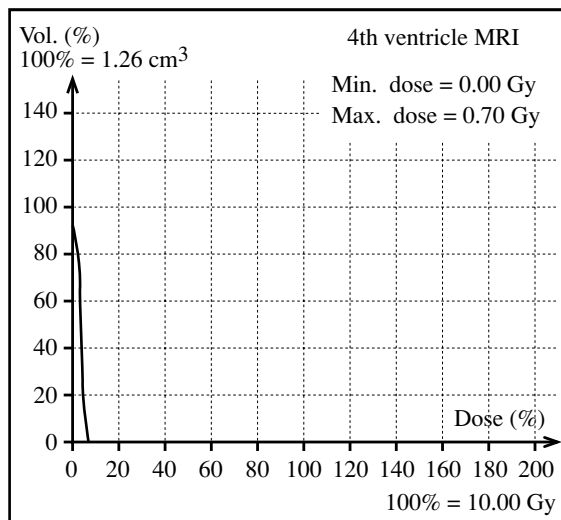


Fig. (5): Dose volume histogram denoting minimal dose contribution to the region of 4th ventricle. The treated lesion is located at the right temporo-parietal region.

DISCUSSION

Stereotactic radiosurgery and radiotherapy are safe and effective alternative to surgery for selected intracranial lesions [6].

Nausea, vomiting and headache were the most commonly encountered immediate side effects reported in 39 (23.9%) and 23 (14%) patients respectively, whereas the incidence of intensification of pre-therapy manifestations as well as convulsive fits were quite low; in 5 (3.06%) and 2 (1.2%) patients respectively. These

results are closely matched to those reported by Wasik and Co-workers in 1999 [20], who documented their experience in treating 78 patients with a variety of intracranial lesions by either (SRS) or (SRT). They reported the incidence of immediate side effects to be 35% (28/78 patients) and the most common complication was headache in 21.1% (17/78 patients). The previous data were emphasized in a series of 101 patients with acoustic neuromas treated by SRS. Linskey and associates [13], reported post-treatment immediate headache of mild to moderate severity in (11%), a finding which matched with our results.

Moreover, in our study, 19% (4/21) of the patients with acoustic neuromas and 14% (3/22) of the patients with arteriovenous malformations had reported developing immediate post-therapy headache and dizziness. Further explanation for such an event and its possible attribution to radiation effect on vestibular brain stem nuclei requires more verification and establishment via the ability to localize brain stem nuclei on SRS/SRT planning images.

Nausea and vomiting were reported to be among the most frequently encountered post-radiosurgery immediate side effects. Loeffler et al. [14], had reported an incidence of 21% development of nausea and vomiting in their series of 101 patients with acoustic neuromas treated radiosurgically. The same finding was emphasized by Alexander and his colleagues [2] who reported the same morbidity in 16% (7/44 patients) with arteriovenous malformations and other intra-cranial tumors. Also they correlated their data with radiation dose > 6.18 Gy to area postrema (Chemoreceptor Trigger Zone). Similar data were published by Bodis et al. [4], who treated 196 patients with brain metastases radiosurgically, where 22 patients (11%) had developed nausea and vomiting within 12 hours of treatment. Moreover, they found that all patients who received > 2.75 Gy to area postrema, had developed nausea and vomiting. Also they emphasized upon the effectiveness of ondansetron in preventing epileptic episodes when administered intravenously prior to radiosurgery with or without steroids.

In our study, there was a little bit higher incidence of developing nausea and vomiting among the entire group of patients (39/163) representing 23.9%. All patients were found to

receive a radiation dose ranging from 0-8.1 Gy with a median value of 1.21 Gy to the region located at the floor of the 4th ventricle and harboring area postrema, but the onset of vomiting was correlated only with doses greater than 2 Gy, contrasting to data reported by Alexander et al. [1].

The discrepancy with data reported by Alexander and co-workers [1] could be attributed to different disease entities treated in our study, where he treated only cases with acoustic neuromas. However, further analysis of our data revealed that 33% (7/21 patients) with acoustic neuromas had developed nausea and vomiting but at a lower threshold dose level (2 versus 6.18 Gy) to area postrema, a finding which requires further clarification via future studies enrolling higher number of patients to establish the threshold radiation dose to area postrema above which, nausea and vomiting are anticipated as immediate post-stereotaxy morbid events. Also, in spite of the relatively close results with those of Bodis et al. [4]; (2 versus 2.75 Gy) as a threshold dose level to area postrema, none of our patients had received ondansetron as a pre-medication; only metoclopramide and steroids which were effective in alleviating such manifestations.

The incidence of developing immediate side effects among patients with malignant cranial lesions was clearly higher than those with benign diseases, 70% versus 43% indicating the need to pay more attention to proper patient selection and adequate pre- as well as post-treatment medications for patients with high grade gliomas and brain metastases.

Only two patients had developed epileptic episodes following stereotaxy. They had the diagnoses of high grade glioma and brain metastasis, also they had a past history of convulsive fits during their disease course and could direct attention to the importance of employing more potent anti-convulsive measures when attempting to treat similar patients.

Worsening of pre-therapy manifestations was reported in one, two and two patients with diagnoses of low grade glioma, high grade glioma and meningioma respectively. All lesions were noted to be located near the motor cortex which could be compromised by either direct radiation effect or more likely due to cerebral oedema

mandating the adequate use of dehydrating measures in both pre- and post-therapy periods. Moreover, It is difficult to conclude that patients with pituitary adenomas are not anticipated to develop immediate post-stereotaxy side effects, as this conclusion cannot be emphasized with the small number of patients enrolled in our trial (8 Patients).

The location of lesions and dose are critical parameters related to the development of post-stereotactic radiosurgery and radiotherapy edema. It is well known that parasagittal meningiomas are a risk group in this respect. Occlusion of bridging veins is a possible though unproven mechanism for this phenomenon. However, this edema did not occur within the time frame of the present study.

Further clinical trials are clearly needed including higher numbers of patients with homogenous characteristics aiming at obtaining more informative data about stereotaxy side effects and its proper management. Also, it should be emphasized to avoid radiation doses greater than 2 Gy to the region in the floor of the 4th ventricle harboring area postrema with the possible use of H3 antagonists if higher dose delivery is an inevitable event.

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