OPTIMIZATION OF BRAIN TUMOURS IRRADIATION
Determining the Set-up Margin

by

***Valerija ZAGER MARCIUS*[1,2*], *Laura DOLENC* [1], *and Uroš SMRDEL*[2]**

[1]Medical Imaging and Radiotherapy Department, Faculty of Health Sciences,
University of Ljubljana, Ljubljana, Slovenia
[2]Teleradiotherapy Department, Institute of Oncology Ljubljana, Ljubljana, Slovenia

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The aim of this work was to evaluate whether the excising margin of the clinical tumor volume and planning target volume correspond with calculated radiation margin based on systematic errors, and definition of radiation margins of individual brain lobes. This research was a retrospective cross-sectional study. We checked the systematic errors and calculated their average and the size of radiation margins. The average systematic errors were calculated in four directions: lateral, longitudinal, vertical, and rotation. The largest average systematic error was calculated in the lateral direction in the cerebellar area, and the error was also statistically significant ($p < 0.05$). In rotational direction we notice the statistically significant difference in frontal lobe ($p = 0.037$), and cerebellar area ($p = 0.002$). The largest safety margin, as measured by the average systematic errors, is required for irradiation of the cerebellum. The safety margin size of 6.94 mm was calculated according to the formula of Van Herk. However, the smallest safety margin can be used for irradiation of the occipital lobe of the brain, namely 4.85 mm. The linear regression results that only cerebellar lesions affect lateral displacements. Based on our calculation of the mean systematic errors, we estimate that the clinical target volume – planning target volume safety margin can't be reduced further from the current 5 mm to a size of 3 mm without the use of image guided radiotherapy.

Key words: brain tumor, geometric verification of radiation, modern radiation therapy technique, radiation treatment margin, radiotherapy

INTRODUCTION

Brain, as the one of the most complex and also the one of the most sensitive human organs did not escape the effects of the cancer, one of the most common and severe disease of the present [1, 2]. Cancer being caused by the uncontrolled proliferation of the cells and their subsequent spread leads to the formation of the tumours [3], these can be separated as primary and secondary tumours, this being the case also in the brain [4, 5].

The mainstay of the treatment of brain tumours are surgery and radiotherapy with systemic treatments gaining a foot. Still despite the importance of other treatments in controlling disease, majority of the patients somewhere in the course of treatment receive radiotherapy. The aim of radiotherapy can be either radical (in minority of patients) or palliative. In most cases radiotherapy is being delivered as tele-radiotherapy, nowadays using 6 MV photons generated by linear accelerator and a range of 3-D techniques (with proportion of patients still being treated with 2-D techniques and on the other end of the spectrum with hadrons). National Cancer Institute defines radiotherapy as a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumours, so as to achieve this goal we must deliver appropriate dose to the tumour while avoiding excessive dose to organs at risk. In central nervous system these are visual apparatus, auditory apparatus, brainstem, and hippocampi. To achieve the goal of adequate dose coverage of tumour we are relying on appropriate margins, which in turn correspond to the planning volumes as defined by ICRU83 report [6]. While the dose limitations are addressed by QUANTEC review [7].

The dose objectives can be achieved by using number of irradiation techniques ranging from three-dimensional conformal radiotherapy (3-DCRT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) in all its guises, stereotactic techniques for well-defined tumours and in some centres also hadron therapies.

Due to the radiotherapy doses being relatively high, thus leading to adverse effects in the case of ex-

* Corresponding author, e-mail: valerija.zager@zf.uni-lj.si

ceeding dose in normal tissues and on the other hand resulting in tumour sparing in case of underdosage within the area of tumour, accuracy is of paramount importance. Accuracy must be ensured by verification procedures, addressing both dosimetric and geometric issues [8]. Our aim is to address the geometric accuracy issues.

The aim of geometric verification is to ensure that geometric accuracy is within the limits of the uncertainty tolerance prescribed in the treatment plan. This can be achieved by comparing images between the current position acquired with the kilovolt or megavolt (kV/MV) image before treatment and the planned/reconstructed radiograph, reconstructing the image based on computed tomography (CT) slices acquired on the simulation device. Of the target volumes created during the planning phase, clinical target volume (CTV) and planning target volume (PTV) are important for calculating the margin according to Van Herk. The aim of the process is to ensure, that at least 90 % of patients receive at least 95 % of prescribed cumulative dose in CTV. The margin is calculated by multiplying the standard deviation of all systematic errors, multiplied by factor 2,5 which gives 90 % confidence level for 3-DCRT to which random error multiplied by factor 0,7 – required for 95% dose level. The equation is a simplified version of the original equation [8].

CTV PTV 2.5 σ

where is the value of systematic error and σ – value of random error.

As it is important for every radiotherapy department to have its own margins calculated, rather than to employ margins from some other department, our aim was to check whether the existing margins of CTV and PTV meet the requirements established by the calculation of margins for brain irradiation and aims to define the margins required for irradiation of specific brain regions.

MATERIALS AND METHODS

The retrospective study was performed to analyse the systematic errors (mm) recorded in the treatment protocols of patients. The systematic errors were recorded as a result of the geometric verification before RT with one of the image guided radiotherapy techniques (IGRT). We included 179 patients who were treated for a primary or secondary brain tumours between 9/1/2018 and 9/1/2019 with any RT technique except opposing lateral fields and gave consent to RT and to the use of their RT data before treatment. Using the recorded displacements in all three directions, we examined and assessed the degree of systematic error as a function of the brain region irradiated. To perform the task patients were divided according to the irradiated region, namely diffuse, frontal, temporal, parietal, occipital, cerebellar, and midline (corpus calossum, pituitary, mesencephalon, hypothalamus, and skull base). Data were collected on the magnitude of systematic errors and then calculated the mean systematic error within groups. We dichotomized the data to assess the differences between the assessed group and the other groups as a whole. Using the Van Herk formula, we calculated the margin to be applied separately for each brain region. As random error, we used the standard deviation of each group (brain region). In the end, the calculated margins were compared with the margins used for brain irradiation.

Treatment preparation

Every patient has been prepared in the same way as per protocol we were using for treating intracranial lesion at the time.

When irradiation is indicated as a treatment, the patient has first be prepared at the CT simulator to determine the treatment position, which should be convenient and reproducible in all subsequent treatments. Also, acquisition of the CT images on which treatment planning is based, as they provide us the information about the electron density of the tissue needed to calculate the absorbed dose is performed. The CT images are then used in the construction of the digitally reconstructed radiograph (DRR), which serves as a benchmark for geometric verification of the treatment [9].

In the treatment of brain tumour, the patient is in the supine position, with a standard-size headrest, while the head is held in place with a thermoplastic fixation mask. The thermoplastic mask is used to immobilise the patient during CT acquisition and further treatment, and to provide a repeatable position during treatment. After completion of the simulation, planning process and dosimetric verification, patients are irradiated at the linear accelerator [9].

Electronic portal imaging

Electronic portal imaging used has a kV source and is used according to a written protocol, with patients' portal images being taken on first three consecutive days of treatment, followed by imaging on 7th day and then weekly. On the first day, an online review is performed by a radiation therapy technologist (RTT) who, prior to the start of treatment, verifies that the actual position, based on the electronic portal imaging device (EPID), matches the planned position, based on the DRR. If the RTT detects a deviation of more than 5 mm from the planned isocentre, the correction, is made and the treatment is continued. On the 2nd and 3rd day, the offline verification is performed, *i.e*., the verification is done after the treatment. All deviations from the DRR are recorded and the mean error

value for all directions is calculated. This is performed every 7 days, as already mentioned. If errors of more than 5 mm are detected again, the corrections are made and the protocol is resumed.

Statistical analysis

Data were processed using Microsoft Excel 2010, followed by statistical analysis using IBM SPSS STATISTICS version 25 (IBM corporation, USA). The Shapiro-Wilk test was used to determine the normality of the distribution. If the distribution was normal ($p > 0.05$), the *T*-test for independent samples and the Mann-Whitney *U*-test ($p < 0.05$) if the distribution was not normal were used. To determine which of the factors had an effect on the directional shifts, the linear regression was used. A p value 0.05 (95 % confidence interval) and a power of 0.8 was considered statistically significant.

RESULTS

We analysed systematic errors in 179 patients treated for primary or secondary brain tumours irradiated with 3D-CRT, IMRT, or VMAT technique in the selected period. Patients were divided into groups according to the location of the tumour. Regarding the displacements required to perform the treatment correctly, the mean systematic error was calculated in four directions: lateral (left/right), longitudinal (cranial/caudal), vertical (anterior/posterior), and rotation. Using the Van Herk formula and the calculated mean systematic errors with respect to tumour location, the safety margin for each tumour location was calculated. As shown in fig. 1, 28 % of the tumours in our sample were located in the frontal lobe, followed by the temporal and parietal lobes (20 % and 16 %, respectively). In 16 % of the cases, the lesions were diffuse. Lesions were least frequent in the cerebellum, midline structures, and occipital lobe (8 %, 7 %, and 5 %, respectively).

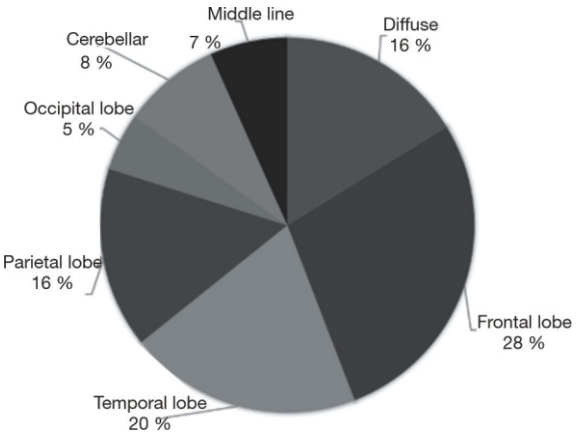

Figure 1. Distribution of patients regarding brain lobes

In the following tables, the systematic errors are given in terms of their direction. In the columns, the magnitudes of the systematic errors, with respect to the brain region, are given with the confidence interval and standard deviation. The p-value of the normality test and the p-value of the test used with respect to the distribution. In the last column, the interpretation of the p-value was described.

As can be seen in tab. 1, the largest mean systematic error was in the cerebellar region (1.61 mm) and the smallest in diffuse lesions (0.58 mm). Other values are in the range of 0.70 mm and midline structures 0.97 mm. The mean systematic errors in the lateral direction are normally distributed in the parietal and occipital lobes and in the midline structures region. The distribution in other regions is not normal. Only in the region of the cerebellum the systematic error differs significantly from other parts of the brain.

In tab. 2 the mean systematic errors are described in longitudinal direction, calculating the largest mean error in the midline structures (1.81 mm) and the smallest (0.85 mm) in the occipital region. Only in the temporal lobe and midline structures the distribution is not normal ($p < 0.05$), in all other regions, the distribution is normal. We did not find statistically significant differences in any region with respect to longitudinal error.

The largest systematic error tab. 3 in the vertical direction was found in the occipital lobe lesions (1.27 mm) and the smallest in the diffuse lesions and frontal lobe (0.91 mm). Systematic errors in the occipital lobe, cerebellum, and midline structures were normally distributed; the errors distribution in other parts of the brain was not normal. No mean systematic error

Table 1. Results in lateral direction

	Mean [mm	Confidence interval [mm]	Standard deviation	Shapiro-Wilk test	Statistical significance	Result
Diffuse	0.58	0.41-0.75	0.45	$p < 0.05$	0.109	NS
Frontal lobe	0.65	0.51-0.80	0.51	p < 0.05	0.157	NS
Temporal lobe	0.80	0.58-1.03	0.67	$p < 0.05$	0.929	NS
Parietal lobe	0.70	0.51-0.90	0.50	$p = 0.065$	0.480	NS
Occipital lobe	0.78	0.28-1.27	0.63	$p = 0.249$	0.962	NS
Cerebellar	1.61	0.96-2.27	1.19	p < 0.05	$p < 0.001$	Sig.
Middle line	0.97	0.58-1.37	0.62	$p = 0.14$	0.327	NS

Abbreviations: NS-nonsignificant ($p > 0.05$), Sig. – significant ($p < 0.05$)

in vertical direction is significantly different from the others.

With respect to the rotation measured in degrees tab. 4, the largest mean systematic error was calculated in the cerebellum (0.56°) and the smallest for the parietal lobe (0.05°), which is a half degree smaller than in the cerebellum. None of the systematic errors are normally distributed. The mean systematic error for rotation in the treatment of lesions in the cerebellum and frontal lobe is statistically significantly different from the others.

So, as to implement the formula for calculating margins, we should first calculate the set-up error. As per original formula (devised for all kinds of sites), we should be using the sum of squares of the measured set-up errors, delineation errors and organ motion. As we are dealing with organ without significant motion, we can simply calculate the set-up error using our measured errors and delineating errors tab. 5.

As shown in tab. 6, the largest safety margin, as measured by the average systematic errors, is required for irradiation of the cerebellum. The safety margin

Table 2. Results in longitudinal direction

	Mean [mm]	Confidence interval [mm]	Standard deviation	Shapiro-Wilk test	Statistical significance	Result
Diffuse	1.29	0.97-1.62	0.86	$p = 0.80$	0.608	NS
Frontal lobe	1.30	1.07-1.52	0.81	$p = 0.228$	0.475	NS
Temporal lobe	1.40	1.15-1.66	0.75	$p < 0.05$	0.655	NS
Parietal lobe	1.54	1.17-1.91	0.95	$p = 0.166$	0.285	NS
Occipital lobe	0.85	0.31-1.40	0.71	$p = 0.155$	0.076	NS
Cerebellar	1.36	0.84-1.87	0.93	$p = 0.130$	0.947	NS
Middle line	1.81	0.82-2.80	1.56	$p < 0.05$	0.323	NS

Abbreiations: NS-nonsignificant ($p > 0.05$)

Table 3. Results in vertical direction

	Mean [mm]	Confidence interval [mm]	Standard deviation	Shapiro-wilk test	Statistical significance	Result
Diffuse	0.92	0.57-1.28	0.93	$p < 0.05$	0.293	NS
Frontal lobe	0.91	0.68-1.15	0.83	$p < 0.05$	0.293	NS
Temporal lobe	1.05	0.76-1.33	0.85	$p < 0.05$	0.624	NS
Parietal lobe	1.22	0.82-1.63	1.04	$p < 0.05$	0.285	NS
Occipital lobe	1.27	0.69-1.86	0.76	$p = 0.914$	0.359	NS
Cerebellar	1.05	0.59-1.52	0.84	$p = 0.200$	0.860	NS
Middle line	0.82	0.42-1.23	0.63	$p = 0.400$	0.561	NS

Abbreviations: NS-nonsignificant ($p > 0.05$)

Table 4. Results in rotation angle

	Mean [°]	Confidence interval [°]	Standard deviation	Shapiro-Wilk test	Statistical significance	Result
Diffuse	0.21	0.03-0.39	0.47	$p < 0.05$	0.836	NS
Frontal lobe	0.11	0.14-0.31	0.30	$p < 0.05$	0.037	Sig.
Temporal lobe	0.27	0.11-0.44	0.50	$p < 0.05$	0.418	NS
Parietal lobe	0.05	–0.01-0.11	0.15	$p < 0.05$	0.294	NS
Occipital lobe	0.23	0.01-0.45	0.29	$p < 0.05$	0.378	NS
Cerebellar	0.56	0.10-1.01	0.83	$p < 0.05$	0.002	Sig.
Middle line	0.12	–0.68-0.32	0.30	$p < 0.05$	0.561	NS

Abbreviations: NS-nonsignificant ($p > 0.05$); Sig. – significant ($p < 0.05$)

Table 5. Systematic and random errors in respect to location

	[mm]	σ [mm]
Diffuse	1.94	1.63
Frontal lobe	1.70	1.14
Temporal lobe	1.92	1.15
Parietal lobe	2.03	1.45
Occipital lobe	1.60	1.22
Cerebellar	2.29	1.73
Middle line	2.21	1.79
Whole brain	1.95	1.44

Table 6. Calculated and rounded safety margin (CTV-PTV) regarding to individual brain lobes

	Calculated safety margin [mm]	Rounded safety margin [mm]
Diffuse	5.99	6
Frontal lobe	5.14	5
Temporal lobe	5.61	6
Parietal lobe	6.09	6
Occipital lobe	4.85	5
Cerebellar area	6.94	7
Middle line	6.78	7
Whole brain	5.89	6

size of 6.94 mm was calculated according to the formula of Van Herk. However, the smallest safety margin can be used for irradiation of the occipital lobe of the brain, namely 4.85 mm.

Finally, linear regression was performed. The influence of factors (tumour position relative to the lobe, device, and irradiation technique) was determined and found that lateral movements and rotation are influenced only by the location of the lesion in the cerebellum ($p < 0.05$). However, longitudinal and vertical movements were not influenced by any of the factors.

DISCUSSIONS

The purpose of the study was to determine, whether the set-up margin being used for treatment of brain tumours was sufficient and whether it would be possible to reduce margin and thus to minimise the irradiation damage to the brain.

Of special interest to us was to determine if there are differences in the size of systematic error due to the location of the lesion and should we apply different margins to the different part of the brain. We thus analysed the anatomic locations of the lesions irradiated and calculated the set-up errors. The lateral displacement and the rotation are the directions where we found most outliers, which is most obvious in the cerebellum. The cerebellar location thus has an important influence on systematic error in lateral translational displacement and rotation. The lesions in frontal lobe also have a significant impact on rotation. The retrospective study by Kanakavelu and Jebaseeian [10] has shown, that the displacement in 90 %, 80 % and practically 100 % of the total image acquisitions were less than 3 mm in lateral, longitudinal and vertical directions, respectively. They determined, that with image guided techniques feasible CTV-PTV margins can be as small as 3.4 mm, 3.4 mm and 19.9 mm in brain patients. While this is true, our study shows, that when not using image guidance, these margins need to be considerably wider, in some regions up to 7 mm. We analysed the data from our older machines, and when using e-NAL protocol, without positioning with the use of cone beam CT, or for instance ExacTrac, tighter margins are no longer safe. The cerebellar and midline regions are requiring the largest margins while the margins of around 5 mm are sufficient for the irradiation of the lesions of the frontal and occipital lobes.

The size of the mean systematic errors is comparably low. But in absence of daily image guidance, the size of CTV-PTV margin is quite substantial. Gildersleve *et al*. [11], came to the same conclusion, when they compared the magnitude of systematic errors in pelvic and brain irradiation and found that systematic errors were much lower in brain irradiation. This is also a consequence of vector nature of the shifts, which when calculating only with vectors with same directions reduce the shift considerably, though when creating an isotropic margin from them the effect remains the same.

Overall, the magnitude of the mean systematic error is low. This can be attributed to the use of thermoplastic three-point mask in all brain tumour patients, this ensures the reproducibility and accuracy of the setup while ensuring that the patient lies still during irradiation. The random error, on the other hand, is not insignificant [12]. The main culprits being the variable performance status of the patient and also (most frequently in glioma patients with long radiation courses) the effect of steroids on soft tissues of head and neck.

While the majority of brain tumour patients are being nowadays treated with the help of image guidance, some are still being treated on older machines and for them the shrinkage of the margins is certainly out of question. But at least in glioma patients, the standard margins from GTV to PTV of 2 to 3 cm seem to be enough, and even with the shrinkage of margins for a couple of mms, would confer adequate coverage of GTV that is contoured on T1 contrast sequence though it might be inadequate should the GTV be contoured based on T2 sequence with comparatively smaller margins. Guram et al found, that reducing the margins did not affect the overall survival and neither the treatment outcome.

As with the regard on cognitive functioning and late adverse effect, the exact effect of margin shrinkage has yet to be determined. As Haldbo-Classen *et al*. [13] suggest, irradiation of normal brain tissue in the frontal and temporal lobes can lead to attention and even motor deficits, with a focus on irradiation of the hippocampus, which can lead to memory and learning deficits. In their study, aimed at determining the relationship between absorbed dose and tissue response in specific brain tissues, they found that higher doses affecting the left hippocampus and other left hemisphere structures significantly impaired learning processes and memory functions, as well as language, information processing and executive functions. Thus, it would be interesting to see if margin reduction and modification can make a difference in this area.

The linear regression results that only cerebellar lesions affect lateral displacements, whereas tumour location has no effect in other directions, are consistent with our predictions based on our familiarity with our fixation system, in which fixation is the best in the cranial part but worse in the cervical part.

CONCLUSION

We calculated the mean systematic errors recorded during radiotherapy of brain tumours. The mean systematic errors were calculated according to the location of the tumour and used the Van Herk formula to calculate the safety margins required for each location. Based on our calculation of the mean systematic errors, we estimate that the CTV-PTV safety margin can't be reduced further from the current 5 mm to a size of 3 mm without the use of image guided radio-

therapy. This now possess les of a problem as only the minority of palliative cases are treated without the use of cone beam CT or ExacTrac system since the introduction of Halcyon units. A prospective dosimetry study to determine the effect of reducing the safety margin on absorbed dose in adjacent structures and at least an observational study to determine the clinical impact on late effects, could provide us with further answers, in contrast to previous studies.

AUTHORS' CONTRIBUTIONS

Preparations of the research plan were made by V. Zager Marcius and U. Smrdel. Data collection and preparation for data analysis was contributed by L. Dolenc and V. Zager Marcius. Data analysis was made by L. Dolenc and U. Smrdel. All the authors have contributed to article preparation.

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ОПТИМИЗАЦИЈА ЗРАЧЕЊА ТУМОРА МОЗГА
Одређивање маргине подешавања

Валерија ЖАГЕР МАРЦИУШ, Лаура ДОЛЕНЦ, Урош СМРДЕЛ

Сврха студије је да се процени да ли маргине ексцитирања клиничке запремине тумора и планиране циљне запремине одговарају израчунатој маргини зрачења на основу систематских грешака и дефиницији маргина зрачења појединачних можданих режњева. Урађена је просечна ретроспективна студија. Проверили смо систематске грешке и израчунали њихов просек и величину маргина зрачења. Затим смо их упоредили са постојећим. Израчунали смо просечне систематске грешке у четири правца: бочно, уздужно, вертикално, и ротационо. Највећа просечна систематска грешка израчуната је у бочном правцу у малом мозгу, а грешка је била и статистички значајна ($p < 0.05$). У ротационом правцу примећујемо статистички значајну разлику у фронталном режњу ($p = 0.037$) и малом мозгу ($p = 0.002$). Највећа маргина зрачења израчуната је за туморе у малом мозгу (0.80 mm), док је за туморе у паријеталном режњу израчунат маргин само 0.31 mm. Величина сигурносне маргине од 6.94 mm израчуната је према формули Ван Херка. Међутим, најмање сигурносна граница може се користити за зрачење потиљачног режња мозга, односно 4.85 mm. Линеарна регресија указује да само церебеларне лезије утичу на бочна померања. На основу нашег израчунавања средњих систематских грешака, процењујемо да се безбедносна маргина клиничке запремине тумора и планиране циљне запремине не може даље смањити са тренутних 5 мм на величину од 3 mm без употребе радиотерапије вођене сликом.

Кључне речи: тумор мозга, геометријска верификација зрачења, савремене технике зрачне терапије, маргина третмана зрачењем, радиотерапија