

Evaluation of doses in the Wernicke and Broca's areas using two different technique in patients with right frontal glioblastoma multiforme

H. Acar¹, G. Yavas^{1*}, C. Yavas²

¹ Selcuk University, Faculty of Medicine, Department of Radiation Oncology, Konya, Turkey

² Konya Training and Research Hospital, Department of Radiation Oncology, Konya, Turkey

ABSTRACT

► Original article

*** Corresponding author:**

Dr. Guler Yavas,

Fax: +90 332 241 60 65

E-mail:

guler.aydinyavas@gmail.com

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Background: Broca's and Wernicke's areas, which are important language areas of brain, are commonly irradiated in patients with right frontal lobe glioblastomamultiforme (GBM). We aimed to compare two different treatment planning techniques in terms of the doses in the Broca's and Wernicke's areas for the patients with right frontal GBM. **Materials and Methods:** Two different treatment planning techniques of right frontal GBM were generated for Rando phantom: two field technique using parallel opposed beams and three field techniques. Both plans were compared for doses in planning target volume (PTV), Broca's and Wernicke's areas. Additionally to test the accuracy of treatment planning system (TPS) dose calculation; thermoluminescent dosimeters (TLD) were used. **Results:** The three field technique allowed the lower doses in the Broca's and Wernicke's areas. The doses calculated in the Broca's and Wernicke's areas were $0.98\% \pm 0.03$ and $0.09\% \pm 0.06$ of the isocenter dose with three field and $1.06\% \pm 0.04$ and $0.133\% \pm 0.03$ of the isocenter dose with two field techniques respectively. When the doses measured by TLD and calculated with TPS were compared; the differences were 3.23% and 2.92 % for Broca's area, and 4.12 % and 3.95% for Wernicke's area for two field and three field techniques respectively. **Conclusion:** There was a good agreement between TPS and TLD calculations for both techniques. Three field techniques seem to be more advantageous than two field technique with respect to doses of Broca's and Wernicke's areas. However this finding should be clarified with further clinical studies.

Keywords: Broca's area, glioblastomamultiforme, Rando phantom, Wernicke's area, thermoluminescent dosimetry

INTRODUCTION

Glioblastomamultiforme (GBM) is the most common primary brain tumor in adults and accounts for approximately 60-70% of all gliomas⁽¹⁻²⁾. In a multicenter study by Eser *et al.*, the estimated age specific and age adjusted

incidence rates for all cancers in Turkey were 230.8 per 100000 among males and 144.7 per 100000 among females. The estimated frequency of the central nervous system tumors was 2.6% (2.3% for men and 3.2% for women) of all tumors⁽³⁾. Malignant glial tumor is a difficult-to-treat disease, which is usually disabling and fatal^(4, 5). The treatment options are with some risk,

often causing further brain injury.

Malignant gliomas are best managed with a combined modality approach, incorporating adjuvant postoperative radiation therapy (RT) and adjuvant chemotherapy following initial surgery. Adjuvant RT directed to residual microscopic and gross disease improves local control and survival after resection^(5, 6). Adequate doses of RT are required to maximize the survival benefit⁽⁷⁻⁹⁾. This was illustrated by a retrospective review of 91 patients with malignant glioma who had a stereotactic biopsy followed by RT⁽⁷⁾. Regardless of extent of resection, patients who had RT doses of 50 to 60 Gy had a longer median survival than those who received lower postoperative RT doses. Stupp and colleagues demonstrated that temozolomide administered in addition to adjuvant radiotherapy significantly prolongs overall survival⁽⁵⁾. Currently, temozolomide concurrent with radiotherapy followed by adjuvant temozolomide has been adopted as the new standard of care^(2, 4, 5).

Most patients with high grade glioma have a relatively short survival. Fortunately, recent advances in available therapies are expected to result in a larger proportion of patients living longer, rendering the functional state of these long-term survivors critically important⁽¹⁰⁾. Combined radio-chemotherapy and other novel treatments may increase the duration of survival. However, these therapies may have severe side effects including toxicity^(5, 11). Therefore, when employing therapies which will improve survival, possible changes on quality of life must be carefully considered.

Language is the mental faculty that we use to communicate. Broca's area, which is associated with the motor images of speech, is located on the third frontal convolution in the left hemisphere. On the other hand Wernicke's area, which is associated with the auditory images of speech, is located in the left posterior superior temporal cortex⁽¹²⁾. Broca and Wernicke's areas are commonly irradiated in patients with right frontal lobe GBM. These two areas are parts of normal brain tissue and their radiation toleration doses are accordingly.

Subsequent advances in RT technique have utilized improved imaging of the tumor and

focused on RT techniques that maximize treatment to the tumor while minimizing radiation to normal brain tissue. Focal external beam RT, termed involved field RT (IFRT), has replaced whole brain (WBRT) as the standard approach. The rationale for limiting the RT field is based upon the observation that recurrent malignant glioma following whole brain irradiation develops within 2 cm of the original tumor site in 80 to 90 percent of cases; while fewer than 10 percent are multifocal^(13, 14). IFRT has become the standard approach for adjuvant RT. During IFRT planning the RT field selection depends up on the localization of the tumor as well as the volume of the tumor. In daily practice two field radiotherapy techniques is frequently used for the treatment of GBM patients. In some patients tumor is located nearby critical structures including eyes, optic nerves and optic chiasm. In order to reduce the doses received by critical organs we should use additional fields. Additional fields allow us to reduce field weights which eventually reduce the doses of the critical structures which locate in that field.

Although the use of three-dimensional (3D) treatment planning has decreased the amount of normal brain irradiation⁽¹⁵⁻¹⁶⁾ to our knowledge there in no study in the English literature evaluating the doses of the Broca's and Wernicke's areas in patients with GBM. In this study we aimed to compare the doses in the Broca's and Wernicke's areas using two different techniques as two field parallel opposed field and three field technique (two field parallel opposed and a vertex field) in patients with right frontal GBM.

MATERIALS AND METHODS

The standard female Rando phantom (Alderson) was used in this study for measuring of the PTV, and organ at risk (OAR) (including Broca's and Wernicke's areas) doses. The phantom mimics a human skeleton, soft tissue of an adult human female. The soft tissue of phantom has an effective atomic number of 7.30 and a density of 0.987g cm⁻³. The Rando

phantom consists of 35 slices, each slice being 2.5 cm in width. To determine the location of OAR on the Rando phantom, the anatomical atlas was used.

The Rando phantom was scanned in the supine position with thermoplastic mask and neck support on a table top. To maintain the treatment position, neck support was fixed to the CT and treatment table with the help of the loc-bars. The whole brain was scanned with 5 mm slice thickness and intervals. The data obtained from CT were transferred to the treatment planning system. The PTV and Broca's and Wernicke's areas contours were delineated by the same radiation oncologist according to anatomical atlas.

Treatment plans

Treatment planning of two different techniques was generated by the same medical physicist. For two field technique, conformal to the PTV, two parallel opposing beams were constructed. With the use of beam's-eye-view projections 90° and 270° gantry angles were determined and multileaf collimators (MLC) with 1 cm margin to PTV was used to achieve maximum avoidance of Broca's and Wernicke's areas.

For the three field technique the plan was performed with the same fields with two field technique and an additional vertex field was generated. MLC with 1 cm margin to PTV was also used in this technique.

Dose measurements with thermoluminescent dosimetry

a. TLD Calibration

In this study, Varian millennium 80-leaf collimators (MLC) (Varian Medical Systems Inc, Palo Alto USA) were used. Prior to the dose measurements, TLD's were sorted into groups of equal sensitivity. A single batch of TLDs was used in this study. All TLD capsules were from the same batch to avoid batch-to-batch variations in sensitivity. The TLDs were calibrated with a dose of 1 Gy in RW3 solid water phantom (PTW, Freiburg) for 6 MV energy applied for breast dose measurement. The calibration group was irradiated at 5 cm depth and 100 cm SSD using 6

MV photon beam. The TLD readings of 1 Gy called "RCF reader calibration factor" were entered into the TLD reading system HARSHAW 3500 (Harshaw chemicals, Solon OH, USA) to convert the reading to absorbed dose. The GR-200A oven anneal cycle was set at a nominal peak temperature of 240 °C. The outputs of the beam were measured with 0.6 cc ionization chamber (PTW 30010 with serial number 651, Freiburg) connected with Unidos Webline electrometer (PTW, Freiburg) in RW3 solid water phantom.

The lithium fluoride TLD rods (PTW) measuring 1 × 1 × 4 mm³ and commercially known as GR-200A (Li, Mg, Cu, P) were used for dose measurement during brain irradiation. A single batch of TLDs was used in this study in order to avoid from batch to batch variation. The selected 60 TLDs have the same responses within ±1.27 % SD. Nineteen groups, each has 3 TLDs, were obtained. One of these 19 groups was used as a calibration group. For two field irradiation, 3 of 19 groups were placed at 3 different points in the PTV to measure absorbed dose of the PTV. The other 6 groups were placed into the Wernicke's and Broca's areas in order to obtain point doses from three different regions. In the same way, the other 9 groups were placed at three different positions of PTV, Wernicke and Broca for the 3 field technique irradiation. The average dose of these three different positions were calculated and represented as the mean dose of the PTV, Wernicke and Broca.

The location of these areas for TLD measurements was decided by radiation oncologist. To measure the absorbed doses, optional 4-mm holes were milled through the phantom's Broca's and Wernicke's areas determined before, in order to place the TLDs.

b. Rando phantom measurements

The Rando phantom was irradiated for the brain irradiation for both two field and three field techniques. Two set-up conditions of brain irradiation were studied. First, two field opposing beams were used to irradiate brain. Second, three field technique (2 opposing beams and a vertex beam) was used to irradiate brain.

RESULTS

The dose response curve of TLDs is generally linear up to 10 Gy for 6 MV photons, so for all phantom irradiations, a dose of 2 Gy was given to the isocenter of the fields. PTV, isocenter, Broca's and Wernicke's areas doses were defined as the mean of all the readings in these organs.

The TLD readings were converted to absorbed dose in tissue using a calibration coefficient from a set of reference TLDs (from the same batch) irradiated with 6 MV. The mean organ dose (and standard deviation) was calculated from all TLDs within each organ.

All TLD measurements were repeated 3 times. The average of the three experiments was taken into consideration. The results were expressed as mean dose \pm SD.

We calculated the point doses from TPS using the same points that were used by TLD. Then, we averaged the results and represented as TPS calculated mean dose. The mean dose measured by TLD was compared with the mean dose calculated by the TPS. The dose difference % was calculated as follows:

$$\text{Dose Difference} = \frac{100\% \times (\text{Dose Eclips} - \text{Dose Measured})}{\text{Dose Eclips}}$$

Table 1 shows the minimum, mean and maximum doses of the PTV, Broca's and Wernicke's areas with two field and three field techniques. We obtained fewer doses in Broca's and Wernicke's areas with three field technique. Additionally the maximum, minimum and mean doses in the PTV were lower with three field techniques when compared to two field techniques. The comparison of dose volume histograms of two different techniques showed in figure 1.

When the doses of the Broca's and Wernicke's areas were expressed as a percentage of isocenter doses, three field techniques allowed us lower doses when compared to two field technique. In three field and two field techniques the doses in the Broca's and Wernicke's areas were $0.98\% \pm 0.03$ and $0.09\% \pm 0.06$; and $1.06\% \pm 0.04$ and $0.133\% \pm 0.03$ of the doses measured in the isocenter respectively as shown in table 2.

When the two field and three field techniques were compared in terms of TLD and

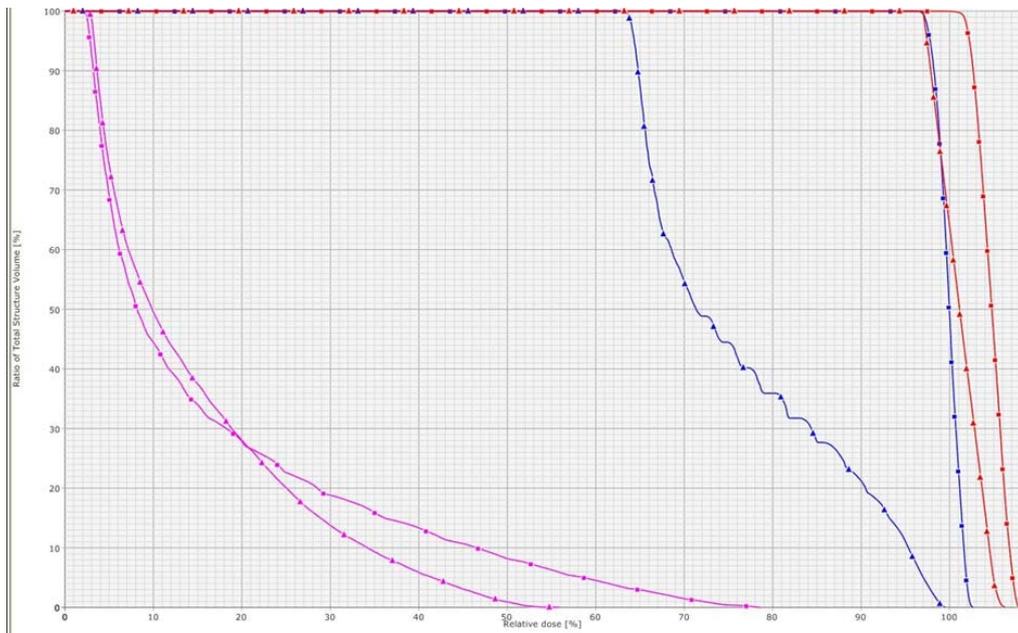


Figure 1. Dose-volume histogram comparison of three field and two field techniques. Red: PTV, blue: Broca's area, magenta: Wernicke's area. (▲: three field technique, ■: two field technique).

TPS compatibility; for the Broca's area they were 3.23 % and 2.92% and for Wernicke's area, they were 4.12 % and 3.95 % for two and three field techniques respectively (table 3).

All differences between the TLD measured and TPS calculated data were within the 7% tolerance recommended by American Association of Physicists in Medicine Radiation Therapy Committee Task Group 53 (TG 53).

Table 1. The minimum, mean and maximum doses measured in the PTV, Broca's and Wernicke's areas with two field and three field techniques.

	Minimum (cGy)	maximum (cGy)	mean (cGy)
Three-field technique			
PTV	5728	6315	6015.8
Broca's area	3782	5856	4753
Wernicke's area	89	1637	559
Two-field technique			
PTV	6059	6445	6282
Broca's area	5825	6189	6032
Wernicke's area	113	4513	860

*PTV: Planning target volume

Table 2: The ratio of Broca's and Wernicke's areas doses to the dose of the isocenter with two different techniques.

Technique	% isocenter dose ± SD	
	Two-field	Three-field
Wernicke TLD	0.133±0.03	0.09±0.06
Wernicke TPS	0.127	0.08
Broca TLD	1.06±0.04	0.98±0.03
Broca TPS	1.02	0.95

*SD: Standard deviation

**TLD: Thermoluminescent dosimetry

***TPS: Treatment Planning System

Table 3. The comparison of the doses in the Broca's and Wernicke's areas measured by TLD and calculated with TPS using two different techniques.

Technique	Two-field doses (cGy)	Three-field doses (cGy)
Wernicke TLD	53.1	34.9
Wernicke TPS	51	33.6
Difference	%3.23	%2.92
Technique	Two-field doses (cGy)	Three-field doses (cGy)
Broca TLD	422	390
Broca TPS	409	379.2
Difference	%4.12	%3.95

**TLD: Thermoluminescent dosimetry

***TPS: Treatment Planning System

DISCUSSION

In the present study we compared two different techniques of RT in patients with GBM, located in the right frontal hemisphere, with respect to doses measured in the Broca's and Wernicke's areas. Our results suggested that by adding a vertex field to two parallel opposed fields the doses measured in the speech areas was decreased. In addition we tested the accuracy of TPS dose calculation with TLD measurements. Our TLD results were compatible with TPS calculation and all the differences between the measured and calculated data using TPS were within the 7% tolerance recommended by American Association of Physicists in Medicine Radiation Therapy Committee TG 53 for both treatment plans.

In radiation oncology clinics the field size, shape and the number of the fields are chosen according to tumor characteristics, including the location and size of the tumor. Radiation oncologists work with medical physicists and dosimetrists to design optimal treatment plans. Considerations in treatment planning include beam energy, field size and shape, beam modifiers, irradiated tissue density and heterogeneity, and radiation tolerance of surrounding normal tissues. For large tumors parallel oppose fields composed of left and right beams are usually selected. However for some patients the tumor may locate nearby critical structures such as, optic nerve, optic chiasm and speech areas. In that patients three to four angled radiation fields are selected. Because additional field allow us to decrease the weight of each field thereby decrease the doses of critical organs located in that field. Adding a vertex field to parallel oppose two fields is the one that usually used in routine practice. However to best of our knowledge there is no study evaluating the doses received by the speech areas in patients with GBM. Therefore the current study is the first study in the English literature evaluating the doses in the speech areas using two different RT technique in patients who undergone irradiation for malign brain tumors.

Most patients with GBM have a relatively short survival but some have prolonged survival well. Recent advances in available therapies are expected to result in larger proportions of patients living longer, thus the functional state of these long-term survivors is critically important⁽¹⁰⁾. The use of three-dimensional (3D) treatment planning has decreased the amount of normal brain irradiated^(13, 14). Current 3D-CRT utilizes CT-based treatment planning with dosimetric software to create composite treatment plans. 3D-CRT allows us to check the doses received by PTV and OAR clearly. Nevertheless no benefit in progression-free or overall survival has been demonstrated although these techniques help avoid excess RT to normal brain^(15,16). In parallel to the developments in the field of the RT, the toxicity profile of cranial RT for GBM has changed. However radiation related side effects inevitably occur. Late toxicity of RT can include somnolence and impaired cognitive function, deterioration in intelligence, impaired cognitive functions and aphasia and usually the side effects depend on the localization of the tumor. Beside radiation related toxicity, these symptoms may be related to tumor progression as well so the discrimination between tumor progression and treatment toxicity should be done.

Murthy and colleagues reported a 12-year-old child with episodes of migraine-like headaches with visual and motor auras a year after the surgical resection and radiation therapy for medulloblastoma⁽¹⁷⁾. The patient presented with an episode of headache, prolonged aphasia, right hemiparesis, status epilepticus, and salt wasting. There was no evidence of a structural lesion. The neurologic deficits resolved over a period of 6 weeks. Because of the progressive deterioration in neurologic deficits, the patient underwent an extensive battery of laboratory tests and multiple neuroimages, all of which were normal. The authors concluded that the patient represented a long-term complication of treatment of children with central nervous system neoplasia.

Chen and colleagues reported a case of recurrent radiation necrosis with rapid clinical

deterioration and imaging findings resembling those of a malignant glioma⁽¹⁸⁾. Their report was about a 68-year-old man, who had a history of a left posterior temporal and thalamic arteriovenous malformation (AVM) treated with linear accelerator radiosurgery 13 years before presentation and complicated by radiation necrosis 11 years before presentation, exhibited new-onset mixed aphasia, right hemiparesis, and right hemineglect. Their patient died 10 weeks after initially presenting to the authors' institution, and the results of an autopsy demonstrated radiation necrosis. The authors therefore concluded that symptomatic radiation necrosis can occur more than a decade after radiation treatment necessitating patient follow up during a longer period of time than currently practiced. Thus a radiation oncologist should be aware of the doses received by critical brain sites during brain irradiation. Broca's and Wernicke's areas are one of the important critical brain structures which have roles in language.

Broca's area enervates adjacent motor neurons subserving the mouth and larynx, and controls the output of spoken language. On the other hand Wernicke's area receives information from the auditory cortex and accesses a network of cortical associations to assign word meanings. The injury of Broca's and Wernicke's areas may lead to aphasia. Aphasia is a neurological disorder caused by damage to the portions of the brain that are responsible for language. The most common cause of aphasia is a stroke, but brain tumors, blows to the head, or trauma may also cause aphasia. Since both of the speech areas are part of normal brain tissue, the tolerance doses of these areas should be same with the normal brain tissue. Radiation injury can involve multiple regions and cell/tissue types, and a large number of physical and biologic factors influence the expression and extent of damage^(19,20). While overt tissue injury generally occurs only after relatively high doses (>60 Gy, fractionated)^(20,21), less severe morphologic changes can occur after relatively lower doses, resulting in variable degrees of cognitive impairment, particularly in children⁽²²⁻²⁴⁾. Therefore the standard dose of GBM is near the toleration dose of the brain and it is very

important to spare normal brain tissue from radiation damage.

The radiation dose, fraction size and volume are the major variables that influence the development of radiation necrosis. Although location does not influence the susceptibility to radiation necrosis, necrosis is far more likely to be symptomatic in certain areas (e.g., corpus callosum and brain stem)⁽²⁵⁾. Other suggested risk factors for radiation necrosis include chemotherapy use, lower conformality index, shorter overall treatment time, older age, and diabetes mellitus^(26,27).

In this experimental study we compared two different techniques of RT, with respect the doses received by the speech areas of the brain. We concluded that adding a vertex field to parallel opposed field helps to spare the speech areas in treating tumors located in the right frontal hemisphere. This finding should be clarified with further clinical studies.

There is no conflict of interest

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