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THREE–DIMENSIONAL CONFORMAL RADIATION THERAPY IN GLIOMAS

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Objective: **the work is aimed on determination of the prognostic factors in patients with brain gliomas following three-dimensional conformal radiotherapy (3-D CRT).** ***Methods***: **between 1998–2001, we treated 28 patients (median age — 47.5 years) with 3-D CRT. 16 patients had total and 12 — partial tumor resection. Histology revealed low-grade — in 9 patients and high-grade gliomas — in 19 patients. 17 patients had a Karnofsky Performans Status (KPS) score ≥ 80, and 11 patients < 80. There were 7 local recurrences before 3D-CRT. All patients received a mean total dose of 59.64 Gy with 3-D CRT emcompassing the margins described as in ICRU 50 reports according to preoperative enhanced computed tomography and/or magnetic resonance imaging. Mean follow-up was 16 months.** ***Results***: **mean survival was 25.6 months, and 3 years survival rate — 55%. Univariate analysis revealed that age ≤ 50 years; KPS score ≥ 80; histologically proven low-grade status and no recurrence before 3D-CRT predicted significantly higher survival probability. There was one late radiation necrosis 12 months after radiotherapy.** ***Conclusion***: **these results suggest that 3-D CRT was well tolerated, and age, KPS, grade and previous recurrence have significance importance on survival.**
Key Words: **glioma, conformal radiotherapy.**

Malignant gliomas are among the most aggressive and lethal tumors. Although surgery is usually undertaken, either for total or partial removal of the tumor, sometimes only biopsy with or without decompression may be feasible. The total dose of 60 Gy in conventional radiotherapy can be delivered. Accelerated hyperfractionated radiotherapy can be effective on tumor repopulation during radiotherapy [1].

Three–dimensional conformal radiotherapy treatment (3D–CRT) planning and delivery has the general goal of conforming the shape of a target volume, and limiting dose to critical normal structures while increasing the tumor dose [2, 3].

Prognostic factors such as age, Karnofsky Performance Status (KPS), tumor volume, type of surgery, histological type and grade affect the treatment results.

Retrospective analysis of survival and prognostic factors of treatment regime was carried out on 28 patients with malignant glioma were treated postoperatively with 3D–CRT in Cebeci Hospital (Ankara, Turkey) between January 1998 and December 2001.There were 14 female and 14 male patients. The median age was 47.5 years (ranged from 21 to 79 years). Histology revealed low–grade in 9 patients (grade I astrocytoma in 3; grade II astrocytoma in 2; grade I oligoastrocytoma in 1; grade II oligoastrocytoma in 1; grade II mixtoligoastrocytoma in 2 patients) and high–grade in 19 patients (grade III astrocytoma in 2; grade IV astrocytoma in 10; glioblastoma multiforme in 5; grade III mixtoligoastrocytoma in 2 patients). Gross total resection performed in 16 and subtotal resection performed in 12 patients. There were 7 primary tumor relaps in patients after primary surgery and before 3D–CRT. KPS score was ≥ 80 in 17 patients and < 80 in 11 patients. Patients were evaluated with clinical examination and computed tomography (CT) and/or magnetic resonance imaging (MRI). Before surgery, the mean maximum tumor diameter was 4.77 cm ± 1.7 (range, 1.5–7.5 cm) and the mean tumor volume was 84.2 cm^3 ± 68.6 (range, 1.5–250 cm^3). In 13 patients, chemotherapy (CMT) was administered.

3D–CRT was performed three weeks after surgery. The CT images were taken by Picker® (Picker International, Inc, USA) I.Q. T/C computed tomography in the treatment position. The target volume, body out–line, right eye, left eye, hypophysis and spinal cord tissue were drawn, target isocenter was fixed, and virtual simulation was done with Picker Voxel Q virtual simulation workstation. Beam's eye view, isodose distribution, inhomogeneity correction, multileaf collimators and dose volume histogram (DVH) were done with a Varian® Cad–plan (Varian Associates Inc, Oncology Systems, USA) treatment modeling workstation. Minimum 3 and maximum 5 coplanar or non–coplanar treatment fields where selected. The cases were planned with 6 MV photon of Varian® (Varian Associates Inc, Oncology Systems, USA) clinac 2300 C/D with one daily fraction, 2 Gy per fraction, 5 fractions per week and total 10 Gy in a week. The wedges were used to enhance the isodose distribution, and the treatment plans and DHVs were compared for the plan optimization. Mean total target dose was 59.64 Gy ± 9.63 (range, 30–70 Gy). 4 patients relapsed after primary surgery and conventional parallel opposed two fields radiotherapy, these 4 patients underwent reoperation and subjected to the mean 38 Gy (range, 30–44 Gy) 3D–CRT.

After the completion of 3D–CRT the patients were followed monthly in the 1st year and every 3 months after 1 year with clinical examinations and CT and/or MRI.

Survival was estimated using the Kaplan — Meier method and the prognostic factors were analysed with log–rank test.

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Abbreviations used: CMT — chemotherapy; CNS — central nervous system; 3–D CRT — three–dimensional conformal radiotherapy; CT — computed tomography; DVH — dose volume histogram; Hb — hemoglobine; KPS — Karnofsky performance status; MRI — magnetic resonance imaging.

The mean follow–up time was 16 months ± 11.4 (range, 1–37 months). All the patients finished their 3D–CRT on time. There was no side effect during radiotherapy. There was no acute central nervous system (CNS) toxicity, but there was one late radiotherapy necrosis proved by biopsy 12 months after radiotherapy. Local relaps occured in 11 patients and 2 patients underwent reoperation. 8 patients died due to primary tumor relaps and 1 of them died 1 month after radiotherapy.

Survival results of patient groups were analysed according to age, sex, histologic grade, type of surgery, relaps after primary surgery, radiotherapy dose, hemoglobine (Hb) level, KPS, maximum tumor diameter, tumor volume and CMT.

The mean overall survival rate of the whole group was 25.6 months ± 2.7 and 3 years survival rate — 55%, and the mean survival rates for age >50 years and age ≤ 50 years were 12.25 months and 32.2 months, the mean survival rates for high–grade and low–grade patients were 19.95 months and 21.7 months, the mean survival rates for relaps after primary surgery and without relaps after primary surgery were 15.5 months and 28.95 months, and the mean survival rates for KPS <80 and KPS ≥ 80 were 16.55 months and 30.7 months.

In univariate analysis (Table) age > 50 years (p = 0.0008), high–grade tumor (p = 0.0105), relaps after primary surgery (p = 0.0381) and KPS < 80 (p = 0.0232) were all significantly associated with reduction in over all survival, but sex, type of surgery, radiotherapy dose, Hb level, maximum tumor diameter, tumor volume and CMT were not significiantly associated with reduction in over all survival.

Table. Patients' characteristics and prognostic factors

Parameter	Number (%)	Mean survival (months)	p–value
Age (year)			
≤ 50	17 (60.8)	32.2	0.0008
> 50	11 (39.2)	12.25	
Sex			
Male	14 (50)	26.9	0.71
Female	14 (50)	24.3	
Grade			
Low	9 (32.1)	21.7	0.01
High	19 (67.9)	19.95	
Surgery			
Total	16 (57.1)	25.2	0.91
Subtotal	12 (42.9)	25.1	
Relaps after primary surgery			
Yes	7 (25)	15.50	0.038
No	21 (75)	28.95	
Radiotherapy dose			
> 60 Gy	12 (42.9)	20.2	0.14
≤ 60 Gy	16 (57.1)	27.9	
Hb level			
< 12 g/dl	13 (46.4)	17.5	0.09
≥ 12 g/dl	15 (53.6)	30.4	
KPS			
≤ 80	17 (60.8)	30.7	0.02
< 80	11 (39.2)	16.55	
Maximal tumor diameter			
> 5 cm	14 (50)	18.2	0.49
≤ 5 cm	14 (50)	27.4	
Tumor volume			
> 80 cm^3	9 (32.1)	19.8	0.99
≤ 80 cm^3	19 (67.9)	25.8	
CMT			
Yes	13 (46.4)	26.6	0.37
No	15 (53.6)	23.8	

Radiation therapy delivered postoperatively has been shown to increase survival rate of completely excised malignant gliomas. Liebel et al [4] were able to demonstrate 5–year survival rate of 46% for irradiated low–grade astrocytoma patients. Approximately 35% of treated patients with high–grade gliomas survive 1 year, but less than 20% will survive 2 years.

Early postoperative conventional radiotherapy for patients with low–grade glioma appears to improve the time to progression, but not overall survival [5]. Do et al [6] showed longer waiting time from presentation at radiotherapy department to treatment to be a significant predictor of overall survival for patients with high–grade glioma.

Accelerated hyperfractionated radiotherapy in malignant glioma [7] showed no significant improvement in survival compared to conventional fractionation [8].

The aim of the 3D–CRT is that higher doses of radiotherapy can be delivered to a target volume with less treatment–related morbidity compared with conventional external beam radiotherapy techniques [9–11]. 3D–CRT limits the dose to the hypothalamic and pituitary gland, and reduces the risk of developing clinical hypopituitarism [12]. The long–term incidence of brain stem toxicity in patients treated for skull base tumors with high dose conformal radiotherapy appears to be steep function of tissue volume included in high dose regions [13]. 3D–CRT should include at least one volumetric imaging study of the patients. Morris et al [2] addressed the clinically relevent issues with regard to malignant gliomas and the role of CT, MRI, functional MRI, and positron emission tomography scans in 3D–CRT planning.

Delineation of the clinical target volume in 3D–CRT planning of high–grade glioma is a controversial issue [14]. Attention is given to the pattern of tumor spread at initial presentation [15]. Clinical target volume definition is depending upon the histological type, the quality of the surgical resection and the medical team [16]. Non–coplanar irradiation technique for malignant glioma shows better dose–volume histograms over coplanar irradiation technique [17].

Nakagawa et al [18] reported 60 Gy to 90 Gy high–dose conformal radiotherapy results of glioblastoma multiforme. The 1–year, 2–year, 5–year, and 10–year overall survival rates were 75, 42, 20, and 15% respectively. But the high–dose conformal radiotherapy did not improve survival.

The age of patients has been evaluated and found to be the single most important prognostic factor for survival [19]. Lutterbach et al [20] performed accelerated hyperfractionated radiotherapy in patients with glioblastoma multiforme and reported that only age ≤ 60 years and lactate dehidydrogenase levels ≤ 240 U/l predicted significantly higher survival probabilities. Performance status and histological type proved to be important prognostic factors as reported by Nelson et al [21]. In an other study only the residual tumor volume of ≤ 5 cc was statistically significant in the high–dose 3D–CRT [18].

In this study, 3D–CRT was well tolerated and the mean survival was 25.61 months, and 3 years survival rate was 55%. In univariate analysis, age ≤ 50 years, KPS ≥ 80,

low–grade histology, and no relaps before 3D–CRT predicted significantly higher survival probability.

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ТРЕХМЕРНАЯ КОНФОРМАЛЬНАЯ РАДИОТЕРАПИЯ ГЛИОМ

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Цель: определение прогностических факторов у больных с глиомами после трехмерной конформальной радиотерапии (3-D CRT). _Методы_: объектом исследования были 28 больных (средний возраст — 47,5 года), получавших курс 3-D CRT в 1998–2001 гг. У 16 пациентов была выполнена полная, а у 12 — частичная резекция опухоли. Гистологически выявлены опухоли низкой степени дифференцировки — у 9 пациентов, высоких — у 19. У 17 пациентов статус Карновского (KPS) составлял ≥ 80, у 11 < 80. До 3D-CRT локальные рецидивы возникли у 7 пациентов. Все пациенты получили среднюю тотальную дозу 59,64 Гр с использованием 3-D CRT в границах, которые соответствуют данным ICRU 50. Средний период наблюдения составил 16 мес. _Результаты_: средняя продолжительность жизни составила 25,6 мес, 3-летняя выживаемость — 55%. Методом универиантного анализа установлено, что возраст ≤ 50 лет, KPS ≥ 80, гистологически подтвержденная низкая степень дифференцировки и отсутствие рецидивов до 3D-CRT значительно повышают вероятность выживания. Некроз, вызванный облучением, был отмечен в единственном случае спустя 12 мес после радиотерапии. _Выводы_: 3-D CRT хорошо переносится, а возраст, KPS, степень дифференцировки опухоли и наличие рецидивов значительно влияют на выживаемость.

***Ключевые слова*: глиомы мозга, конформальная радиотерапия.**