CAN HYPOFRACTIONATED REIRRADIATION PLUS TEMOZOLAMIDE BE A WISE CHOICE FOR RECURRENT HIGH AND LOW GRADE BRAIN TUMORS?

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ABSTRACT

Aim: To report outcome, toxicity, and survival of reirradiation with hypofractionated radiotherapy concurrently temozolamide which is a novel approach to recurrent high- and low-grade glioma patients.

Material and Methods: Twenty patients (8 males and 12 females; age between 26 and 70 years) with recurrent gliomas treated in our clinic were included in our study. The primary pathology was low grade in 12 patients and high grade in 8 patients. For recurrence hypofractionated radiotherapy, 350 cGy/fraction, totally 3500 cGy with concomitant temozolamide 75 mg/m2/day was applied.

Results: Median OS was 55.42 months, median progression free survival was 38.26 months, and median survival from reirradiation was 9.3 months. Neither gender nor primary pathology had got effect on any of the survivals. Although being reoperated for recurrence did not affect progression free survival or survival after reirradiation, it has got statistically significant impact on overall survival. No severe toxicity was seen other than minor side effects. No interruption was needed so all of the patients were able to complete the treatment according to the scheduled plan.

Conclusion: Reirradiation as hypofractionated radiotherapy with concomitant temozolamide is an effective, safe, and well-tolerated treatment for recurrent high and low gial tumors.

1. Introduction

It is well known that postoperative radiotherapy improves overall survival in majority of gliomas (Combs et al., 2008; Mirimanoff et al., 2006). It was shown that concomitant temozolomide ameliorates the survival in European Organisation for Research and Treatment of Cancer 22,981/26,981/National Cancer Institute Of Canada Clinical Trials Group CE.3 (Ataman et al., 2004; Krauze et al., 2017; Minniti et al., 2011).

Although there are improvements in surgery, radiotherapy, and medical oncology, recurrences occur in all patients with high-grade brain tumors (Bräutigam et al., 2019; Krauze et al., 2017). For recurrence surgery, radiotherapy and chemotherapy can be performed as salvage treatment (Shen et al., 2018). Extended surgery cannot be carried out always because of infiltrative nature of gliomas (Minniti et al., 2011). Treatment options in recurrent gliomas are limited (Combs et al., 2008; Shi et al., 2018).

In historical knowledge, in relapsed brain tumors, reirradiation using conventional techniques was considered to have risks like toxicity and white matter necrosis (Mayer & Sminia, 2008; Nieder et al., 2016; Paul et al., 2018). So, attention must be paid while performing reirradiation. In recurrence of glial tumors interstitial brachytherapy, radiosurgery, fractionated stereotactic radiotherapy, or conventional external radiotherapy can be used (Kazmi et al., 2019; Krauze et al., 2017). The tolerance of brain to the reirradiation depends on the cumulative dose, the interval between first radiotherapy and reirradiation, and concurrently given therapies (Mayer & Sminia, 2008). Also the techniques that are used (hypofractionated radiotherapy, fractionated stereotactic radiotherapy, single fractional stereotactic radiosurgery) and the volume which is reirradiated play a role in the toxicities and outcome of the treatment. Temozolamide as concurrent therapy was not shown to have addictive effect on toxicity (Brandes and Fiorentino, 1996; Torok et al., 2011).

Until new techniques were developed, reirradiation using conventional techniques was used to be the cause of treatment-related side effects and toxicities (Stupp et al., 2005). However introduction of sophisticated techniques (intensity modulated radiotherapy, image guided radiotherapy) had given chance to deliver high local doses while sparing organs at risk (Stupp et al., 2005). Sophisticated radiotherapy is a non-invasive way to deliver high...
2. Material and methods

Data regarding recurrent glioma patients who underwent reirradiation (re-RT) between January 2010 and September 2017 in Ankara Numune Training and Research Hospital Radiation Oncology Clinic, were collected. This study was based on a retrospective analysis of treatment charts and received approval from local Ethical Committee (E-19-2639). All patients were treated in agreement with the Helsinki declaration and provided written informed consent. Data of patients, tumor, treatment characteristics, and toxicity at diagnosis and at progression were recorded.

Twenty patients with recurrent gliomas treated in our clinic were included in our study. Of the patients 8 (40%) were males and 12 (60%) were females. Age was between 26 and 70 years (median 45.45 yrs). All of the patients had ECOG ≤ 2. Patients characteristics are summarized in Table 1.

All patients had undergone surgical procedure before initiation of primary radiotherapy. The surgical intervention was only biopsy in 5 patients (25%), subtotal excision in 11 patients (55%), and gross total removal in 4 patients (20%). Pathologic classification was glioblastoma in six patients (30%), astrocytoma WHO grade II in eight patients (40%), oligodendroglioma WHO grade II in four patients (20%), and anaplastic oligodendroglioma (WHO grade III) in two patients (10%).

The dose of primary radiotherapy was 5400 cGy for WHO grade II tumors (12 patients (60%)) and 6000 cGy for high grade tumors (8 patients (40%)). Temozolomide was given concurrently to eight patients with high grade tumors (WHO grade III and grade IV) as 75 mg/m²/day, every day including weekends. Twelve patients with WHO grade II tumors were not given concurrent temozolamide. Tumor volume for the primary radiation was between 78.47 cm³ and 534.25 cm³ (median 150 cm³).

The median interval time between primary radiation and re-RT was 41.18 months (14.86–115.26 months).

In ten patients (50%) after recurrence, surgery was performed whereas in ten patients (50%) there was no surgical approach. The pathology of reoperation was glioblastoma (WHO grade IV) in four patients (40%), anaplastic astrocytoma (WHO grade III) in two patients (20%), and anaplastic oligodendroglioma (WHO grade III) in four patients (40%).

For all patients the fractionation for reirradiation was 350 cGy/fraction, five times a week totally 3500 cGy in ten fractions, concomitantly with temozolomide 75 mgr/m²/day daily including weekends. The volume of reirradiation was between 4.96 cm³ and 340.40 cm³ (median 81.56 cm³).

For treatment thermoplastic individual fixation head masks were used. All simulations were done by computed tomography (GE, BRIGHT SPEED). For contouring and planning Eclipse contouring system was used. The gross tumor volume (GTV) was defined from contrast enhancing tumor edges using T1C on MRI, the planning target volume was created from GTV by adding 0.1–0.5 cm. The defined planning target volume (PTV) was covered by the 95% isodose line.

Radiotherapy was administered by Varian Trilogy (RapidArc) unit. Using ARC therapy with image guided radiotherapy technique (IGRT)

Once a week during the radiotherapy and six weeks after completion of radiotherapy patients were seen as first follow-up visit. Later, the follow-up visits were done every threemonths or as needed clinically.

Survival was the primary end point of the study. Overall survival (OS) was calculated from initiation

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Table 1. Patient characteristics.

| Patient characteristics | Mean | Median | Range |
|-------------------------|------|--------|-------|
| Age (years)             | 45.45| 26–70  |       |
| Gender                  | 8    |        |       |
| Male                    | 12   |        |       |
| Surgical attempt        | 5    |        |       |
| Only biopsy             | 11   |        |       |
| Subtotal                | 4    |        |       |
| Gross total             | 4    |        |       |
| Initial pathology       | 8    |        |       |
| Astrocytoma WHO grade II| 4    |        |       |
| Oligodendroglioma WHO grade II| 2| | |
| Anaplastic oligodendroglioma (WHO grade III)| 6| | |
| Glioblastom             | 4    |        |       |
| Pathology of reoperation| 4    |        |       |
| Oligodendroglioma WHO grade III| 2| | |
| Anaplastic oligodendroglioma (WHO grade III)| 4| | |
| Glioblastom             | 4    |        |       |
| Temozolamide concurrent to primary therapy| 8| | |
| Yes                     | 12   |        |       |
| No                      | 8    |        |       |
| CTV of primary radiotherapy (cm³) | 150 | | |
| Median                  | 78.47|        |       |
| Range                   | 354.25| | |
| CTV of reirradiation (cm³)| 81.56| | |
| Median                  | 4.96 |        |       |
| Range                   | 340.40| | |
| Interval between primary radiotherapy and reirradiation (months) | 41.18 | 14.86 | 115.26 |
| Median                  | 41.18|        |       |
| Range                   | 115.26| | |
of primary radiotherapy. Initiation of reirradiation was taken into account as the survival from reirradiation (Re-RTS). Disease free survival was calculated from primary radiotherapy to reirradiation. Survivals were determined by Kaplan-Meier Method. Statistical analyses were done by PASW statistics SPSS 17.

3. Results

Twenty patients who were given 3500 cGy (350cGy x 10 fractions) re-RT and concurrent temozolamide (75 mgr/m²/day) for recurrence of glial tumors were enrolled in the study. Progression free survival that is the interval between primary radiotherapy and re-RT was 38.26 months as median (range; 28.47–48.05 months). As part of their primary therapy eight patients were given temozolomide 75 mgr/ m²/day. Reoperation was performed in ten patients, and all of the pathology was high-grade tumors (glioblastoma (WHO grade IV) in four patients (40%), anaplastic astrocytoma (WHO grade III) in two patients (%20), and anaplastic oligodendroglioma (WHO grade III) in four patients (%40)). Two patients out of 20 were alive at the time of analysis and 18 were dead. The cause for death was related to the disease.

3.1. Overall survival

The overall survival was calculated from initiation of primary radiotherapy. Median OS was found to be 55.42 months (18.96–148.56) (Figure 1)

Gender has got no impact on overall survival (p = 0.738). Also primary pathology has got no significant association with overall survival (p = 0.296). The statistical significance was seen between operated and non-operated for recurrence patients (p = 0.014)

3.2. Progression-free survival

Median PFS was 38.26 months (range 28.47–48.05) and mean PFS was 44.66 months (range 30.85–58.47) (Figure 2).

Figure 1. Overall survival.

Figure 2. Progression-free survival.
Figure 3. Survival from reirradiation.

Gender ($p = 0.9$) and primary pathology ($p = 0.13$) were not found to have impact on PFS.

3.3. ReRTS

Median survival from reirradiation (ReRTS) was 9.83 months (range 6.25–13.4). Actuarial PFS rates were 75% at 6th month and 45% at 12th month (Figure 3).

Gender ($p = 0.41$), primary pathology ($p = 0.14$), and being reoperated for recurrence ($p = 0.99$) were not significantly associated with survival from reirradiation.

3.4. Toxicity

The toxicity was graded according to the National Cancer Institute common toxicity criteria. In general, the treatment was tolerated very well by all of the patients. There was no need for interruption in any patient.

The minor side effects including hair loss, headache, fatigue, and nausea/vomiting were seen and medicated as needed. No hematological side-effects occurred. No other severe side-effects were seen.

Table 2. Prognostic factors for OS, PFS, and reRTS.

|                | OS [Median survival (95% CI)] | PFS [Median survival (95% CI)] | reRTS [Median survival (95% CI)] |
|----------------|-------------------------------|-------------------------------|-------------------------------|
| Gender         |                               |                               |                               |
| Female         | 47.43 (18.12–76.74)           | 38.26 (14.36–62.19)           | 10.96 (0.00–22.67)            |
| Male           | 52.86 (20.66–85.06)           | 34.43 (18.08–50.78)           | 9.33 (7.07–11.59)             |
| $P$            | $p = 0.738$                   | $p = 0.9$                     | $p = 0.41$                    |
| Pathology      |                               |                               |                               |
| Glioblastoma   | 26 (16.95–35.04)              | 20.26 (16.34–24.18)           | 5.56 (3.08–8.04)              |
| Anaplastic     | 27.30                         | 21.30                         | 1.10                          |
| Oligodendroglioma | 72.80 (61.17–84.42)         | 41.26 (20.19–62.33)           | 13.83 (0.00–28.79)            |
| Oligodendroglioma grade 2 | 53.13 (51.51–54.75) | 39.03 (29.10–48.96) | 14.60 (10.55–18.64) |
| $P$            | $p = 0.296$                   | $p = 0.13$                    | $p = 0.14$                    |
| Operation for recurrence |                       |                               |                               |
| Yes            | 63.23 (37.38–89.08)           | -                             | 6.00 (1.92–10.08)             |
| No             | 30.66 (22.45–38.87)           | -                             | 15.00 (1.27–28.72)            |
| $P$            | $p = 0.014$ *                 | -                             | $p = 0.99$                    |

*Statistically significant

4. Discussion

In glial tumor treatment providing local control is the main purpose. For this purpose neurochirurgical resection, radiotherapy, and chemotherapy can be used alone or together. Instead of radiotherapy alone radiochemotherapy approaches have shown better impact on survival (Combs et al., 2005; Stupp et al., 2005).

Nevertheless recurrence is very common in glial tumors, especially in high-grade tumors, treatment options are also very limited due to the risk of neurological sequelae. Treatment approaches for recurrence usually include surgery and radiotherapy and chemotherapy.

In recurrence, surgical intervention cannot be possible in every patient. Also, with chemotherapy not very good results could be achieved (Brandes et al., 1996; Korones et al., 2003; Levin et al., 1990). Similarly, previous radiotherapy treatments did not reach the desired results (Chan et al., 2005; Leibel et al., 1989; Park et al., 2000; Shrieve et al., 1995).
With the advances in techniques, novel techniques for reirradiation in glial tumors recently have been started to be used to deliver safer doses with less side-effects (Combs et al., 2008).

Although using multimodality treatment is more common, there is no consensus yet (Combs et al., 2005; Nieder et al., 2016). For recurrent or progressive glioblastoma treatment consideration of second course of radiotherapy is recommended in The National Comprehensive Cancer Network (NCCN) guidelines (Scholtyseck et al., 2013).

The present study analyzes the combined use of hypofractionated radiotherapy and temozolamide in recurrent both high- and low-grade glial tumors.

Histological grade plays the main role for survival. High-grade tumors have shorter survival than low-grade tumors and this is supported in many studies (Cho et al., 1999; Combs et al., 2005; Shepherd et al., 1997; Veninga et al., 2001). In a study evaluating the relapse of different histologic types median survival was found to be 21 months for glioblastoma, 50 months for WHO grade III glium tumors, 111 months for WHO grade II glial tumors. Histological grading, extent of surgical resection, and the age at the time of diagnosis were predictive factors. The same study reported the median survivals after reirradiation as 8 months, 16 months, and 22 months for glioblastoma, WHO grade III glium tumors and WHO grade II glial tumors respectively (Ataman et al., 2004). In another study consisting of high-grade glial tumors (i.e. glioblastoma and WHO grade III glial tumors) the median survivals were given as 8 and 16 months (Combs et al., 2005).

In the study with 25 patients with glioblastoma, WHO grade III glium tumors and low-grade tumors which was done by Combs et al., 2008, the median overall survival was reported as 59 months, median survival from reirradiation as 8 months, and PFS as 5 months (actuarial PFS rates at 6th and 12th month as 48% and 16% respectively). Age, gender, and extent of surgical resection had no effect on survival.

In another study the time to first progression was found to be 13 months (range, 2–145 months) (25). The interval between the primary radiotherapy and reirradiation was accepted to be the progression free survival (PFS). The median PFS was calculated as 38.26 months. Primary pathology or gender has got no effect on PFS.

In a reviw done by Dong et al. (2016) the range for survival after reirradiation was given as 7.4 – 16.5 months. In our study the survival after reirradiation (ReRTS) was 9.83 months.

Most of the studies figured out that gender does not play a role in overall survival (5,8,27). Only one study which was done by Scholtyseck et al. (2013) revealed a positive impact of female gender in multivariate analysis. In our study median overall survival was 55.42 months, median PFS was 38.26 months, and median reRTS was 38.26 months. Acturial PFS rate was 75% at 6th month and 45% at 12th month. Neither gender nor primary pathology has got impact on overall survival. Only being operated or non-operated for recurrence played a role on overall survival (p = 0.014). Although there is no consensus about reoperation for recurrent tumors, in a review, 29 studies out of 31 showed a benefit for survival with reoperation. It was mentioned that age was not a contraindiction for operation. Interval time and Karnofsky Performance Status were predictors for the benefit (Hervey-Jumper & Berger, 2014). In the situation whenever reoperation can be done, it will improve the survival. This statement puts forward the importance of reoperation in recurrent glial tumors.

In most of the studies evaluating reirradiation for recurrent glial tumors, only minor side-effects (alopecia, headaches, nausea/vomiting and skin erythema) were reported (Combs et al., 2005; Combs et al., 2008; Scholtyseck et al., 2013). Even in a multicenter study of the Radiation Oncology Italian Association (AIRO) acute and subacute grade 1 and 2 toxicity were reported in 14.3% patients (Navaria et al., 2019). We also did not see any other side-effects than minor neither during nor after the treatment. Using medications for minor side-effects as needed, the treatments were completed without any interruptions.

5. Conclusion

On the basis of these results and the present study, it can be concluded that reirradiation with new techniques as hypofractionated radiotherapy with temozolomide is an effective, safe, and well-tolerated treatment for recurrent high and low glial tumors. Also reoperation for recurrent glial tumors has got importance on survival and must be considered whenever possible. However, it must be taken in care that results are collected from small numbered patient groups. Further studies with large groups will offer more accurate treatment approaches for recurrent glial tumors.

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