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ORIGINAL ARTICLE

Current Clinical Practices in Glioblastoma Management: A Nationwide Survey of Radiation Oncologists, TROD 07-004 Study

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OBJECTIVE

Glioblastoma is the most common primary brain tumor with a poor prognosis. Despite the guidelines, treatment management in elderly or progressing patients may be scarce. Our objective was to determine the current clinical practice patterns for glioblastoma management through a nationwide survey.

METHODS

Different scenarios and situations were prepared for a web-based online questionnaire emailed to radiation oncologists.

RESULTS

A total of 195 radiation oncologists responded to the survey. There was a consensus for concurrent adjuvant chemoradiotherapy for patients younger than 70 years old with good performance. However, physicians disagreed on the course of adjuvant temozolomide, whereas they administered the chemotherapy six courses (44%), 12 courses (34%), or until progression (19%). For patients older than 70 years and with good performance, most physicians (80%) preferred the standard treatment approach. However, standard approaches differed among the physicians for older adults with poor status, and diverse strategies were recommended for managing this patient group. Stereotactic approaches (73%) are recommended for reirradiation in progression. The systemic treatment recommendation was bevacizumab (87%) in the patient who progressed after standard chemoradiotherapy. Surgery was requested for younger patients who have good performance and small tumors. In symptomatic radionecrosis, steroids, bevacizumab, and surgery were the alternatives, respectively.

CONCLUSION

Physicians take different approaches to treatment, such as adjuvant chemotherapy cycles in younger patients, radiotherapy schemes in older adults, and treatment choices for progression. Despite the continuing investigations in high-grade gliomas, it may be suggested that the guidelines include detailed clinical scenarios for optimal management.

Keywords: Glioblastoma; older adults; practice patterns; radiosurgery; radiotherapy.

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INTRODUCTION

Grade IV astrocytoma (glioblastoma) is the most common primary malignant brain tumor in adults.[1] Moreover, the incidence increases with age, which is most common in patients older than 70.[1,2] Maximal safe resection and adjuvant chemoradiotherapy in 60 Gy with concomitant and adjuvant temozolomide are standard treatments; however, despite the aggressive treatment approach, the median survival is almost 15 months in glioblastoma.[3] While improved survival has been reported with the standard approach, there are still open questions about managing aggressive high-grade tumors in older adults. Some physicians may prefer more conservative approaches when treating patients in elderly patients.[4] However, this paradigm has recently been faced with increasing evidence to suggest that elderly patients also benefit from maximally safe resection and chemoradiotherapy.[5]

Another question is the optimal treatment and treatment sequences in terms of the progression of glioblastoma. Unlike de novo disease, there is no standard of care in treating recurrent disease, and the preferred treatments are not superior. Options include resection, reirradiation, chemotherapy, and systemic therapies (i.e., bevacizumab).[6] However, more evidence-based, high-quality knowledge is required in recurrent situations.

There is a need for more data about managing various scenarios and for more consensus on managing patients with glioblastoma. Hence, through a nationwide survey, we aimed to determine the prevailing clinical practice patterns in radiotherapy for glioblastoma management.

MATERIALS AND METHODS

This study was performed in accordance with the principles of the Declaration of Helsinki and ethical approval was obtained from our Marmara University Faculty of Medicine ethics committee (the reference number: 02.07.2021 and 09.2021.921). A cross-sectional survey of radiation oncology practitioners in Türkiye was undertaken between January 2021 and March 2021. The web-based online questionnaires were prepared on the Google.doc site, and the invitation was sent to registered members of the Turkish Society of Radiation Oncology via e-mail. The questionnaire contained 13 items, including different scenarios and situations. The questions were determined to identify the current practice of treating patients with glioblastoma, surgery, reirradiation, or systemic treatments in routine care, commonly used dose fractionation in older patients, and those with worse performance status. The responses were collected using custom-built software.

RESULTS

The Participants' Profiles and Their Facilities

A total of 195 radiation oncologists responded to the survey. The characteristics of study participants are summarized in Table 1. All participants utilized intensity-modulated radiotherapy; some had access to (30%) stereotactic radiosurgery and linear accelerator-based stereotactic body radiotherapy (67%) facilities. A multidisciplinary tumor board is held in all academic centers, and patients are treated both within this center and in other centers based on the board's decisions. One-third of these centers are reference hospitals with a high patient load; physicians saw more than five new patients diagnosed with glioblastoma, and 31% followed more than ten patients per month.

Radiotherapy Time and Planning Details

Approximately 60% of the participants initiated postoperative radiotherapy for glioblastoma patients either three weeks after surgery or immediately following suture removal. Most participants favored the two-phase approach for defining target volumes in radiotherapy planning (61%). Phase I was described as tumor and/or the cavity and edema, and phase II was defined as the same but without edema. The rest of the physicians defined the target volume in a single phase as tumor and/or cavity ± edema (21%) or tumor and/ or cavity ± edema with a simultaneous integrated boost technique (Table 1).

The Scenarios and Situations

Table 2 provides all scenarios and situations, and Figure 1 sketches the results. Among the physicians, the Karnofsky Performance Status Scale (KPS) (96.9%), the patient's age (53.6%), and tumor characteristics (45.9%) were factors in deciding the radiotherapy fraction scheme.

The Patient Younger Than 70 Years and KPS More Than 60 After Resection or Biopsy

All participants agreed on the standard adjuvant treatment, which included 60 Gy radiotherapy and concurrent temozolomide. However, following the concurrent therapy, the number of adjuvant chemotherapy courses administered varied: 44% of physicians prescribed six courses, 34% opted for 12 courses, and 19% continued treatment until disease progression.

Table 1 Participants' professional features, treatment time, planning, and fractionation preferences

Participants	n	%
Residents	38	19.5
Specialists	76	39
Specialist-Lecturer	81	41.5
Physicians' practice settings in		
Private hospital	36	18.5
State Hospital	60	30.8
University Hospital	96	49.2
Physicians treated newly diagnosed patients		
≥5 patients/month	56	28.7
5> patients/month	139	71.3
Physicians made follow-ups for patients in the outpatient clinic		
10>/month	135	69.2
10-20/month	45	23.1
≥20/month	15	37.7
Available radiotherapy techniques in the center		
IMRT/VMAT	184	94.8
LINAC-based stereotactic radiotherapy	131	67.5
Cyberknife/Gammaknife	57	29.4
Proton therapy	-	-
Time of radiotherapy following biopsy/resection		
Waiting ≥3 weeks after surgery	110	57
Immediately after sutures are removed	102	52.8
Immediately after biopsy	34	17.6
Other	4	2
Radiotherapy target volume definition*		
Two phases planning	119	61
Single phase planning	42	21.5
Single-phase planning with a simultaneous integrated boost	28	14.4
Other	6	3
Factors affecting the decision of the radiotherapy fraction scheme		
Performance status	177	90.8
Age	147	75.4
Tumor location, volume, edema	126	64.6
Tumor MGMT** status	18	9.2

*: If the critical organ doses are appropriate; **: O^6-Methylguanine-DNA Methyltransferase. IMRT/VMAT: Intensity Modulated Radiotherapy/Volumetric Modulated Arch Therapy

The Patients Older Than 70 Years After Resection or Biopsy

The physicians preferred the standard approach (80%) rather than the short fraction scheme (20%) in elderly patients who have good performance status (KPS≥60). However, the standard approach (8.8%), short fraction radiotherapy (24.7%), temozolomide (28.4%), or short fraction and chemotherapy (37.1%) were administered to patients with KPS<60.

Treatment Decisions in Progress

Considering re-irradiation in recurrence after standard treatments in patients younger than 70 years and KPS more than 60, stereotactic radiosurgery (73%) was the most common treatment preference, and the systemic treatment recommendation was bevacizumab (87%) in the patients who progressed. Surgical consultation was requested for patients who had good performance (95%), had limited tumors (84%), and were younger (64%). In these patients, re-irradiation was applied to the cavity following surgery (43.5%).

Treatment Decisions for Radionecrosis

In symptomatic radionecrosis, steroids (86%), bevacizumab (60%), and surgery (64%), respectively, were recommended. The decision not to administer radiotherapy was based on performance (96%), age (54%), tumor characteristics (46.6%), and methylation status (21.5%).

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Table 2 Survey scenarios and situations

Scenario 1 and 2: Radiotherapy approach in a patient younger or older than 70 years and with good performance (KPS≥60) after resection or biopsy*
- 60 Gy in 30 fractions with concurrent and adjuvant temozolomide
- 34 or 40 Gy in 10 to 15 fractions with concurrent and adjuvant temozolomide
- 34 or 40 Gy in 10 to 15 fractions with adjuvant temozolomide
- 34 or 40 Gy in 10 to 15 fractions

Scenario 3: The adjuvant systemic treatment approach in a patient <70 years old and with good performance (KPS≥60)
- Six courses of temozolomide
- 12 courses of temozolomide
- Temozolomide until the progression

Scenario 4: Radiotherapy approach in a patient ≥70 years old with poor performance (KPS<60) after resection or biopsy*
- 60 Gy in 30 fractions with concurrent and adjuvant temozolomide
- 34 or 40 Gy in 10 to 15 fractions with concurrent and adjuvant temozolomide
- 34 or 40 Gy in 10 to 15 fractions with adjuvant temozolomide
- 34 or 40 Gy in 10 to 15 fractions

Scenario 5: The treatment recommendation for a patient <70 years old with good performance (KPS≥60) in progression following a standard approach
- Surgery, if appropriate, followed by systemic therapy.
- If not suitable for surgery, re-RT followed by systemic therapy.
- Whether or not suitable for surgery, reirradiation followed by systemic therapy
- Surgery, if suitable, radiotherapy to the cavity, followed by systemic treatment.

Scenario 6: The reirradiation schedule in a patient under 70 years old with good performance (KPS≥60)**
- 36 Gy in18 fractions
- 40 Gy in 15 fractions
- 34 Gy in 10 fractions
- 30 Gy in 5 fractions
- Stereotactic approach for appropriate location and volume

Situation 1: The decision criteria for not delivering radiotherapy to a glioblastoma patient.**
- Performance score
- Age
- Tumor location, volume, edema
- MGMT¶ status

Situation 2: Systemic treatment recommendation in progression immediately after the standard approach
- Bevacizumab+/-Irinotecan
- Temozolomide in alternate dose schemes
- Procarbazine, lomustine, and vincristine (PCV) chemotherapy

Situation 3: The decision criteria for surgical consultation progressed after the standard approach**
- <70 years of age
- Good performance score
- Tumors are located at a distance from critical areas in the brain.
- Limited tumor dimension

Situation 4: The treatment decision in symptomatic radionecrosis**
- Surgery if appropriate
- Bevacizumab
- Steroid
- Hyperbaric oxygen

*: If critical organ doses are appropriate; **: Multiple options can be selected; ¶: MGMT: O^6-Methylguanine-DNA Methyltransferase. RT: Radiotherapy

DISCUSSION

Current management of newly diagnosed glioblastoma includes postoperative chemoradiotherapy, although survival is worse for older patients. In all patients, including elderly patients, standard approaches are preferred for the first diagnosis in line with the guidelines. The first point that radiation oncologists pay attention to when choosing

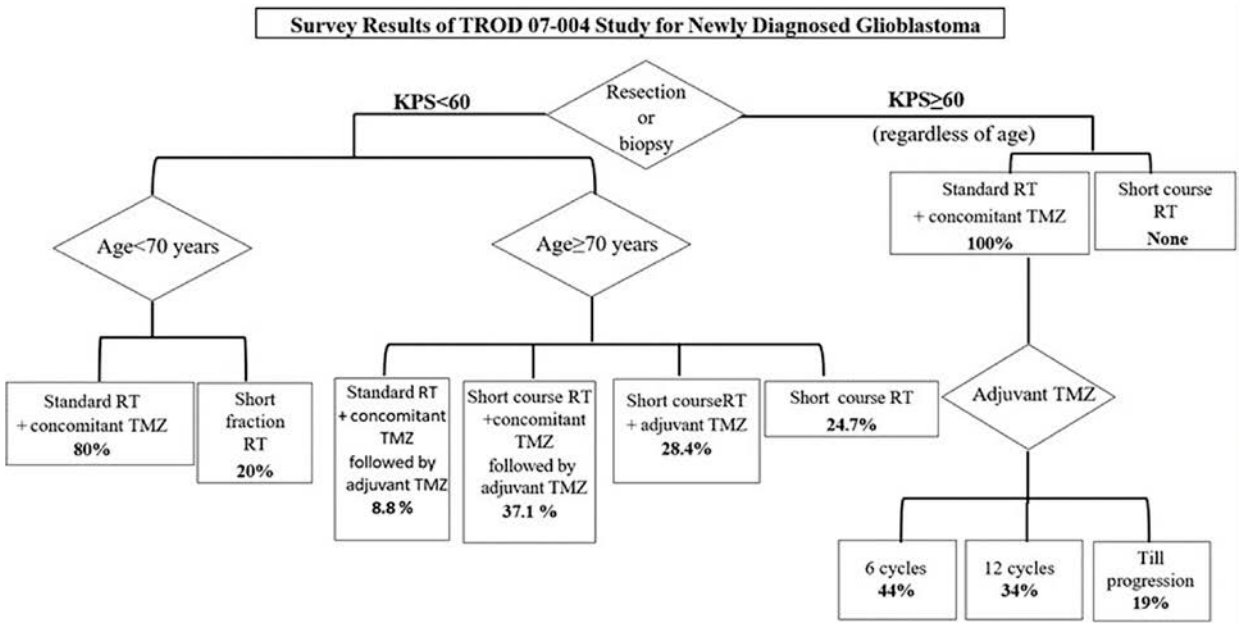

Fig. 1. Results from all the scenarios and situations provided from Table 2.
KPS: Karnofsky Performance Status Scale; RT: Radiotherapy; TMZ: Temozolomide.

a fractionation schema is the patient's performance, even for elderly patients. In those patients, evaluating clinical criteria or evaluation tools other than performance at the beginning of radiotherapy may be beneficial. Temozolomide alone is not associated with survival advantages in elderly patients with unmethylated tumors. Hypofractionated radiotherapy may be considered for patients unsuitable for combined chemoradiotherapy.

The optimal time from surgery to the beginning of radiotherapy is uncertain, and guidelines vary widely. In our study, participants also suggested varying waiting times before initiating radiotherapy following surgery. According to the Dutch Cancer Society Glioma Guideline, radiotherapy should begin up to 6 weeks after surgery.[6] Laureiro et al.,[7] in a meta-analysis of 19 retrospective studies published between 1974 and 2014, examined the effect of prolonging the time from surgery to radiotherapy. No significant correlation was observed between the prolongation of the time from surgery to radiotherapy and overall survival (OS). (HR=0.98; 95% CI 0.90–1.08; p=0.70). However, this meta-analysis included studies published before the Stupp regime era. A more recent study showed that delayed postop chemoradiotherapy may result in worse survival.[8,9] Seidlitz et al.[8] published their retrospective cohort study; 369 patients treated between 2001 and 2014 were included, and the effect of waiting time was investigated. In this large series of patients, the time between surgery and adjuvant radiotherapy (median 27 days, range 11–112 days), duration of radiation therapy (median 45, range 40–71 days), and total time from surgery to the end of radiotherapy (median 54, range 71–154 days) did not show any effect on OS or progression-free survival (PFS). Buszek et al.[9] analyzed 45,942 glioblastoma patients archived in the National Cancer Database. They revealed that delays of more than eight weeks in patients with a gross total resection and delays of less than four weeks in patients with a subtotal resection or biopsy resulted in worse survival. They concluded that the impact of time delay from surgery to radiotherapy, in conjunction with the extent of resection, should be considered in the clinical management of patients and future designs of clinical trials.

Several studies compare the efficacy and safety of standard and extended adjuvant temozolomide following concurrent chemoradiotherapy in patients with newly diagnosed glioblastoma multiforme. Attia et al.,[10] in a retrospective study evaluating a total of 121 patients, showed that extended temozolomide therapy was safe and tolerable but did not significantly improve PFS or OS compared to the standard cycle course. Feldheim et al.[11] showed that temozolomide causes loss of methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter hypermethylation and triggers migratory behavior. After temozolomide administration, cells with the unmethylated MGMT promoter

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showed more aggressive behavior.[11] GEINO-14-01, a randomized trial comparing prolonged adjuvant temozolomide (n=80) and six courses of temozolomide (n=79) treatment according to MGMT status and the presence or absence of residual disease in 159 patients, found no difference in OS or PFS.[12] In our study, we observed that the participants had different approaches regarding adjuvant treatment duration. No patients were without adjuvant treatment, but the application times differed. Extensive, randomized studies in which patients are categorized according to MGMT and other molecular markers are needed to elucidate the current issue.

There is no clear standard of care or salvage treatment when recurrence occurs in glioblastoma patients. Treatment guidelines make recommendations for these patients, such as surgery, re-administration of temozolomide, nitrosoureas, bevacizumab, and re-irradiation.[13] Neither of these methods is superior to the other. In our study, the participants stated that they recommend bevacizumab-based systemic treatment at a rate of 86% in cases of recurrence.

In our study, 84% of the participants recommended resection if the patient was suitable for surgery in case of progression. Here, the determining factors were performance, a small tumor, a location far from risky areas, and patients younger than 70. A prospective, randomized, multicenter study, DIRECTOR, compared a 2-dose intensified temozolomide regimen in relapsed glioblastoma patients.[14] In this study, a total of 61 patients were examined, and a difference in post-recurrence survival was found between surgery with total resection (12.9 mo [95% CI: 11.5–18.2] vs. 6.5 mo [95% CI: 3.6–9.9], $p<0.001$). In a study examining current models of care in the Australian population for recurrent glioblastoma, 76% of patients received re-resection, and 24% received medical therapy.[15] Surgery may contribute to symptomatic and large lesions, but this patient group should be carefully selected. There are also publications trying to develop algorithms for choosing between re-irradiation and second surgery for relapsed glioblastoma.[16]

In our study, the determining factor in the radiotherapy recommendations of the radiation oncologists was primarily the patients' performance. In addition, the patient's MGMT status and age were also influential. In elderly patients with poor performance, hypofractionated treatments were chosen in addition to the standard fraction. Similarly, the patient's performance status was the definitive factor for hypofractionated regimes. In the study of 488 patients with a diagnosis of glioblastoma, Malakhov et al.[17] showed better outcomes for patients receiving chemoradiotherapy rather than radiation alone, regardless of the performance status. In another study, among the 70 glioblastoma patients who were 60 years old or older, gross total resection provided significantly longer overall survival, and patients who received postoperative adjuvant therapy had more prolonged overall survival than those with no postoperative adjuvant therapy.[18]

For patients with symptomatic radionecrosis, corticosteroids were the first choice (76%), followed by surgery (64%) and bevacizumab (60%) in our survey. Corticosteroids reduce inflammatory signals and cytokines from necrotic tissue and reduce blood-brain barrier leakage.[19] Bevacizumab, the vascular endothelial growth factor inhibitor, is also widespread and is an essential mediator in radionecrosis.[20] In a study evaluating 71 patients diagnosed with radionecrosis, bevacizumab administration showed a 97% radiographic response rate, 79% clinical improvement, and a mean 6 mg reduction in dexamethasone.[20,21] Previous publications have demonstrated that surgical application in treating radionecrosis carries the risk of morbidity.[22] The approach to treating radiation necrosis, a complication of radiation therapy, varies depending on the severity of the necrosis and the individual patient's symptoms and may involve a combination of the treatments.

Limitations

Our survey has some limitations. Although almost 1000 radiation oncologists work in our country, 195 participants responded to our survey. Given this number, the actual clinical practice may not be fully reflected in these results, and physicians with a particular interest and neurooncological experience may have been overrepresented in our survey. Beyond the limitations, our survey provides essential insights into how care is delivered nationally for glioblastoma. More research to examine the effects of preferred treatments on patients' quality of life will be of great importance in the future.

CONCLUSION

Substantial parallelism was observed between the questionnaire responses and the guideline recommendations, especially in treating younger glioblastoma patients at diagnosis. However, further research and standardization are necessary for adjuvant chemotherapy cycles, radiotherapy fractionation schemes in elderly patients, and treatment options for glioblastoma progression. Consequently, guidelines should encompass diverse clinical scenarios supported by more robust evidence for the enhanced management of glioblastoma.

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