



Treatment for glioblastoma multiforme: current guidelines and Canadian practice

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ABSTRACT

Purpose

Our survey aimed to document variability in the practice patterns of Canadian radiation oncologists treating high-grade brain tumours.

Materials and Methods

A 20-question survey was developed to address various aspects of treatment:

- Guidelines used
- Types of fusion protocols used
- Number of treatment phases
- Margins for volume delineation
- Dose constraints

The survey was sent to Canadian radiation oncologists currently treating the central nervous system (CNS) as one of their primary sites.

Results

We attained a 56% response rate from radiation oncologists across Canada treating CNS sites. In their practice, 14% of respondents reported following guidelines from the European Organisation for Research and Treatment of Cancer; 32%, from the Radiation Therapy Oncology Group; and 56%, centre-specific guidelines. Single-phase treatment was reported by 60% of clinicians, and two-phase or multi-phase treatments, by 37%. For clinicians treating in single phase, margins from the gross treatment volume (GTV) to the planning treatment volume (PTV) included 0.5 cm (6%), 1 cm (6%), 1.5 cm (25%), 2.0 cm (56%), 2.5 cm (25%), and 3 cm (12.5%), with some respondents selecting more than one standard margin. For clinicians treating in multiple phases, margins from GTV to PTV in phase 2 included 1 cm (10%), 2.0 cm (40%), 2.5 cm (30%), and 3.0 cm (20%). Variability was also observed in dose constraints to critical structures. All respondents trimmed their margins to bony structures.

Conclusions

Our survey shows considerable variation in the current treatment by Canadian radiation oncologists of high-grade brain tumours, especially with respect to guidelines followed, number of phases, and overall volume treated. Further studies are thus required to establish the evidence for optimal radiation volumes and phases, especially as brain tumour treatments evolve in the age of MR imaging and chemotherapy.

KEY WORDS

Glioblastoma multiforme, margins, Canadian, survey, treatment, radiation, volumes

1. INTRODUCTION

Glioblastoma multiforme (GBM) is a World Health Organisation stage IV astrocytoma with an annual incidence in North America of 5 per 100,000 population. The male:female ratio is 3:2, and the tumour is usually diagnosed in the 5th or 6th decade of life¹. Pathologically, these tumours are infiltrative, with oligodendroglial, astrocytic, or mixed histopathologic characteristics. High-grade gliomas may develop *de novo* or from low-grade gliomas. They are characterized by nuclear atypia, increased cellular density, vascular proliferation, and pseudopalisading glioma cells².

Over the years, management of GBM has progressively changed. Earlier standards of treatment included surgery and adjuvant radiotherapy^{3,4}. More recently, management of GBM has progressed to incorporate surgery with postoperative radiotherapy and concurrent chemotherapy⁵.

Since the start of the 1990s, guidelines for the treatment of GBM have been established by the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG). Furthermore, the Canadian GBM committee recently published consensus recommendations for the treatment of GBM in *Current Oncology*⁷. Our objective was to determine the extent to which

Canadian radiation oncologists have incorporated these guidelines into their practice. Specifically, we were interested in determining whether radiation oncologists across the country rigorously follow either of the RTOG or EORTC guidelines, or whether they have modified the guidelines to create individual or institution-specific prescriptions.

2. MATERIALS AND METHODS

Canadian radiation oncologists treating central nervous system (CNS) malignancies were identified from individual cancer centre directories and Web sites, and through telephone queries to individual cancer centres. It was possible to identify 39 radiation oncologists across the country who, as one of their primary sites, treat CNS malignancies.

A 20-item questionnaire (Table I) was developed to survey various aspects of GBM external-beam radiation therapy:

- Guidelines used
- Types of fusion protocols used
- Number of treatment phases
- Margins for volume delineation
- Constituents of treatment volumes
- Anatomic constraints
- Dose constraints

An online survey tool, Survey Monkey (www.surveymonkey.com), was used to collect the data. Each of the 39 identified radiation oncologists was sent an e-mail message with a link to the online survey. Message recipients that did not respond within 2 weeks were contacted by repeat e-mail message or a telephone call, or both. Responses were tabulated for presentation, but statistical analyses were not performed because of the limited sample size.

3. RESULTS

The survey response rate was 56%. Representative responses were received from academic centres across Canada, with the exception of the University of Saskatchewan, whose radiation oncologists did not respond to the survey. Community radiotherapy centres were not polled. As shown in Table II, the responses were otherwise well distributed across the country, thus eliminating overrepresentation from any individual centre.

3.1 Guidelines and Imaging

Table III summarizes the recommendations by RTOG and EORTC for the radiotherapy component of GBM treatment. Of the survey respondents, 32% reported that they strictly follow RTOG guidelines, and 14.3%, that they strictly follow EORTC guidelines. However, most respondents (56%) reported following in-house

or centre-specific guidelines [Figure 1(A)]. Figure 1(B) shows the distribution of guidelines used within each responding centre.

All respondents (100%) reported using MR fusion with planning computed tomography (CT) images. With regard to fusion type, 45% fuse both axial FLAIR (fluid-attenuated inversion-recovery) series and T1 Gd images; 17% fuse axial FLAIR only; and 38% fuse T1 Gd only with the planning CT scan. Within those respondents, 17% reported using other modalities when indicated—for example, SSFP (steady-state free precession), T1 without Gd, or adaptive planning with volumetric T1 Gd before boost.

3.2 Treatment Phases and Target Volumes

All respondents use either a 1- or 2-phase treatment plan, with 64% prescribing 1 phase of radiation treatment, and 37% prescribing treatment in 2 phases. Of the respondents treating in 1 phase, 61% treat the surgical cavity and enhancing tumour with a margin; 33% include the tumour edema in addition to the surgical cavity and tumour (Figure 2). For a prescription involving single-phase treatment, the total margin from gross tumour volume (GTV) to planning target volume (PTV) used by the respondents (Figure 3) was reported as 0.5 cm (6%), 1 cm (6%), 1.5 cm (25%), 2.0 cm (56%), 2.5 cm (25%), or 3 cm (12.5%), with some respondents selecting more than one standard margin.

Of respondents treating in 2 phases, 90% include peritumoural edema in phase 1 of the treatment. In phase 2, respondents reported using total margins from GTV to PTV (Figure 4) of 1 cm (10%), 2.0 cm (40%), 2.5 cm (30%), 3.0 cm (20%).

3.3 Dose and Fractionation to Targets

Our survey showed good agreement among respondents with respect to dose to primary targets. Doses to 60 Gy are prescribed by 90% of respondents. One respondent reported prescribing to 61.8 Gy, and another, to 59.40 Gy. For all respondents prescribing 60 Gy, fractionation was 2 Gy per fraction. The respondent prescribing 61.8 Gy reported using adaptive planning for treatments and prescribing 2.5 Gy per fraction. The respondent prescribing 59.40 Gy reported using 1.8 Gy per fraction.

Half of the respondents reported following centre-specific guidelines in specifying dose to critical structures. Another 35% reported strict use of RTOG guidelines, and 7%, strict use of EORTC guidelines. Seven percent of respondents reported that they did not follow any specific guidelines (Figure 5).

Critical structures include optic chiasm, brainstem, and optic nerve. Individual answers about dose constraints to each of those structures ranged from 45 Gy to 60 Gy for chiasm, 54 Gy to 60 Gy for brainstem, and 45 Gy to 60 Gy for optic nerve.

TABLE 1 Treatment for glioblastoma multiforme: patterns of practice survey

<p>1. Do you treat CNS?</p> <ul style="list-style-type: none"> • Yes • No <p>2. For treatment planning and volume delineation of high-grade CNS lesions, do you utilize MR fusion imaging?</p> <ul style="list-style-type: none"> • Yes • No <p>3. If applicable, MR fusion images consist of:</p> <ul style="list-style-type: none"> • Single fusion axial FLAIR • Single fusion T1 Gad • Double fusion axial FLAIR and T1 Gad • Single fusion other series • Double fusion other series • Fusion is not utilized • Other protocol (please specify) <hr/> <p>4. Do you have specific guidelines at your centre for delineating GTV, CTV, and PTV?</p> <ul style="list-style-type: none"> • Yes • No <p>5. Your GTV, CTV, and PTV volume delineations for high-grade CNS disease adhere to:</p> <ul style="list-style-type: none"> • EORTC guidelines • RTOG guidelines • Centre-specific guidelines • No specified guidelines <p>6. For high-grade CNS disease, the total margin from GTV to PTV (including CTV) that you use is:</p> <ul style="list-style-type: none"> • 0.5 cm • 1.0 cm • 1.5 cm • 2.0 cm • 2.5 cm • 3.0 cm <p>7. Do you treat high-grade CNS tumours in one, two, or multiple phases?</p> <ul style="list-style-type: none"> • One phase (go to question 8) • Two phases (go to question 9) • More than two phases (go to question 11) <p>8. If treating in one phase only, the volume treated includes:</p> <ul style="list-style-type: none"> • Surgical cavity only, plus margin • Enhancing tumour only, plus margin • Surgical cavity, plus enhancing tumour, plus margin • Surgical cavity, plus enhancing tumour, plus edema, plus margin • I do not treat in one phase <p>9. If treating in two phases, phase 1 volume includes:</p> <ul style="list-style-type: none"> • Surgical cavity, plus edema, plus margin • Surgical cavity, plus margin • I do not treat in two phases <p>10. If treating in two phases, phase 2 includes:</p> <ul style="list-style-type: none"> • Enhancing tumour, plus margin • Surgical cavity, plus margin • Surgical cavity, plus enhancing tumour, plus margin • I do not treat in two phases <p>11. Do you limit volumes/margins to anatomic barriers?</p> <ul style="list-style-type: none"> • Yes • No 	<p>12. If applicable, please select all structures that margins are limited to:</p> <ul style="list-style-type: none"> • Skull • Bone • Tentorium • Corpus callosum • Falx • I do not limit treatment volumes <p>13. What margins do you allow for CTV into skull and bone?</p> <ul style="list-style-type: none"> • 0.5 cm • 1.0 cm • 1.5 cm • I do not limit margins <p>14. What margins do you allow for CTV into tentorium and corpus callosum?</p> <ul style="list-style-type: none"> • 0.5 cm • 1.0 cm • 1.5 cm • I do not limit margins <p>15. What is the total dose for treatment of grade 4 disease within your practice (cGy)? Please specify</p> <hr/> <p>16. What is the fraction size of treatment for grade 4 disease within your practice (cGy)? Please specify</p> <hr/> <p>17. PTV (including PTV1 and PTV2, if applicable) is covered by which isodose line?</p> <ul style="list-style-type: none"> • 100% • 95% • 90% • Other (Please specify) <hr/> <p>18. Do you use pre-specified guidelines for limiting dose to critical structures?</p> <ul style="list-style-type: none"> • Yes • No <p>19. If yes, which set of guidelines do you use for limiting dose to critical structures?</p> <ul style="list-style-type: none"> • EORTC guidelines • RTOG guidelines • Centre-specific guidelines • I do not use guidelines • Other (please specify) <hr/> <p>20. What is your maximum allowable dose to (cGy): Optic chiasm (please specify)</p> <hr/> <p>Brainstem (please specify)</p> <hr/> <p>Optic nerve (please specify)</p> <hr/> <p>CNS = central nervous system; MR = magnetic resonance; FLAIR = fluid-attenuated inversion recovery; Gad = with gadolinium; GTV = gross tumour volume; CTV = clinical treatment volume; PTV = planning treatment volume; EORTC = European Organisation for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group.</p>
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4. DISCUSSION AND CONCLUSIONS

Recently in *Current Oncology*, the Canadian GBM committee published recommendations for the treatment of GBM⁷. The recommendations call for a multidisciplinary approach to treatment; tissue banking; establishment of 1p, 19q, and MGMT methylation status; and incorporation of primary surgery, follow-up MR imaging, and adjuvant chemoradiotherapy into overall treatment of GBM. Specifically, the radiotherapy component is recommended to consist of external-beam radiation to a dose of 50–60 Gy in 2-Gy

fractions given over 5–6 weeks. In addition, the committee recommended that the clinical target volume (CTV) be identified with T1 Gd-contrast-enhanced MR imaging with a margin of 2–3 cm.

The current guidelines for the treatment of GBM, as they pertain to details of radiotherapy, are put forward with consideration of aggressive local recurrence, which ultimately accounts for poor outcome. Initial surgical data by Wallner *et al.*⁸ on patients with recurrent GBM after primary treatment with surgery showed that 78% of patients recurred within 2 cm of the presurgical margin. Moreover, 56% recurred within 1 cm of the presurgical margin. In that study, the extent of edema did not correlate with greater distance to recurrence, and large tumours were not more likely to recur at greater distances. A subsequent study by Liang *et al.*⁹ on patients with grade 3 or 4 astrocytomas treated with radiotherapy to the original tumour showed that 100% of patients recurred within 2 cm and that 10% had multifocal recurrences. In that study, 4500 cGy was given to the primary tumour plus 3 cm, with a 1500-cGy boost to the primary plus 1.5 cm. Some of the patients received intra-arterial bromodeoxyuridine, but administration of that agent did not affect the results. In a retrospective series of 34 patients treated either with whole-brain radiotherapy and conformal boost, or entirely with three-dimensional conformal radiotherapy, Oppitz *et al.*¹⁰ showed that all GBM recurrences occurred within the 90% isodose line when targets were contoured around the original preoperative contrast-enhancing tumour plus a 2-cm margin. More recently, Chang *et al.*¹¹ looked at the relationship between peritumoural edema location and recurrence patterns. In their series, 48 patients were treated with postoperative radiotherapy. The prescribed dose was 50 Gy to the original resection cavity and residual tumour (GTV)

TABLE II Distribution of survey respondents across Canada

Institution	Respondents (n)
British Columbia Cancer Agency, BC	3
Tom Baker Cancer Centre, AB	2
Cancer Care Manitoba, MB	2
London Health Sciences Centre, ON	2
Hamilton Health Sciences, ON	1
Sunnybrook Regional Health Centre, ON	3
Princess Margaret Hospital, ON	3
The Ottawa Hospital Cancer Centre, ON	1
McGill University, QC	2
Centre hospitalier de l'Université de Montreal, QC	1
Nova Scotia Cancer Centre, NS	1
New Brunswick Cancer Network, NB	1

TABLE III Guidelines (radiotherapy details) from the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) for the treatment of glioblastoma multiforme

Guideline			
RTOG (from RTOG 97-10 ⁶)		EORTC (from EORTC 22981/22961 ⁵)	
<i>Phase 1 of 2</i>		<i>Phase 1 of 1</i>	
Treatment volume	Contrasting enhancing lesion, plus peritumoural edema, plus 2-cm margin to PTV	Treatment volume	Contrast enhancing lesion (GTV), plus 2-cm (or 3-cm) to CTV
Treatment dose	46 Gy in 2.0-Gy fractions	Treatment dose	50–60 Gy in 1.8-Gy to 2.0-Gy fractions
<i>Phase 2 of 2</i>			
Treatment volume	Contrast enhancing lesion (preoperative MR imaging), plus 2.5-cm margin to PTV		
Treatment dose	14 Gy boost in 2.0-Gy fractions		

PTV = planning target volume; GTV = gross tumour volume; CTV = clinical target volume; MR = magnetic resonance.

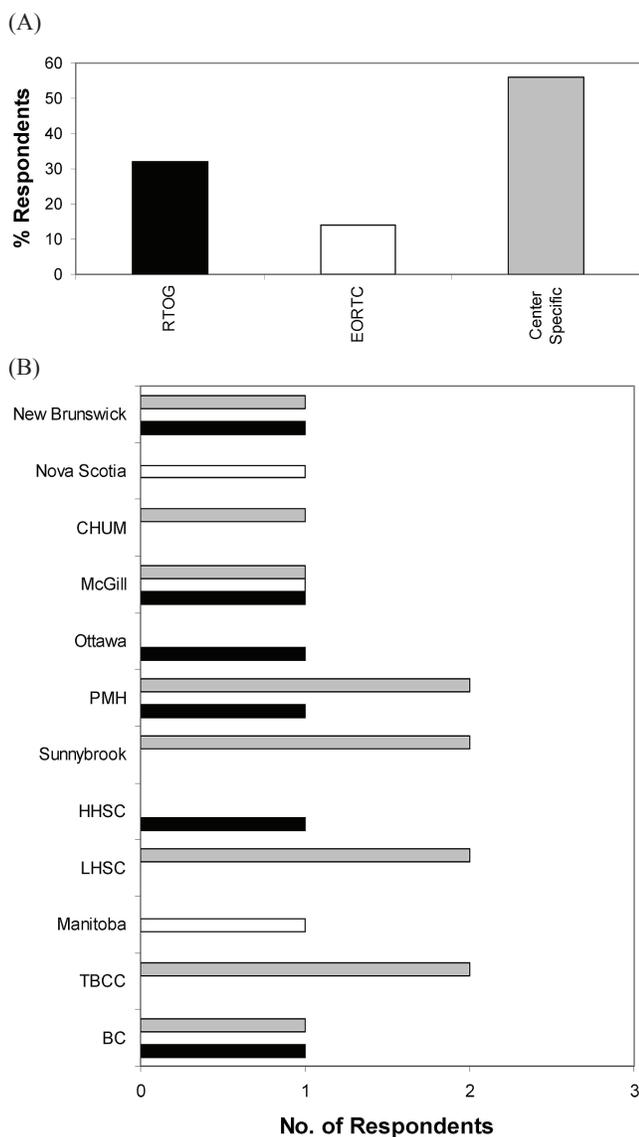


FIGURE 1 (A) Variability in the use of guidelines by radiation oncologists across Canada prescribing treatment for glioblastoma multiforme. (B) Breakdown, by institution, of guideline use. Black bars = Radiation Therapy Oncology Group (RTOG) guideline; white bars = European Organisation for Research and Treatment of Cancer (EORTC) guideline; grey bars = centre-specific guideline; BC = British Columbia Cancer Agency; TBCC = Tom Baker Cancer Centre, Calgary, AB; Manitoba = Cancer Care Manitoba; LHSC = London Health Sciences Centre, London, ON; HHSC = Hamilton Health Sciences, Hamilton, ON; Sunnybrook = Sunnybrook Health Sciences Centre, Toronto, ON; PMH = Princess Margaret Hospital, Toronto, ON; Ottawa = The Ottawa Hospital Cancer Centre, Ottawa, ON; McGill = McGill Cancer Centre, Montreal, QC; CHUM = Centre hospitalier de l'Université de Montreal, Montreal, QC; Nova Scotia = Nova Scotia Cancer Centre, Halifax, NS; New Brunswick = New Brunswick Cancer Network.

plus a 2-cm margin, followed by a boost of 10 Gy to the GTV alone. Hypothetical plans incorporating edema (based on RTOG 97-10 guidelines) were

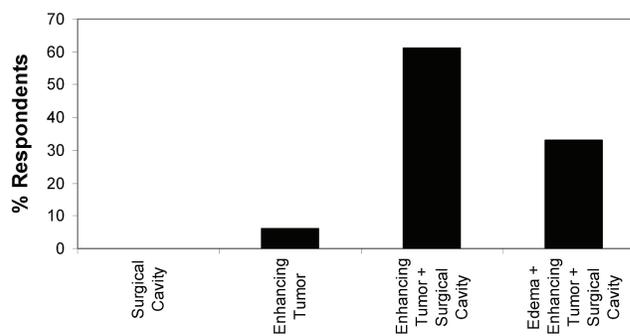


FIGURE 2 Variability in target volume components within a single-phase treatment plan.

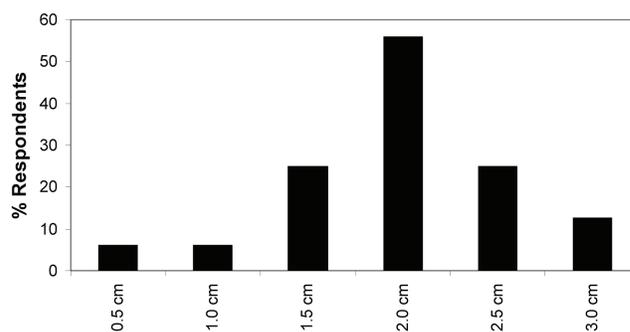


FIGURE 3 Variability in margin (from gross treatment volume to planning treatment volume) used in a single-phase treatment plan.

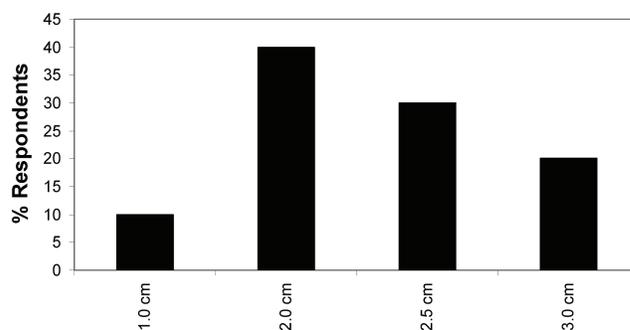


FIGURE 4 Variability in margin (from gross treatment volume to planning treatment volume) used in phase 2 of a 2-phase treatment plan.

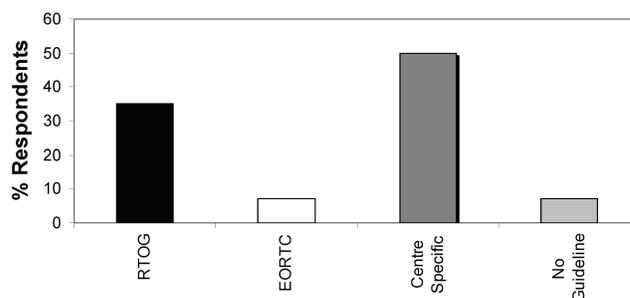


FIGURE 5 Variability in the use of guidelines by radiation oncologists across Canada to limit dose to critical structures. RTOG = Radiation Therapy Oncology Group guideline; EORTC = European Organisation for Research and Treatment of Cancer guideline.

constructed, but not given. Of all failures, 90% (43 patients) were in-field or within the smaller treatment volumes (excluding edema). The 5 remaining marginal and distal recurrences failed to be covered by the 46-Gy isodose line, even when overlaid by the RTOG plan incorporating edema volume, showing them to be true marginal recurrences.

As treatment of GBM has evolved to incorporate temozolomide, patterns of recurrence have been studied further. McDonald *et al.*¹² examined a series of 62 patients who were treated postoperatively with radiation and chemotherapy. Initial CTV volume included residual tumour plus cavity plus 0.7 cm (median margin), followed by a boost volume of residual tumour plus 0.5 cm. The PTV margin varied from an additional 0.3 cm to an additional 0.5 cm. Initial dose was 46–54 Gy, followed by a boost to 60 Gy. Within the follow-up time, 37 patients progressed. On progression, 36 had imaging available, and for 34 of the 36, the recurrences were in-field; the other 2 patients had marginal recurrences.

Recognizing that local recurrence is critical to disease control, a number of dose-escalation studies have been done.

A phase II EORTC study¹³ looked at cohorts receiving 42 Gy, 48 Gy, 46 Gy, and 60 Gy in a 3-times-daily fractionation schedule. Acute toxicity (nausea and vomiting) was absent in 91% of the patients; 58% required steroids to be started or increased. The group receiving 60 Gy required more steroids. Overall, however, there was no difference in survival between the groups.

A phase II RTOG trial by Cardinale *et al.*¹⁴ evaluated the benefit of fractionated stereotactic boost. All patients were treated to 50 Gy, followed by weekly stereotactic boosts to 70 Gy or 78 Gy, with sequential carmustine. Grade 4 toxicity occurred acutely in 3 patients and late in 1 patient. A comparison with historical controls showed no survival difference. As previously known, survival correlated with extent of resection.

Sultanem *et al.*¹⁵ studied a series of 25 patients treated with intensity-modulated radiotherapy in a hypofractionated protocol. The PTV received at least 40 Gy in 20 fractions; the GTV received 60 Gy in 20 fractions (3 Gy per fraction). Treatments were well tolerated, and no acute or late toxicities were observed at the median follow-up of 8.8 months.

More recently, RTOG 98-03¹⁶ evaluated four groups of patients all receiving 46 Gy in phase 1 and then receiving a boost of 66 Gy, 72 Gy, 78 Gy, or 84 Gy. Radiation was given concurrently with carmustine. Grade 3 or 4 toxicity was not higher with higher doses, and no dose-limiting acute toxicities were observed. Median survival was found to be higher with doses of 84 Gy than with doses of 66 Gy, regardless of whether the irradiated volume was small ($PTV < 75 \text{ cm}^3$) or large ($PTV > 75 \text{ cm}^3$).

The greater frequency of GBM tumour recurrence in-field (and less so marginally) suggests that optimal disease control depends on dose to the primary tumour as opposed to extent of margins incorporating tumoural edema. Our survey demonstrates variability in the margins and guidelines used in GBM treatment across Canada:

- More than half of responding radiation oncologists (53%) indicated that they follow in-house guidelines when treating GBM. A smaller fraction of physicians (32%) indicated that they follow RTOG guidelines strictly, and an even smaller fraction (14%), that they follow EORTC guidelines strictly.
- In defining treatment volumes, we observed variability in the MR imaging modality of choice, ranging from single fusion of T1 Gd (38%) and single fusion of MR FLAIR (17%), to double fusion of T1 Gd and FLAIR (45%) with planning-CT simulation series.
- The ratio of physicians treating GBM in 1 phase to those treating in 2 phases is roughly 3:2.
- Within the group of physicians treating in 1 phase, we observed heterogeneity in the treatment of edema (33%) as compared with no edema (61%). And regardless of the number of phases, we also observed variability in the margin between the GTV and PTV (for treatment in 2 phases, this observation is applicable to phase 2 only). There is, however, very good agreement in prescribed doses.

The variability in margins, phases, and imaging likely reflect personal and anecdotal experience of balancing optimal treatment outcome with consideration of treatment toxicity. In light of the studies just discussed, it would appear that most recurrences are found in close proximity to the original tumour and that the extent of peritumoural edema may not necessarily correlate with recurrence pattern. Dose to the primary tumour is certainly a key factor in treatment outcome, but no head-to-head trial has yet confirmed the best modality of treatment with respect to optimal volumes, margins, and phases in the current era of temozolomide, MR imaging, and conformal delivery. Initial guidelines were developed before the use of chemotherapy and MR imaging as standards of treatment, and physicians may be recognizing those factors and therefore modifying their own prescriptions and volumes when treating with greater conformal technology. Conformal radiotherapy and MR imaging mean that smaller volumes can be treated more precisely, sparing normal structures and toxicities to a larger extent than in the past. Those factors are likely reflected in our survey. Thus, in the current era of MR imaging, fusion, and more-conformal radiotherapy, new studies are needed to further define optimal treatment volumes, doses, and phases and to determine whether smaller and more-conformal volumes can maintain (or even improve) known outcomes while continuing to reduce treatment toxicity.

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