The Population Benefit of Radiotherapy for Malignant Brain Tumors: Local Control and Survival Estimates for Guideline-Based Use

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Abstract

Objective: To estimate the population benefit of radiotherapy (RT) for primary malignant brain tumors if evidence-based guidelines were routinely followed. **Methods:** This study investigated 5-year local control (LC) and 2- and 5-year overall survival (OS) benefits. RT benefit was the absolute proportional benefit of RT alone over no RT for radical indications, and over surgery alone for adjuvant indications. Chemo-radiotherapy (CRT) benefit was the absolute incremental benefit of concurrent chemotherapy and RT over RT alone. Decision tree models were adapted to define the incidence of each indication. Citation databases were systematically queried for the highest level of evidence defining indication benefits. Meta-analysis was performed if there were multiple sources of the same evidence level, and deterministic and probabilistic sensitivity analysis was also performed. **Results:** Among all patients with malignant brain tumors, 82% had indications for curative- or adjuvant-intent RT. The magnitude of benefit was based on level I or II evidence in 44% of all patients. A total of 25 relevant studies were used to quantify indication benefits. All RT benefit included in the model was irreplaceable. For malignant brain tumors, the estimated population benefit for RT alone was 9% for 5-year LC (95% CI, 7%–10%), 9% for 2-year OS (95% CI, 8%–11%), and 5% for 5-year OS (95% CI, 4%–5%). The incremental benefit of CRT was 1% for 5-year LC (95% CI, 0%–2%), 7% for 2-year OS (95% CI, 4%–11%), and 3% for 5-year OS (95% CI, 1%–5%). The model was robust in sensitivity analysis. **Conclusions:** When optimally used, RT provides an important benefit for many patients with malignant brain tumors. The model provided a robust means for estimating the magnitude of this benefit.

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Background

Radiotherapy (RT) is vital to the management of primary malignant brain tumors. It has been estimated that 80% of patients with malignant brain tumors have an indication for RT because of superior local control (LC), survival, or palliative outcomes.¹ The magnitude of the population benefit of RT, if optimally used according to guidelines, in patients with malignant brain tumors has not previously been estimated. This infor-

mation would be of use for economic analysis, planning, and priority setting.^{2,3}

This study aimed to estimate the population overall survival (OS) and LC benefits of RT for malignant brain tumors. The distinct benefits of RT, separate from the benefits of other treatment modalities, are considered. The incremental benefit of radiosensitizing concurrent chemoradiation (CRT) over RT alone is described. This study used an evidence-based approach,

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building on well-described whole-population RT demand models.¹⁻⁴

Methods

Definitions of Benefit

End Points: This study investigated 5-year actuarial LC and 2- and 5-year OS benefits. The distinct LC and OS benefits of RT alone and concurrent CRT were considered. Palliative benefits were not investigated.

RT Benefit: RT benefit was defined as the absolute proportional benefit (LC or OS) of RT alone over no treatment for radical RT indications. For adjuvant indications, RT benefit was the benefit of RT over surgery alone. For radical indications, the survival benefit was estimated to be equal to the survival of patients treated with RT alone (eg, 5-year RT benefit of 20% if 5-year OS was 20%), unless otherwise stated. LC was defined based on disease control within the radiated field. When these data were unavailable, LC was conservatively estimated based on progression-free survival (PFS). When PFS was unavailable, other survival data was used as described in Table 1.

CRT Benefit: CRT benefit was the incremental benefit (LC or OS) of CRT over RT.

Irreplaceable Benefit of RT: Irreplaceable benefit of RT was defined based on indications where there was no standard-of-practice alternative to RT agreed upon by guidelines. Irreplaceable population LC and OS benefits were estimated.

Population Benefit of RT: Population benefit of RT described the proportion of the population deriving benefit from RT if used according to guidelines compared with no use of RT. This benefit was the proportion of patients benefiting from RT among all patients with malignant brain tumors, rather than an average benefit among patients requiring RT.

Estimation of Incidence of RT Indications

We used a previously developed RT demand model describing the malignant brain tumor population.^{1,4} This decision tree model described the proportion of patients requiring RT according to evidence-based guidelines. TreeAge Pro 2008 (TreeAge Software, Inc, Williamstown, MA) was used for model development, population benefit estimation, and sensitivity

analysis. Each tree described groups of patients, with each additional branch further subdividing patients into progressively smaller subgroups. Each terminal branch described a unique set of conditions defining groups for which RT was or was not indicated. RT was indicated based on better survival, LC, or was quality of life, or a combination of these. The proportion of cases with each RT indication was defined based on epidemiologic data defining the incidence of disease- and patient-related factors. The highest level of epidemiologic data was used, according to a predefined hierarchy.⁵

The RT demand model was adapted in cases for which there were subgroups in a given branch or terminal node with different RT benefits (eg, groupings of age, performance status [PS]) or different RT indications (eg, radical, adjuvant). The same method used to develop the original demand model was applied in these cases.

Systematic Review for RT Indication Benefits

Systematic review was performed in order to identify the highest level of valid and generalizable evidence defining each RT indication benefit. Data identified from the highest evidence level were used according to the National Health and Medical Research Council (NHMRC) evidence hierarchy.⁶ MEDLINE, all evidence-based medicine sources, and Embase records in Ovid were queried ([see supplemental eAppendix 1, available with this article at JNCCN.org](#)). Only studies published in 1990 or later were considered, except where stated otherwise. Literature searches were completed January 2015 through March 2015. Consideration was given to the technical quality of RT used wherever possible (eg, use of MRI for treatment planning, dose, target volume). Population-based SEER data were also queried. To ensure completeness of the search strategy, hand searches of journal article reference lists were performed. In cases when there were multiple sources of the same evidence level, meta-analysis was performed for homogeneous sources.

Statistical Analysis

A generic inverse-variance meta-analysis was used to determine pooled estimates. Review Manager 5.3 (The Nordic Chochrane Centre, Copenhagen, Denmark) was used. Standard errors were determined for each benefit estimate. Estimates derived from pub-

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Table 1. Malignant Brain Tumor OS and Local Control Benefit of RT for Patients With Good Performance Status by Indication (Absolute)

Clinical Attribute	Proportion of All Cases	Treatment Indication	5-y Local Control ^b (SE)		2-y OS (SE)		5-y OS (SE)		Level of Evidence ^b (RT/CRT)	References (RT/CRT)
			RT	CRT	RT	CRT	RT	CRT		
Glioblastoma, age <70 y, CRT	.30	IC	1% (0.7)	3% (1.5)	11% (1.8)	18% (8%, 28%) ^c	2% (1.0)	9% (3%, 17%) ^c	I/I	(53,57)/(21,53,58)
Glioblastoma, age <70 y, RT alone	.09	IC	0% ^d	0%	7% (3.9)	0%	0%	0%	IV/NA	(22)/NA
Glioblastoma, age ≥70 y	.14	IC	0% ^d	0%	0%	0%	0%	0%	II/NA	(26)/NA
Anaplastic astrocytoma	.07	IC	16% ^d (4.1)	0%	31% (4.6)	0%	16% (4.1)	0%	IV/NA	(38–40)/NA
Anaplastic oligodendroglioma & anaplastic oligoastrocytoma	.03	IC	24% (1.9)	0%	24% (1.9)	0%	24% (1.9)	0%	IV/NA	(43–45)/NA
Low-grade glioma, adjuvant RT	.01	IA	46% (4.8)	0%	0%	0%	0%	0%	IV/NA	(46–49)/NA
Low-grade glioma, salvage RT	.04	IC	40% ^d (14.1)	0%	0%	0%	0%	0%	IV/NA	(48,50,51)/NA
Ependymoma, low-grade, subtotal resection	.02	IC	7% (2%, 13%) ^c	0%	3% (1%, 5%) ^c	0%	3% (1%, 5%) ^c	0%	III-2/NA	(59,60)/NA
Ependymoma, high-grade	.02	IC	38% (5.0)	0%	38% (5.0)	0%	38% (5.0)	0%	IV/NA	(59)/NA
Medulloblastoma, age <3 y	<.01	IC	21% ^e (9.2)	0%	21% (9.2)	0%	21% (9.2)	0%	IV/NA	(61)/NA
Medulloblastoma, age 3–17 y, M0–M1	.01	IC	60% ^e (5.5)	0%	84% (3.9)	0%	65% (5.6)	0%	IV/NA	(62)/NA
Medulloblastoma, age 3–17 y, M2–M3	<.01	IC	64% (7.0)	0%	81% (5.1)	0%	73% (6.0)	0%	IV/NA	(63)/NA
Medulloblastoma, age >17 y	.01	IC	65% (9.0)	0%	93% (4.3)	0%	75% (9.0)	0%	IV/NA	(64)/NA
PNETs and other embryonal tumors	.01	IC	46% ^e (2.0)	0%	57% (1.9)	0%	46% (2.0)	0%	IV/NA	(65)/NA

Abbreviations: CRT, chemoradiotherapy; IA, irreplaceable adjuvant treatment; IC, irreplaceable curative treatment; NA, not applicable OS; overall survival; PNETs, primitive neuroectodermal tumors; RT, radiotherapy alone.

^aLocal control was defined based on progression-free survival, except where noted.

^bNational Health and Medical Research Council evidence hierarchy: I: systematic review of level II studies; II: randomized controlled trial; III: comparative studies (III-2, III-3) or pseudorandomised controlled trial (III-1); IV: case series with either posttest or pretest/posttest outcomes.

^c95% CI reported as distribution is skewed. Supplemental eAppendix 2 describes the benefit estimation for this indication.

^dLocal control defined based on OS, because no local control or progression-free survival data were available.

^eLocal control defined on event-free survival or relative survival.

lished survival curves were used if error estimates were not provided in data sources. Estimates were derived based on Borkowf's hybrid variance estimator,⁷ with the number of events and censored cases estimated using an approach derived from Parmar et al⁸ and a publicly available spreadsheet published by Tierney et al.⁹

Estimation of the Population Benefit of RT

The benefit of RT for each indication was associated with the relevant terminal branch in the decision tree. The population benefit of RT was estimated by determining the product of the population proportion with an RT indication and its estimated benefit, and summing all such products.

Sensitivity Analysis

Deterministic and probabilistic sensitivity analysis was performed. Uncertainties in the incidence of each RT indication and in its associated benefit were considered. Uncertainties in incidence were due to (1) uncertainty regarding epidemiologic data defining the incidence of indications, (2) uncertainty/controversy regarding indications for RT, and (3) uncertainty regarding frequency of optimal use when other equal options existed. Probabilistic multivariate analysis was performed using Monte Carlo simulation. All sources of uncertainty, including statistical uncertainty in each benefit estimate, were simultaneously considered for LC and OS benefits. RT and CRT benefits were separately considered. We performed 10,000 iterations of each simulation. A 95% CI for each set of iterations was determined based on 2.5th and 97.5th percentile benefit estimates.

Results

According to guidelines, 3 general uses of curative-intent RT for primary malignant brain tumors were: (1) radical treatment, (2) adjuvant (postoperative) treatment, and (3) treatment of recurrent or progressive disease (Figures 1 and 2). Modifications of the original malignant brain tumor RT demand model are summarized herein.

Radical RT for Good PS Glioblastoma Multiforme

Given uncertainties in management and RT benefit for elderly patients with good PS, the updated model was stratified based on age with a cutoff of 70 years or

older, defining 'elderly' ([supplemental 1](#)). The small group of patients younger than 70 years with good PS who were unfit for concurrent temozolomide was also considered.

Grade II Glioma

Given that key trials reported outcomes on low-grade astrocytoma, low-grade oligodendroglioma, and low-grade oligoastrocytoma together, these were grouped together in the updated model ([supplemental eTable 1](#)).

Most guidelines considered use of adjuvant RT a standard option for high-risk grade II glioma, with use of salvage RT for symptomatic, progressive, or recurrent disease after surgery.^{10–19} The EORTC scheme was used to stratify patients ([supplemental eTable 1](#)).²⁰ Because of uncertainty in the proportion of high-risk patients in the population with RT indications, and optimal risk definition, a sensitivity analysis was performed.

As in the original model, patients identified as having "astrocytoma not otherwise specified" or "other astrocytomas" were considered to most closely represent those with low-grade gliomas (LGGs).

Medulloblastoma and Other Embryonal Tumors

Given its heterogeneity, this group was stratified. Medulloblastoma was the predominant variety. Medulloblastoma was stratified by age given variation in outcome by age group, and also given that studies often reported only on specific ages ([supplemental eTable 1](#)).

RT Indication Benefits

RT benefits are summarized in Table 1. Key findings and decisions made in defining RT indication benefit are summarized herein. LC was often defined based on PFS (Table 1). Considerations for less common histologies are provided in [supplemental eAppendix 2](#).

Glioblastoma

Patients Younger Than 70 Years With Good PS:

The 2013 Cochrane meta-analysis was used to estimate the survival benefit of CRT for patients with indications.²¹ No data were identified to adequately estimate the benefit of RT for the small group of patients younger than 70 years with good PS treated with RT alone due to contraindications to temozolomide. Out-

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Figure 1. Five-year overall survival benefit of RT alone for malignant brain tumors (embryonal tumor model collapsed; see Figure 2). A similar tree was generated for RT alone local control benefit and for CRT benefits. The value in the rectangular boxes (rollback values) is the population RT benefit for the adjacent stem of the model. The summary benefit estimates for all brain cancer in Table 2 were the rollback values taken from the primary stem (labeled “Malignant Brain Tumors”). The column labeled “Benefit” is the absolute proportional RT benefit associated with each adjacent treatment indication; “Total Proportion” is the proportion of all patients with malignant brain tumors with each treatment indication. Abbreviations: Astro, astrocytoma; CRT, chemoradiotherapy; NOS, not otherwise specified; OG/OA, oligodendroglioma/oligoastrocytoma; PS, performance status; RT, radiotherapy.

comes for patients younger than 70 years treated with more than 30 Gy but less than 60 Gy of RT alone from a large temozolomide-era case series were used.²²

Patients Aged 70 Years or Older With Good PS:

The literature was searched for relevant studies. Because both age and PS were strong prognostic factors for survival in glioblastoma, strict inclusion criteria were set for both.^{23–25} Studies were included if they reported on patients with a Karnofsky PS (KPS) of 70 or greater and aged 70 years or older, with a sample size of 20 or more ([supplemental eAppendix 1](#)). A total of 293 abstracts were identified.

One randomized trial was identified comparing RT and best supportive care.²⁶ There were significant benefits to RT, although there were no 2-year survivors in either study arm. Case series similarly reported poor outcomes.^{24,27–30}

CRT benefit was also considered. There were no randomized trials, but 9 nonrandomized studies were identified.^{24,27,30–36} Because nearly all series re-

ported 2-year survivors with CRT (range, 0%–24%), a 2-year survival benefit was considered in sensitivity analysis (Table 1). The median study values for 5-year LC and OS with CRT were nil; 5-year benefit was considered nil in the model.

RT for Anaplastic Glioma

RT outcomes for adult anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AOG), and anaplastic oligoastrocytoma (AOA) were considered ([supplemental eAppendix 1](#)). Studies published after 1999 were considered.

For AA, 2 Australian guidelines favored RT alone versus CRT.^{10,37} Studies reporting on patients treated with adjuvant or concurrent chemotherapy were excluded for the RT-alone benefit. An RT dose of 59 to 60 Gy delivered in 1.8 to 2.0 Gy per daily fraction was required and a sample size of 40 or greater.³⁷ A total of 3 case series were identified ([supplemental eTable 2](#)).^{38–40} OS was estimated based on the

Figure 2. Five-year overall survival benefit of radiotherapy alone for brain cancer (glioma tumor model collapsed; see Figure 1). A similar tree was generated for radiotherapy alone local control benefit and for chemoradiation benefits. Abbreviations: PNET, primitive neuroectodermal tumors; PS, performance status.

median study value due to data heterogeneity. LC benefit was conservatively estimated to be equal to the 5-year OS benefit, due to the lack of LC data.

AOG and AOA guidelines most often recommended postoperative RT, often in addition to adjuvant chemotherapy.^{10,12,15,18,37,41,42} Given the substantial impact chemotherapy had on survival, the OS benefit of RT was equated to the LC achieved with postoperative RT (supplemental eTable 3).^{43–45}

RT for Grade II Glioma

RT benefit was estimated for the common subtypes: astrocytoma, oligodendroglioma, and oligoastrocytoma. A systematic review was undertaken (supplemental eAppendix 1). Because there was no high-level evidence supporting improved OS with RT for LGG, only LC benefits were estimated. Adult studies published after 1999 reporting on more than 20 patients were considered. Studies reporting on adjuvant RT for unselected patients were excluded, as were data where most patients received adjuvant chemotherapy. Three studies were identified that described postoperative RT LC outcomes for patients with adverse features (supplemental eTable 4).^{46–49} Given the heterogeneity of risk definitions, the median study value of PFS was used to estimate LC benefit. There were limited data on salvage RT outcomes and a case mix of recurrent LGG.^{48,50,51} Sensitivity analysis was performed.

RT Population Benefit for Malignant Brain Tumors

Of all patients with primary malignant brain tumors, 82% had indications for adjuvant or curative RT ac-

cording to evidence-based guidelines. The magnitude of benefit was based on level I or II evidence in 44% of all patients. All RT benefits were considered irreplaceable. Overall, in univariate analysis, there was an 11% 5-year LC benefit (10% RT, 1% CRT), 15% 2-year OS benefit (9% RT, 6% CRT), and 8% 5-year OS benefit (5% RT, 3% CRT) (Figures 1 and 2). Table 2 provides a summary of RT population benefits for malignant brain tumors and common subtypes.

Sensitivity Analysis

In univariate sensitivity analysis, there were uncertainties in LC benefit for patients with LGG (proportion of patients without RT who experience recurrence and are then recommended to undergo salvage RT: 50%–100%; high-risk adjuvant RT LC benefit: 23%–46%; salvage RT LC benefit: 22%–40%; LGG that are high risk with RT indicated: 9%–50%) and ependymoma (grade II total resection LC benefit: 0%–7%). For OS benefit, there was uncertainty about the 2- and 5-year RT benefit for patients with grade II ependymoma who underwent total resection (0%–3%) and the 2-year CRT benefit for patients with glioblastoma multiforme (GBM) aged 70 years or older with good PS (0%–24%). The model was robust. The population RT LC benefit was most sensitive to the proportion of LGG without prior RT with salvage RT indicated (LC, 7.9%–10%), followed by LGG salvage RT benefit uncertainty (LC, 8.1%–10%) and LGG high-risk adjuvant RT benefit uncertainty (LC, 9.1%–10%); other variables had

little impact on RT LC. OS benefit variation was negligible for RT (eg, 5-year OS, 4.5%–4.6%), although CRT 2-year OS varied from 5.5% to 8.8% due to uncertainty regarding benefit in elderly patients with GBM.

Considering all of these uncertainties as well as statistical uncertainties in benefit simultaneously in multivariate sensitivity analysis, the 5-year population LC benefit of RT for malignant brain tumors was 8.5% (95% CI, 6.9%–10.3%), the 2-year OS benefit was 9.2% (95% CI, 7.7%–10.6%), and the 5-year OS benefit was 4.5% (95% CI, 3.7%–5.4%). The incremental population benefit of CRT over RT for malignant brain tumors was 0.9% for LC (95% CI, 0.0%–1.8%), 7.1% for 2-year OS (95% CI, 3.6%–10.8%), and 2.7% for 5-year OS (95% CI, 1.0%–5.1%).

Discussion

The population benefit of RT was estimated for malignant brain tumors when optimally used according to guidelines, including the incremental benefit of concurrent CRT over RT alone. Estimates were robust in sensitivity analysis. RT alone provided a 5-year population LC benefit of 8.5% (95% CI, 6.9%–10.3%), a 2-year OS benefit of 9.2% (95% CI, 7.7%–10.6%), and a 5-year OS benefit of 4.5% (95% CI, 3.7%–5.4%). The incremental population benefit of CRT over RT was 0.9% for LC (95% CI, 0.0%–1.8%), 7.1% for 2-year OS (95% CI, 3.6%–10.8%), and 2.7% for 5-year OS (95% CI, 1.0%–5.1%). It is emphasized that these benefits are factors that may be used with cancer incidence data to estimate the number of patients that could optimally benefit from RT in a population. For example, there are approximately 1,700 malignant brain tumors diagnosed in

Australia annually.⁵² Our findings suggest that each year in Australia, approximately 140 people (95% CI, 120–180) would derive a 5-year LC benefit and 80 people (95% CI, 60–90) a 5-year OS benefit from RT alone. CRT was estimated to provide additional benefits, with 20 people deriving a 5-year LC benefit (95% CI, 0–30) and 50 people deriving a 5-year OS benefit (95% CI, 20–90).

There are limitations. Most importantly, the model is limited by the quality of the available epidemiologic and RT outcome data. LC data were limited. For many indications, randomized trials were not available to define RT benefits; for example, involving the use of concurrent chemotherapy with RT for anaplastic (grade III) glioma or elderly patients with GBM and good PS. Uncertainties most often only impact subgroups in the model, limiting their impact on overall population benefit estimates. Where uncertainties were identified, sensitivity analysis was performed. Also, limitations in response assessment due to pseudoprogression may have led to underestimation of the CRT LC benefit for GBM.^{53,54}

RT benefits for malignant brain tumors were only considered for LC and OS, and only for specified time points (5-year LC and OS, 2-year OS). RT has other benefits for malignant brain tumors, which include maintaining and improving quality of life, limiting steroid requirements, and reducing the extent of surgery required for LC. RT may also provide shorter-term benefits in both survival and LC not considered in this report. For example, randomized trial evidence supports such benefits for elderly patients with GBM and good PS.²⁶ Other modalities are involved in malignant brain tumor management. Distinct benefits of treatments other than RT were not quantified. None of these are limitations fundamental to the method, and should be investigated in further studies.

Table 2. Malignant Brain Tumors OS and Local Control Population Benefit of Radiotherapy (Absolute)

Population of Interest	Clinical Attribute	Proportion of All Cases	5-y LC		2-y OS		5-y OS	
			RT	CRT	RT	CRT	RT	CRT
Malignant brain tumors	Whole population	1.0	10%	1%	9%	6%	5%	3%
Malignant brain, good PS	Glioblastoma	.53	1%	2%	8%	10%	1%	5%
Malignant brain, good PS	Grade III glioma (Astro, OG, OA)	.09	18%	0%	29%	0%	18%	0%
Malignant brain, good PS	Grade II glioma (Astro, OG, OA)	.05	42%	0%	0%	0%	0%	0%
Malignant brain, good PS	Ependymoma	.05	13%	0%	12%	0%	12%	0%
Malignant brain, good PS	Medulloblastoma	.02	57%	0%	77%	0%	63%	0%

Abbreviations: Astro, astrocytoma; CRT, concurrent chemoradiation; LC, local control; OA, oligoastrocytoma; OG, oligodendroglioma; OS, overall survival; PS, performance status; RT, radiotherapy alone.

The model used has a number of notable strengths.³ It is robust to uncertainties underlying the incidence of RT indications or the associated treatment benefit. The greatest uncertainty in the malignant brain tumor model was for patients with GBM aged 70 years or older with good PS. However, this impacted only the CRT 2-year OS benefit model. A broad range of possibilities were considered (0%–24% of patients deriving a 2-year OS benefit). Despite this broad range, the absolute proportional 2-year OS population CRT benefit varied from 5.5% to 8.8%. In multivariate sensitivity analysis considering this and all other uncertainties, the CRT 2-year OS benefit was still robust (95% CI, 3.6%–10.8%).

Additionally, the model is rapidly adaptable. For example, where epidemiologic parameters have been reported, RT population benefit estimates can be estimated for other settings. Globally, there were 256,213 brain and nervous system tumors diagnosed in 2012 alone.⁵⁵ Adaption of the model to the global cancer population requires consideration. Because the results are reported in terms of absolute proportional benefit, they can be readily adapted when the number of incident malignant brain tumor cases in a population is known according to case mix. Results generated in this way for other cancers were used by the Union for International Cancer Control's Global Task Force on Radiotherapy for Cancer Control to develop an investment case for RT in developing countries.⁵⁶ The model is transparent, with assumptions visible to audit and review. As new data becomes available, the model can be readily updated. For example, if a new CRT benefit were proven in randomized controlled trials, this could be included.

Conclusions

RT provides important and irreplaceable benefits to many patients in the malignant brain tumor population when optimally used according to guidelines. This includes an important contribution from protocols with radiosensitizing concurrent chemotherapy. The benefit model that was used was robust in sensitivity analysis.

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