

Hypofractionated Stereotactic Radiation Therapy: An Effective Therapy for Recurrent High-Grade Gliomas

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A B S T R A C T

Purpose

Salvage options for recurrent high-grade gliomas (HGGs) are limited by cumulative toxicity and limited efficacy despite advances in chemotherapeutic and radiotherapeutic techniques. Previous studies have reported encouraging survival results and favorable toxicity with fractionated stereotactic radiotherapy, and small studies have shown similar benefit using a shortened course of hypofractionated stereotactic radiation therapy (H-SRT). We sought to determine the efficacy and toxicity profile of H-SRT alone or in addition to repeat craniotomy or concomitant chemotherapy.

Patients and Methods

Between 1994 and 2008, 147 patients with recurrent HGG were treated with H-SRT (median dose, 35 Gy in 3.5-Gy fractions). Cox regression models were used to analyze survival outcomes. Variables included age, surgery before H-SRT, time to first recurrence, reirradiation dose, inclusion of chemotherapy with H-SRT, and gross tumor volume (GTV).

Results

Younger age ($P = .001$), smaller GTV ($P = .025$), and shorter time between diagnosis and recurrence ($P = .034$) were associated with improvement in survival from H-SRT. Doses of radiation ≥ 35 Gy approached significance ($P = .07$). There was no significant benefit of surgical resection or chemotherapy in this population when analysis was controlled for other prognostic factors.

Conclusion

H-SRT was well tolerated and resulted in a median survival time of 11 months after H-SRT, independent of re-operation or concomitant chemotherapy. Patients who experienced recurrence within 6 months after initial treatment had an excellent response and should not be disqualified from H-SRT. This is the largest series to examine the efficacy and tolerability of H-SRT in recurrent HGG.

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INTRODUCTION

Malignant gliomas are the most frequently diagnosed primary brain tumor, with 2.96 newly diagnosed occurrences per 100,000 people per year in the United States,¹ and invariably recur despite definitive primary therapy.^{2,3} Treatment options for recurrent gliomas include resection, chemotherapy, focused radiation therapy (RT), and investigational treatment modalities. Resistance to chemotherapy agents and cumulative toxicity associated with retreatment limits the efficacy of salvage treatments despite recent advances in chemotherapeutic and radiotherapeutic techniques.^{3,4}

Both single-fraction stereotactic radiosurgery (SRS) and brachytherapy have been reported to have modest utility as palliative salvage interventions; however, both have been associated with high rates of re-operation because of associated

toxicity.⁵⁻¹² Fractionated stereotactic radiotherapy (SRT) may offer some improvement in overall survival with minimal toxicity for patients with previously treated malignant gliomas. SRT allows precise treatment delivery while decreasing the dose to surrounding critical structures,¹³ thus obviating the toxicity commonly seen with SRS.

Hypofractionated SRT (H-SRT) utilizes these principles but is able to deliver treatment over 2 weeks versus 3 to 4 weeks with standard fractionation schemes. Given the grim prognosis of patients with high-grade gliomas, it is imperative to consider quality of life when evaluating treatment options. We therefore sought to determine the efficacy and toxicity profile of H-SRT alone or with other modalities in patients with recurrent malignant glioma. To our knowledge, this is the largest cohort of high-grade patients with malignant gliomas treated with H-SRT for recurrent disease.

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PATIENTS AND METHODS

Study End Points

The Thomas Jefferson University institutional review board approved this single-institution, retrospective study. The primary end point of the study was survival from the start of H-SRT. Other end points included survival from diagnosis, objective responses, and toxicity, which was graded by Radiation Therapy Oncology Group (RTOG) criteria.

Patients had bimonthly follow-up clinical exams and magnetic resonance imaging (MRI) scans. CNS toxicity was defined as the development of any new neurologic symptoms or signs after radiation felt attributable to H-SRT.

All patients were diagnosed with recurrence identified on the basis of radiographic presence of tumor progression on T1 weighted MRI. Pseudoprogression, a fairly novel concept, was not a consideration in older occurrences; however, of the 21 patients who experienced recurrence within 3 months, 10 had pathologic confirmation of progression and others had symptoms of progression in addition to MRI findings. Clinical judgment was used to define eligibility for H-SRT. In general, our institution determined patients were eligible for treatment if the tumor volume could be included within a 10 × 10 cm field, the Karnofsky performance score (KPS) was ≥ 60, and the patients were able to lie flat for treatment planning and delivery.

All 147 patients were followed with MRI scans, which were obtained 6 to 8 weeks after H-SRT and at 3-month intervals thereafter. Response was determined as defined by Macdonald et al.¹⁴

Treatment Planning and Delivery

Patients were fitted with the Gill-Thomas-Cosman (GTC) relocatable frame and were taken to the MRI and/or computed tomography (CT) scanning suite, where the Brown-Roberts-Well fiducial cage was placed on the GTC frame and transaxial images were obtained.¹⁵ Before 2004, treatment planning was conducted with the X-Knife 3-D planning system (Radionics, Burlington, MA), which used 6 MV photons delivered stereotactically with a dedicated 600SR linear accelerator (Varian, Palo Alto, CA). After June 2004, treatment planning was carried out with Brain Lab (Novalis), with mMLC leaves and an Exac Trac feature.

Gross tumor volume (GTV) was defined by the gadolinium-enhanced tumor edge using T1 weighted series. The planning target volume was considered equivalent to the GTV, and edema was not included in the treatment volume. Tumors were treated to the 85% to 90% isodose line. H-SRT was delivered using daily fractions of 3.5 Gy, with a median dose of 35 Gy.

Statistics

The outcome measures considered were overall survival, defined as survival from time of diagnosis to death or loss to follow-up, and survival from re-irradiation. Cox regression models were used to analyze these outcomes. Because the study was observational in nature, a time-dependent covariate model was utilized, when needed, to control for the timing of treatments that occurred over time, such as additional surgeries; additional chemotherapy treatments; and observation time of prognostic variables such as tumor volume, number of lesions, and dose, all of which were measured at the time of re-irradiation. Variables included in the multivariable models were those determined to be clinically relevant to prognosis as well as those involving specific hypotheses of interest; variables included time in between initial treatment and retreatment, tumor grade, extent of initial surgical resection, age, initial treatment with temozolomide, treatment with temozolomide or other systemic agent during H-SRT, surgery before re-irradiation, tumor volume, number of lesions, and whether patients had surgical resection after H-SRT. Survival from re-irradiation included a covariate controlling time from diagnosis until H-SRT to balance the populations with respect to starting condition. Results of multivariable Cox models are reported as odds ratios, 95% CIs, and *P* values. Statistics were performed with SAS (version 9.2, SAS Institute, Cary, NC) and Stata (version 8.0, Stata, College Station, TX).

RESULTS

Patient Population

We identified 147 patients with either grade 3 astrocytoma or glioblastoma multiforme (GBM) who had clinical and radiographic evidence of tumor progression that was treated with H-SRT between 1994 and 2008. Patient characteristics are listed in Table 1. All patients received initial postoperative conformal fractionated RT to a mean and median dose of 60.0 Gy in daily 2.0-Gy fractions. One hundred ten patients received chemotherapy at the time of initial diagnosis, and 48 received chemotherapy at recurrence with H-SRT.

All patients underwent neurosurgical intervention at initial diagnosis, and 84 patients (60%) had resection at recurrence before salvage

Table 1. Patient, Tumor, and Treatment Characteristics

Parameter	All Patients (N = 147)	
	No.	%
Glioblastoma multiforme	105	71
Anaplastic astrocytoma grade III	42	29
Age at diagnosis, years		
Median	53	
Range	19-86	
Initial RT dose, Gy		
Median	60	
Range	28-80	
Mean*	60.4	
SD	5.2	
Follow-up time from diagnosis, months		
Median	21	
Range	4-227	
Time to H-SRT from diagnosis, months		
Median	8	
Range	4-205	
Tumor volume at recurrence, mL		
Median	22	
Range	0.6-104	
Received salvage dose < 35.0 Gy	23	16
Received surgery after H-SRT	31	21
Multiple lesions at time of H-SRT	24	16
Surgery at diagnosis		
Gross total resection	41	28
Subtotal resection	99	67
Biopsy	7	5
Salvage surgery prior to re-irradiation		
Gross total	24	29
Subtotal	60	71
Chemotherapy with H-SRT		
Temozolomide	15	31
Temozolomide, bevacizumab, and irinotecan	3	6
Bortezomib and temozolomide	8	17
Epothilone	10	21
Sunitinib	6	13
Sorafenib	2	4
Bevacizumab and irinotecan	1	2
Vincristine	1	2
Carboplatin	2	4

Abbreviations: RT, radiation therapy; SD, standard deviation; H-SRT, hypofractionated stereotactic radiation therapy.

*No. of patients = 147.

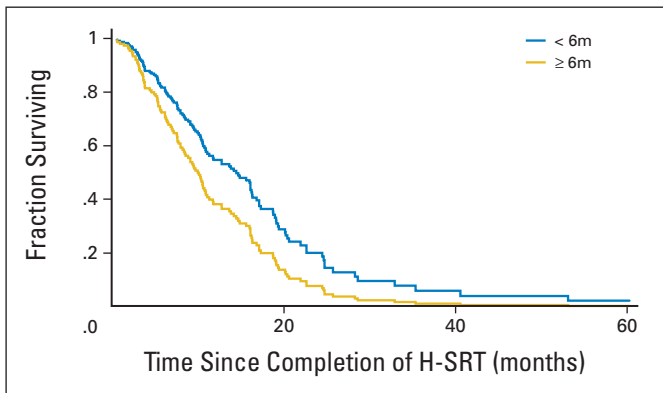


Fig 1. Median survival time from hypofractionated stereotactic radiation therapy (H-SRT) of patients who experienced recurrence less than 6 months v \geq 6 months from initial treatment.

H-SRT. Overall, the groups with resection plus H-SRT and with H-SRT alone were balanced with respect to initial treatment regimen, time to progression, dose of re-irradiation, and presence of multiple lesions. The GTV in patients who underwent resection before H-SRT was 33 mL after debulking surgery versus 14 mL in patients who did not undergo resection ($P = .001$).

Toxicity

No patients demonstrated clinically significant acute morbidity, and all patients were able to complete the prescribed radiation dose without interruption. No patient required hospitalization or surgery for early acute or delayed toxicity. One patient, who received a dose of radiation of 40.0 Gy, experienced grade 3 late CNS toxicity, in the form of severe headaches, at 4 months after salvage H-SRT.

Overall Survival, Survival From H-SRT, and Progression-Free Survival

The median time from diagnosis to H-SRT was 8 months (range, 4 to 205 months) for all patients, 11 months for grade 3 patients, and 8 months for grade 4 patients. Median survival times (MSTs) from the date of diagnosis (on the basis of Kaplan-Meier estimates) were 23 months (95% CI, 18 to 26 months) for grade 4 patients and 24 months (95% CI, 18 to 27 months) for grade 3 patients. MST from the start of H-SRT was 10 months (95% CI, 8 to 12 months) for patients with grade 3 tumors and 11 months (95% CI, 9 to 14 months) in grade 4 patients. MST from re-irradiation of patients who had experienced recurrence less than 6 months after initial treatment was 11 months (95% CI, 10 to 16 months) versus 8 months (95% CI, 6 to 14 months) for patients who experienced recurrence greater than 6 months after original treatment (Fig 1; $P = .034$). MST from re-irradiation of patients who received \geq 35 Gy was 11 months (95% CI, 8 to 14 months) versus 10 months for patients who received less than 35 Gy (95% CI, 8 to 13 months; Fig 2; $P = .077$). MST from re-irradiation of patients who received any chemotherapy concurrently with H-SRT was 11 months (95% CI, 7 to 17 months) versus 10 months for patients who did not receive chemotherapy (95% CI, 9 to 12 months; Fig 3; $P = .791$). At the time of analysis, 128 of 147 patients had died.

On multivariate analysis, factors that positively affected survival from re-irradiation (Table 2) were younger age ($P < .001$), smaller GTV ($P = .025$), and shorter interval between first RT and H-SRT

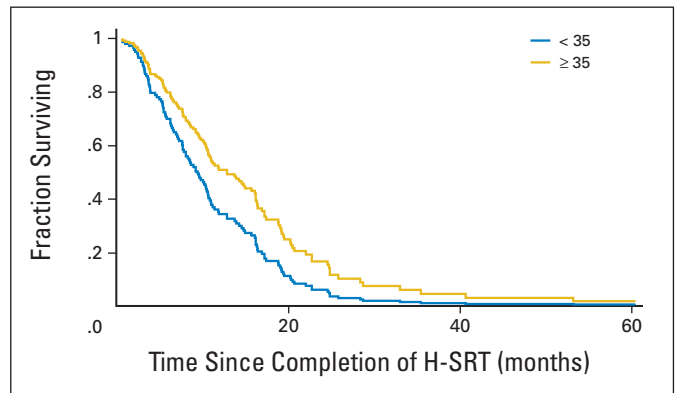


Fig 2. Median survival time from hypofractionated stereotactic radiation therapy (H-SRT) of patients who received \geq 35 Gy v $<$ 35 Gy.

($P = .034$). A dose of \geq 35 Gy approached statistical significance ($P = .077$). Factors not found to influence survival after re-irradiation were chemotherapy delivered with re-irradiation ($P = .791$) and salvage resection before re-irradiation ($P = .513$).

On multivariate analysis, factors that influenced overall survival (Table 3) were younger age at diagnosis ($P < .001$), smaller GTV ($P < .001$), and increasing number of lesions ($P = .011$). Of 147 patients with serial post-treatment MRI scans, 88 patients had scans that revealed progression before death. For patients receiving chemotherapy with H-SRT, there were no significant differences between patients who had previously received temozolomide or other chemotherapy to those patients who were chemotherapy naïve.

There were no reoperations attributable to H-SRT-related toxicity. Thirty-one patients underwent surgical resection after H-SRT, because follow-up imaging demonstrated radiographic progression corroborated by pathology in all 31 specimens.

Response

Of the patients placed on corticosteroids before H-SRT, dose was increased in 15 patients and decreased in 50 patients at 6-week follow-up. Seventy-three patients presented with neurologic symptoms in addition to progressive findings on MRI. The most common symptoms were seizures, headaches, and motor dysfunction. Of those patients, 19 patients experienced improvement in neurologic symptoms

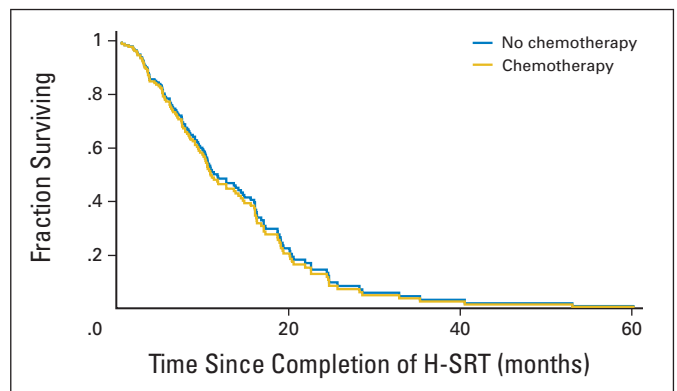


Fig 3. Median survival time from hypofractionated stereotactic radiation therapy (H-SRT) of patients who received any chemotherapy concurrently with H-SRT v no chemotherapy.

Table 2. Multivariate Survival in Months From H-SRT (N = 147)

Variable	Comparison	HR	95% CI	P
Age, years	Continuous	1.04	1.03 to 1.06	< .001
Grade	4 v 3	0.69	0.45 to 1.05	.083
Time between diagnosis and first radiation course, months	Continuous	1.00	0.94 to 1.06	.975
Time between first RT and H-SRT, months	≥ 6 v < 6	1.60	1.04 to 2.45	.034
Initial resection	Total v subtotal	1.41	0.93 to 2.15	.106
Initial resection	Biopsy v subtotal	1.36	0.62 to 2.98	.448
Tumor volume at H-SRT, mm ³	Continuous	1.01	1.00 to 1.03	.025
No. of lesions at H-SRT, 1-4	Continuous	0.80	0.52 to 1.23	.312
Dose of H-SRT, Gy	≥ 35 v < 35	0.63	0.38 to 1.05	.077
Chemotherapy concurrent with H-SRT	Yes v no	1.06	0.69 to 1.63	.791
Temozolomide-naïve	No v yes	0.90	0.61 to 1.32	.581
Second resection before H-SRT	Yes v no	0.87	0.57 to 1.33	.513
Surgery after H-SRT*	Yes v no	1.00	0.62 to 1.64	.988

Abbreviations: HR, hazard ratio; RT, radiation therapy; H-SRT, hypofractionated stereotactic radiation therapy.

*Time-dependent covariate (on the basis of date of surgery, if known, or midpoint of date of H-SRT and date of last follow-up, if unknown).

after RT at 6-week follow-up, and only one patient experienced worsening of symptoms.

The 3-month follow-up MRI scans after H-SRT indicated stable disease in 89 patients (60%). Minimal response as defined by Macdonald criteria was noted in 15 patients (10%), and progression was noted in 43 patients (30%).

DISCUSSION

There are many approaches currently available for the salvage treatment of patients with recurrent HGG after initial RT, including resection, re-irradiation, or systemic agents, but no standard of care exists. Prognosis is grim in this patient population; therefore, assessment of toxicity and quality of life, when considering treatment options, is critical.

The role of chemotherapy at recurrence is unclear and has resulted in a MST from recurrence of 7.5 months.^{16,17} Bevacizumab is US Food and Drug Administration approved for the treatment of recurrent GBM, with phase II trials indicating prolonged 6-month progression-free and overall survivals.¹⁸

Fractionated stereotactic RT is advantageous in treating recurrent, previously irradiated, tumors, particularly when located in eloquent areas, as it allows the therapeutic dose to be delivered over a number of fractions, while minimizing normal tissue toxicity. The

largest series of re-irradiation of recurrent gliomas examined the efficacy of 36 Gy delivered in 2-Gy fractions in 172 patients, of which 111 had high-grade gliomas.¹⁹ This regimen was well tolerated and resulted in modest survival.

Although the role of chemotherapy combined with RT has been well established for patients with newly diagnosed primary GBM,^{2,20} there is a paucity of data reporting on the combination of chemotherapy and RT for recurrent gliomas.²¹⁻²³ Combs et al²⁴ examined the combination of temozolomide with fractionated re-irradiation in 25 patients with recurrent gliomas. The treatment was well tolerated, and MST from retreatment was 8 months. Their results corroborate ours, with no difference noted between temozolomide-naïve patients and patients previously exposed to temozolomide, and no statistically significant benefit to pre-re-irradiation resection. Other studies combining re-irradiation with chemotherapy have demonstrated similar results.²⁵⁻²⁸ Although it was not a randomized trial, our study did not demonstrate a survival advantage in combining chemotherapy with H-SRT at recurrence compared with patients who received H-SRT alone.

Some chemotherapy agents have shown comparable results to RT alone but with increased toxicity compared with the minimal toxicity noted in our patient population. For example, survival times

Table 3. Multivariate Results for Survival From Diagnosis (N = 147)

Variable	Comparison	HR	95% CI	P
Age, years	Continuous	1.04	1.02 to 1.06	< .001
Grade	4 v 3	0.65	0.42 to 1.01	.057
Initial resection	Total v subtotal	1.27	0.84 to 1.93	.252
Initial resection	Biopsy v subtotal	1.96	0.90 to 4.26	.088
Tumor volume at H-SRT, mm ³ *	Continuous	1.03	1.01 to 1.04	< .001
No. of lesions at H-SRT, 1-4*	Continuous	1.51	1.10 to 2.07	.011
Chemotherapy concurrent with H-SRT*	Yes v no	1.23	0.79 to 1.92	.365
Temozolomide-naïve	No v yes	0.89	0.60 to 1.34	.589
Second resection before H-SRT*	Yes v no	0.99	0.63 to 1.54	.955
Surgery after H-SRT*	Yes v no	0.80	0.50 to 1.28	.350

Abbreviations: HR, hazard ratio; H-SRT, hypofractionated stereotactic radiation therapy.

*Time-dependent covariate (on the basis of the date of H-SRT).

at progression comparable to H-SRT have been reported with bevacizumab alone but with associated adverse effects of hypertension and thromboembolic events as well as the inconvenience and cost of maintenance therapy. The results are, however, promising, and it may be that finding the appropriate sequence with which to deliver these therapies may lead to longer overall survival times.

Literature is sparse regarding the toxicity or efficacy of H-SRT in this setting of re-irradiating progressive high-grade gliomas.²⁹ H-SRT is an outpatient-based, noninvasive approach that takes advantage of the stereotactic precision as well as the properties of a standard fractionation schedule but is able to shorten the number of weeks of treatment. This is not only more beneficial to patients with respect to quality of life and convenience but also may represent a decrease in cost associated with retreatment. Although the cost of re-irradiation is already a fraction of the cost of systemic maintenance therapy, examination of Medicare reimbursement rates for H-SRT demonstrated a cost savings of 20% (ie, \$4,498.07 compared with \$5,705.47) with 10 treatments compared with the 18 treatments of a typical fractionation schedule.

Previous studies looking at small populations treated with H-SRT have reported higher rates of necrosis but have utilized a wide range of doses. An association has been noted between higher rates of re-operation and doses greater than 40 Gy.^{30,31} Of note, the 5- to 6-Gy fractions used in these studies are significantly larger than the 3.5-Gy fractions used in our patient population. Certainly, higher doses per fraction are noted to be associated with increased long-term toxicity in late responding tissue in other disease sites.

In contrast to prior reports of re-operation rates for SRS, brachytherapy, and other H-SRT fractionation schemes,^{5-8,10-12,23,29-37} all patients who underwent surgical resection after H-SRT demonstrated radiographic progression confirmed by pathology, indicating these patients underwent re-operation because of tumor progression rather than treatment-related effects. Our initial experience with H-SRT used 3.5-Gy fractions to 35 Gy and reported no grade 3 toxicities or re-operation secondary to toxicity, providing additional support that this dose and fraction size is well tolerated.²⁹ Our data suggest that higher doses of H-SRT result in an improved survival; yet, doses greater than 40 Gy have been associated with increased toxicity, indicating the small therapeutic window.

There is currently no consensus regarding the appropriateness of salvage irradiation in patients who experience recurrence shortly after initial treatment. Grosu et al³⁸ examined 44 patients with recurrent HGG and found the most important prognostic factor associated with improved survival after re-irradiation was an increased interval between initial diagnosis and recurrence. In contrast to this, Mayer and Sminia³⁹ reviewed 10 years of re-irradiation studies and did not find a correlation between the time interval from the initial therapy and re-irradiation and improved prognosis.

Our study did not demonstrate an inferior survival from H-SRT in patients who experienced recurrence within 6 months of original treatment. It may be that the larger number of patients examined in our study allowed us to more accurately assess this phenomenon. This

finding is of critical importance, as, currently, eligibility to clinical trials is often limited to patients who have survived at least 6 months from initial treatment.

Our patient population was uniform with respect to the technique, dose, and fractionation of RT but differed with respect to time to progression; use of chemotherapy, either with initial treatment or with H-SRT; or use of pre-H-SRT resection. Despite this variability, we observed that all groups of patients benefited similarly from H-SRT, achieving a uniform MST of 11 months. This is comparable to the best reported results in the literature with systemic agents but with an improved toxicity profile, suggesting that H-SRT should be considered standard salvage therapy for previously irradiated HGGs. We noted that patients who experienced recurrence within 6 months after initial treatment had an unexpectedly good prognosis, suggesting they should not be disqualified from H-SRT or other salvage therapy.

In conclusion, we have demonstrated that H-SRT was associated with favorable survival benefit independent of re-operation or concomitant chemotherapy and was well tolerated with minimal adverse effects in patients with recurrent HGG. This study represents, to our knowledge, the largest series to examine the efficacy and tolerability of salvage H-SRT as well as the role of resection and/or chemotherapy combined with H-SRT for HGG. Survival results are comparable to the best-reported results in the literature examining systemic agents (ie, bevacizumab) but with an improved toxicity profile and decreased cost compared with that of systemic maintenance therapy. These results warrant a prospective evaluation of H-SRT in future studies as standard salvage therapy for previously irradiated HGGs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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CORRECTIONS

Author Correction

The October 1, 2005, article by Roman-Gomez et al, entitled, "Lack of CpG Island Methylator Phenotype Defines a Clinical Subtype of T-Cell Acute Lymphoblastic Leukemia Associated With Good Prognosis" (J Clin Oncol 23:7043-7049, 2005), contained an error.

An erroneous image was given as Figure 1. The corrected figure is reprinted here in its entirety.

The authors apologize to the readers for the mistake.

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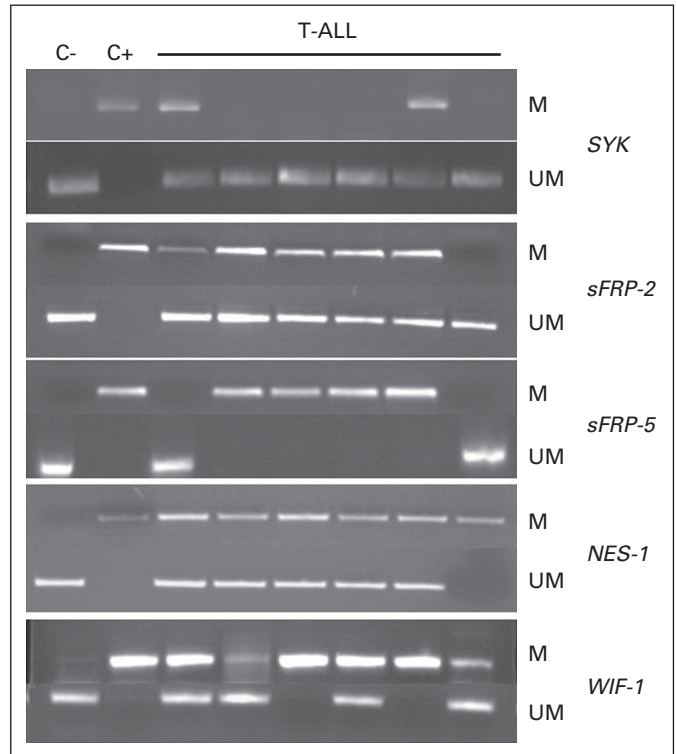


Fig 1. Aberrant promoter methylation of different genes in T-cell acute lymphoblastic leukemia (T-ALL) samples. C-, peripheral blood lymphocytes from healthy donors; C+, human male genomic DNA universally methylated for all genes (used as a positive control for methylated alleles); M, methylated alleles; UM, unmethylated alleles.

Journal Correction

The June 20, 2010, article by Fogh et al, entitled, "Hypofractionated Stereotactic Radiation Therapy: An Effective Therapy for Recurrent High-Grade Gliomas" (J Clin Oncol 28:3048-3053, 2010), contained an error.

In the affiliations section, the Kimmel Cancer Center at Thomas Jefferson University should have been listed instead of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, as follows:

From the Department of Radiation Oncology, Neurological Surgery, Kimmel Cancer Center, and the Division of Biostatistics, Department of Pharmacology and Experimental Therapeutics, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA.

Journal of Clinical Oncology apologizes to the authors and readers for the mistake.

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