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Incorporation of Biomarker Assessment in Novel Clinical Trial Designs: Personalizing Brain Tumor Treatments

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Abstract

Advances in molecular genetics have aided the identification of potential biomarkers with significant clinical promise in neurooncology. These advances and the evolution of targeted therapeutics necessitate the development and incorporation of innovative clinical trial designs that can effectively validate and assess the clinical utility of biomarkers. In this article, we review the use and potential of several such designs in neurooncology trials in order to support the development of personalized treatment approaches for brain tumor patients.

Keywords

Biomarkers; Glioma; Neurooncology trials; Biomarker enrichment design; Marker by treatment interaction design; Adaptive design

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Introduction

Recent advances in molecular genetics have led to the identification of distinct tumor subtypes and important molecular pathways underlying gliomagenesis; translating these findings into effective clinical strategies, and treatment individualization, remains an ongoing challenge however. Biomarkers have the potential to increase the success of novel treatment approaches by incorporating possible predictors of efficacy in specific mechanism-based therapeutic strategies, thus optimizing treatment selection for individual patients. Nevertheless, biomarker validation and incorporation into clinical trial design in a manner that can result in rapid and successful integration into clinical practice remains a significant challenge. This is, in part, due to a multitude of marker assessment methods, variable assay sensitivity, specificity and reproducibility, as well as additional costs to assess marker status in individual patients. The relatively low incidence of primary brain tumors as compared to other malignancies further complicates biomarker validation efforts.

Biomarkers can generally be classified as prognostic markers, which predict disease outcome regardless of specific treatment, and predictive markers which are associated with likelihood of a particular clinical outcome in response to a specific drug or drug class. While prognostic markers are significantly easier to identify and validate, and can be used in clinical trial design for patient stratification and in order to ensure balance between arms of controlled trials, their optimal use for treatment personalization can be more challenging to define. Predictive biomarkers are the gold standard for personalization of treatment, but the barriers and difficulties for discovery and validation of these highly sought biomarkers are much higher, and the methods for incorporation into prospective trials are more complicated.

Prognostic markers separate the population as it pertains to the outcome of interest independent of the treatment received. Statistical methods to validate prognostic markers are relatively straightforward and have been well developed [1–4]. Retrospective studies are usually used as the first step to test the association between a biomarker and a clinical end point. Biomarkers identified through this step are optimally validated on an independent dataset. In an ideal scenario, biomarkers identified via retrospective validation will eventually be tested prospectively.

On the other hand, predictive biomarkers are more difficult to identify, and their prospective validation in almost all cases requires randomized trials. A predictive marker is defined as a characteristic or genetic signature that separates a population with respect to the outcome of interest in response to a particular treatment, ie, it could be used to guide the choice of therapy. A validated predictive marker can prospectively identify individuals who are likely to have a favorable clinical outcome such as improved response rate or survival if they receive a specific treatment. Predictive markers have been incorporated in the standard management of other malignancies including c-kit expression in the treatment of GIST; K-ras mutation status to determine the use of anti-EGFR antibodies in the treatment of colorectal cancer; and ER, PR, and HER-2 status in the management of breast cancer. In contrast, most of the efforts in neurooncology to personalize treatment regimens focus on prognostic biomarkers. Such biomarkers, discussed in more detail below, include the 1p/19q status of anaplastic gliomas and the MGMT methylation status in glioblastoma multiforme (GBM). Both biomarkers have been demonstrated to predominantly have prognostic utility, and may have some predictive value, although, at the present time, there is lack of unanimous agreement on the latter.

There are increasing efforts in testing and validating pure predictive markers in neurooncology trials, such as EGFRvIII expression status in newly diagnosed GBM patients

treated with a peptide vaccine. A retrospective analysis also identified the presence of the EGFRvIII mutation in combination with PTEN expression as predictive of response to the EGFRtk inhibitor erlotinib [5]. However, this finding could not be confirmed prospectively in an EORTC trial of erlotinib in recurrent GBM patients [6]. Such discrepant results highlight some of the potential challenges associated with identification and characterization of predictive markers in GBM treatment, given the complexity and redundancy of molecular pathways that decrease the likelihood of a single genetic change being able to predict treatment response. Optimal design of neurooncology trials must increasingly take this molecular variability into account, both to ensure comparability between study arms and different trials and to improve the efficiency for identification and validation of predictive biomarkers. Based on this rationale, molecular profiling and classification of tumors in clinical trials may better account for this genetic variability and result in a higher likelihood of finding useful predictive biomarkers of outcome as compared to analysis of single molecular alterations.

Among different biomarkers with potential value in guiding the management of glioma patients, 1p/19q deletion status, MGMT methylation status, and GBM gene expression profiling represent the furthest developed biomarker strategies with high potential to result in personalized glioma treatment. Using these biomarkers as examples, we will discuss statistical designs that could be used to evaluate predictive biomarkers and expand on innovative designs that could be incorporated in future neurooncology trials to personalize treatment regimens.

1p/19q Deletion

1p/19q co-deletion represents a hallmark of oligodendroglial tumors. This co-deletion has been associated with better prognosis as well as sensitivity to cytotoxic therapy and is mediated by an unbalanced translocation of 19p to 1q. An association exists between 1p/19q co-deletion and the characteristic oligodendroglial histologic appearance. 1p/19q co-deletion is present in 62% to 90% of anaplastic oligodendroglioma cases, but only in 13% to 20% of cases of anaplastic oligoastrocytoma [7–9].

Initial studies reported that objective response and survival rates were better in 1p/19q deleted oligodendroglioma patients than those without 1p and 19q loss [8, 10, 11]. Median survival was 6 to 7 years in 1p/19q deleted patients, but only 2 to 3 years in the absence of co-deletion among anaplastic oligodendroglioma patients. Similarly, for low-grade patients, median survival was 12 to 15 years for 1p/19q co-deleted patients, but only 5 to 8 years for patients without the deletion [8, 10, 11]. The improved survival in these studies was observed not only in chemotherapy-containing arms, but also among patients treated with radiotherapy alone, indicating that 1p/19q co-deletion is likely a prognostic factor as opposed to a predictive factor. In RTOG 9402, a trial randomizing newly diagnosed anaplastic oligodendroglioma and oligoastrocytoma patients to PCV+ RT versus RT following surgery, patients with 1p/19q co-deletion had a better survival independently of the treatment they received [12]. EORTC 26951, a trial targeting a similar patient population and randomizing them to RT versus RT+PCV reached similar conclusions [13]. These data indicate that the presence of 1p/19q co-deletion might not be a predictive biomarker for the use of specific chemotherapy, because RT also resulted in treatment benefit [12, 13]. However, they do support the first biomarker driven randomized phase III trials in neurooncology using an enrichment design where study eligibility is determined based on characterization of the tumor 1p/19q status rather than histopathologic diagnosis (CODEL and CATNON trials).

Biomarker Enrichment Designs: Determining Management of Anaplastic Glioma Patients Based on 1p/19q Status

In an enrichment design, all patients are screened for the presence or absence of a marker or a group of biomarkers, but only patients with tumors expressing a certain biomarker feature are enrolled into the randomized component of the trial. Examples of enrichment design in brain tumor research are two currently open intergroup studies: the CODEL (NCCTG N0577) and CATNON (EORTC26053/22054) trials.

The CODEL trial targets newly diagnosed anaplastic glioma patients with 1p/19q co-deletion. Patients are randomized among three arms: RT alone arm, RT with concomitant temozolomide followed by adjuvant temozolomide arm, and a temozolomide-alone arm. The primary goal of the study is to assess whether patients who receive temozolomide with concomitant RT have a significantly better overall survival than patients who receive RT alone; secondary goals are to explore whether patients who receive temozolomide alone or temozolomide with concomitant RT have a significantly longer time to progression or neurocognitive decline as compared to patients who receive RT alone. Thus, this study also explores the key question of whether upfront chemotherapy can delay RT administration in this subset of good-prognosis anaplastic glioma patients. With a sample size of 219 eligible patients in the RT alone and RT/temozolomide arms, respectively, the study has 80% power to detect a 33% decrease in the hazard rate of death using logrank test, assuming a one-sided significance level of 0.05.

Complementary to the CODEL trial, the CATNON (EORTC26053/22054, RTOG 0834) trial explores treatment optimization for newly diagnosed anaplastic glioma patients without the 1p/19q co-deletion. Eligible patients are randomized to one of the four study arms: RT alone; RT combined with concurrent temozolomide; RT combined with adjuvant temozolomide; and RT combined with concurrent and adjuvant temozolomide. The primary goal of the study is to assess whether the addition of temozolomide concurrently with radiotherapy and/or as adjuvant therapy improves overall survival as compared RT alone in non-1p/19q co-deleted anaplastic glioma patients. Using overall survival as the primary end point, the study is designed to both test for the superiority of concurrent temozolomide, and also to test for the superiority of the adjuvant temozolomide. With a total sample size of 748 patients, the study has 83% power to detect a reduction of risk of death of 22.5% for each test using a two-sided logrank test, assuming an overall significance level of 5%.

Both these trials address the question of using a biomarker to optimize treatment in newly diagnosed anaplastic glioma patients by appropriately focusing on patient subgroups with distinct prognosis and possibly different treatment sensitivities. In addition, these two enrichment studies target complementary patient populations, and thus are well designed to optimize patient enrollment by capitalizing on a collaborative international effort. Thus, a patient with confirmed anaplastic glioma on central pathology review could be registered to one or the other study according to the 1p/19q status. This overall approach is expected to significantly increase accrual for both studies.

MGMT Methylation Status

In 2005, the EORTC/NCIC CE3 randomized phase III trial showed that addition of concomitant and adjuvant temozolomide to standard postoperative radiotherapy improved median survival and 2-year survival relative to postoperative radiotherapy alone [14] and established the new standard of care for newly diagnosed GBM patients. Furthermore, a retrospective assessment demonstrated that patients whose tumors had a methylated promoter for the gene encoding O6-methylguanine DNA methyltransferase (MGMT) were

more likely to benefit from the addition of temozolomide [15]. Recently updated results from this study were presented with median follow-up of more than 5 years [16]. In this 573-patient trial, sufficient tumor material was available in a subgroup of 206 patients to retrospectively determine the MGMT promoter methylation status. The analysis revealed that MGMT promoter methylation status was the strongest predictive factor for survival. Survival was significantly longer in patients treated with temozolomide and radiotherapy than patients treated with radiotherapy alone, both in patients with methylated and unmethylated MGMT promoter. At 3 and 5 years, 27.6% and 13.8%, respectively, of MGMT-methylated patients who received combination treatment were alive as compared to 11.1% and 8.3% of MGMT-unmethylated patients who received combination treatment. For patients treated with radiation alone, MGMT promoter methylation was associated with a 7.8% and 5.2% survival at 3 and 5 years, respectively, while no MGMT unmethylated patients survived beyond 3 years (Table 1). Analysis of progression-free survival showed an advantage only for patients whose tumor had methylated MGMT promoter and who were treated with temozolomide and radiotherapy [10]. These data support a prognostic value of MGMT methylation in newly diagnosed GBM patients and predictive value as it pertains to progression-free survival after temozolomide therapy, but not overall survival [16]. Interpretation of these retrospective data is further complicated by the fact that this analysis is based on a subgroup of the trial patients (206/573) in whom tissue was available. As a result, although withholding temozolomide in newly diagnosed patients with unmethylated MGMT promoter is considered to be acceptable in Europe, especially in the context of clinical trial opportunities, this practice has not been adopted by North American neuro-oncologists.

Of note, prospective evaluation of the MGMT methylation status has been incorporated in the recently completed RTOG phase III trial 0525 comparing standard temozolomide dosing to a dose-dense adjuvant temozolomide schedule in newly diagnosed GBM patients. This trial can serve as an important prospective validation of the prognostic role of the MGMT methylation status in newly diagnosed GBM patients. It is unlikely, however, that it will clarify further any possible predictive role as it pertains to temozolomide response, since both arms of the trial included TMZ, ie, there was not an RT-alone arm.

Results in other glioma histologies also point toward MGMT methylation status being prognostic of outcome. In the NOA-04 trial in which there was no difference in progression-free survival or overall survival for anaplastic glioma patients treated with RT versus temozolomide or PCV as initial treatment, MGMT promoter methylation predicted prolonged progression-free survival irrespective of the initial treatment [17]. Similar results were obtained in EORTC 26951, a randomized phase III trial comparing radiotherapy to radiotherapy followed by PCV [18] for anaplastic glioma patients. Furthermore, there was significant correlation of MGMT promoter methylation with 1p19q co-deletion [18–20] and isocitrate dehydrogenase (IDH) gene mutation [21], both known to be favorable prognostic factors in anaplastic glioma [12, 13, 17]. These data support that MGMT promoter methylation status is primarily a prognostic marker rather than a predictive marker in anaplastic gliomas.

Marker by Treatment Interaction Design, Using Separate Tests: Assessing the Predictive Value of MGMT Methylation in Newly Diagnosed GBM Patients

Marker by Treatment Interaction Design is a prospective marker validation design [22•]. In this design, all patients with a valid marker result are assigned to a marker-based subgroup, and within each subgroup, patients are randomized between two or more treatment arms.

The hypothesis to be tested, the sample size calculation and power estimation, and the randomization procedure are independent among subgroups. The design is similar to conducting simultaneous multiple independent randomized clinical trials for each marker subgroup.

An example of implementing this type of design is the NCI-sponsored North Central Cancer Treatment Group study N0975, a randomized phase II study testing the PARP inhibitor MK4827 in addition to temozolomide and radiotherapy (TMZ/RT/MK4827) as first-line therapy in newly diagnosed glioblastoma. The trial is based on preclinical data demonstrating that MGMT status and tumor sensitivity to temozolomide can predict benefit from PARP inhibitors, when combined with temozolomide and RT [23]. The primary hypothesis being tested is that MGMT promoter hyper-methylation can be used to enrich for a population of patients most likely to respond to combined therapy with TMZ/RT/MK4827. All patients enrolled are required to submit tissue samples for MGMT promoter methylation analysis prior to registration. Patients then will be separated into two subgroups, MGMT promoter hyper-methylated and hypo-methylated subgroups, and within each subgroup, patients will be randomized at a ratio of 1:2 to either the standard therapy arm (TMZ/RT) or the experimental arm (TMZ/RT/MK4827). The primary comparisons will be progression-free survival between the two corresponding arms within each subgroup. The protocol specified sample size of 129 patients will yield 85% power to detect a hazard ratio of 1.56 for the MGMT hyper-methylated group using a one-sided logrank test, and the sample size of 201 patients will yield 85% power to detect a hazard ratio of 1.4 for the MGMT unmethylated group using a one-sided logrank test, assuming a significance level of 0.15 for each. If TMZ/RT/MK4827 is superior in both groups, or in neither group, the predictive effect of MGMT promoter methylation will be disproven, while a significant benefit only in the MGMT-methylated group would provide the impetus for a confirmatory phase III trial. In addition to analyzing each group separately, the data can be pooled thus enhancing the power for the group as a whole to test for the efficacy of MK4827 in combination with the standard chemotherapy.

Gene Expression–Based GBM Profiling

Global expression studies in GBM have been successful in defining clinically relevant molecular tumor subtypes. Gene expression studies have established that over-expression of a mesenchymal gene expression signature and loss of a proneural signature are associated with a poor-prognosis group of glioma patients [24]. A recent publication from the Cancer Genome Atlas Network effort in GBM highlights the importance of the genetic analysis in GBM outcome. In this analysis, using samples from 200 GBM patients and an independent validation set of 260 GBM expression profiles, an 840 gene-based expression based molecular classification segregated GBM tumors into proneural, neural, classical, and mesenchymal subtypes. Aberrations in copy number and/or gene mutations of EGFR, NF1, and PDGFRA/IDH1 defined classical, mesenchymal, and proneural subtypes, respectively. Response to combined-modality therapy differed by subtype, with the greatest benefit being observed in the classical subtype and no benefit in proneural subtype. Proneural tumors were associated with higher rates of PDGFRA amplification, IDH1 and p53 mutations, and high expression of oligodendrocytic development genes such as OLIG2. In contrast, mesenchymal tumors were characterized by higher rates of NF1 gene deletions or mutations, and expression of mesenchymal markers such as MET and CHI3L1. Another gene expression subtype, named classical, was associated with a higher rate of amplification of chromosome 7, including amplifications of EGFR and CDKN2A homozygous deletions [25]. In an independent analysis, a 9-gene subset was found to be an independent predictor of outcome after adjusting for clinical factors and MGMT methylation status [26]; patients with the mesenchymal-angiogenic profile, based on this signature, had the worst outcome.

Taken together, these data suggest that distinct molecular subtypes exist within the broader pathologic diagnosis of GBM, and raise the possibility that response to specific treatments may vary based on the molecular subtype. Prospective molecular subtyping based on the 9-gene signature along with MGMT promoter methylation is included as a stratification factor in the ongoing RTOG trial 0825 and will help address the question of whether angiogenesis inhibition by using the anti-VEGF antibody bevacizumab in newly diagnosed GBM patients is of benefit in specific molecular GBM subgroups.

Marker by Treatment Interaction, Test of Interaction Design: Evaluating the Predictive Value of Genetically Defined GBM Subtypes in Newly Diagnosed GBM Patients Receiving anti-angiogenesis Treatment

The marker by treatment interaction design can also be used for prospective marker validation using a statistical test for interaction [22•] (the so-called marker by treatment, test for interaction design). In this design, although the randomization scheme is identical to the previously described marker by treatment interaction using separate tests design, the sample size is calculated to provide adequate power to test for a different treatment effect in the two marker groups. By using all patients in one single test, the efficiency of testing to detect difference between the two marker groups is maximized. On the other hand, this approach can be criticized for not providing enough power for detecting the treatment efficacy in each marker subgroup individually, depending on the hypothesized nature of the treatment effects in the marker-defined groups.

As one example, this design is used in the NCI-sponsored ongoing phase III study of temozolomide and radiation therapy with or without bevacizumab in patients with newly diagnosed glioblastoma (RTOG 0825). The study is designed to explore the additive effect of bevacizumab in terms of overall survival and/or progression-free survival when combined with the standard RT/TMZ therapy. With a sample size of 612 analyzable patients, the study provides 80% power to test a hazard ratio of at least 1.33 for overall survival and a hazard ratio of at least 1.43 for progression-free survival, given a one-sided significance level of 0.025 overall. For testing the major treatment effect, the study is powered to detect two reasonable hazard ratios, one for overall survival and one for progression-free survival, with a modest sample size as a phase III study. However, this is not the case when potential interactions are considered and tested. One secondary aim of the study is to explore the interaction between treatments received, MGMT methylation status, and patient molecular profiling status. Treatment is considered as one factor with two levels: RT/TMZ versus RT/TMZ/Bev. The MGMT methylation status (methylated vs unmethylated) and the molecular profile (favorable vs unfavorable) are jointly considered as the other factor with four levels. In other words, the study could be considered as a 2*4 factorial design for testing the interaction, or the marker by treatment interaction (test interaction) design as introduced above. For the subset of patients with MGMT unmethylated and an unfavorable molecular profile, the study could provide 86% power to detect a survival hazard ratio of 1.6 or greater at the final analysis. However, the study provides only 19% power to detect the interactions for time-to-failure outcome based on the hypothesized hazard ratios among the 4 subsets at the final analysis. The small power in detecting the interaction is not surprising. In general, a study testing interaction would require four times as many patients as compared to a study testing a single main effect with the same magnitude. Given the limited number of brain tumor patients, testing the interaction between a treatment and a biomarker within a reasonable timeframe represents a substantial challenge unless a marker is expected to result in a quantitative interaction, that is, predict benefit in one group but harm in another group.

Other Novel Statistical Designs that can be Applied for Predictive Marker Validation in Neurooncology Trials

In validating predictive biomarkers in neurooncology trials, two other types of designs might be considered: the marker-based strategy design and the modified marker-based strategy design. In the marker-based strategy design, each patient with known marker status is randomly assigned to two strategy groups: the marker-based strategy group, and the non-marker-based strategy group. All patients assigned to the marker-based strategy group are assigned to different treatments (standard or experimental) based on their biomarker status, while patients assigned to the non-marker-based strategy group all receive the standard treatment. The biomarker's predictive effect is evaluated by comparing the outcome from all patients in the biomarker-based treatment group to all those receiving standard treatment. The difference between the marker-based strategy design and the modified marker-based strategy design is that in the latter, all patients in the non-marker-based strategy group will have a second randomization and are assigned to one of the two treatments being used in the marker-based group. These two designs can be attractive when evaluating multiple biomarkers or the predictive value of molecular profiling between several treatment options is to be assessed. An example of the marker-based strategy design is a recently reported, randomized controlled trial in recurrent platinum-resistant ovarian carcinoma [27]. A total of 180 patients were randomized to tumor chemosensitivity assay-directed therapy or physician's-choice chemotherapy, with the primary aim of the study being to compare the two groups in terms of response rate and progression-free survival [27].

Adaptive Designs

In cases where multiple biomarkers are used to screen and identify multiple experimental regimens that are effective in subgroups of a patient population, a Bayesian adaptive design such as those proposed by Berry [28•] might be considered (Fig. 1). While adaptive designs have been used to assess clinical end points in brain tumor trials, this design has not been applied for prospective evaluation of biomarker-treatment associations in any brain tumor trials to date. Of note, this design was incorporated into a recently launched clinical trial, the I-SPY 2 study, which is designed to screen promising new regimens as part of neoadjuvant treatment for high-risk breast cancer patients, and provides an illustrative example of the potential applications in brain tumor trials. In this trial, women with measurable invasive breast cancer are screened using the MammaPrint 70 gene microarray analysis (Agendia). The additive effect of five different novel agents (Figitumumab, Neratinib, ABT-888, AMG386, and Conatumumab) will be assessed in combination with standard chemotherapies for the HER2-positive (doxorubicin/cyclophosphamide/paclitaxel/trastuzumab) and HER2-negative patient groups (doxorubicin/cyclophosphamide/paclitaxel). When compared to the standard therapy, regimens presenting a high Bayesian predictive probability of better efficacy will be considered for a follow-up phase III study in patients with corresponding biomarker signatures, while regimens associated with a low probability of better efficacy will be replaced by new regimens. This adaptive design can thus significantly shorten the time for screening regimens that might be more effective in certain patient subpopulations. Given the numerous novel targeted therapeutic agents that could be tried and the low incidence of primary brain tumors, this design could potentially have significant applicability in the development of personalized treatments for brain tumor patients. Critical to such designs is a reliable, short-term end point that can be consistently evaluated to allow early changes in trial arms.

Conclusions

In the current era, advances in molecular genetics have aided the identification of potential biomarkers with significant clinical promise. However, the process of biomarker identification, validation, and clinical application remains logistically complicated, expensive, and can require larger sample sizes that are not always practical in brain tumor studies. In addition, care will be required to distinguish those that provide merely prognostic input from those that also offer predictive capability. Examples of biomarkers currently under evaluation for malignant glioma patients include chromosome 1p/19q co-deletion, MGMT expression, and gene expression array data. Ongoing laboratory efforts will unquestionably identify additional biomarkers in the near future. Further development and incorporation of clinical trial designs that can effectively assess the clinical utility of biomarkers is thus of paramount importance. Biomarker identification and validation is clearly enhanced when prospective consideration is given to the design and analysis of clinical trials. In this paper we have reviewed the use and potential of several such designs that may be applied in neurooncology trials. While the limited patient population with brain tumors limits the designs that may be feasible, we have provided several examples of ongoing neurooncology trials, that if successful, will prospectively validate several biomarkers and as such possibly guide future therapeutic choices and ultimately improve outcome for brain tumor patients through personalized treatment approaches.

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¹Any number of arms.

²Arm stops due to not meeting predetermined efficacy rule.

³Possible design modifications at assessment time points include (but not limited to) dropping arms, altering the randomization ratio, to randomizing a higher proportion of patients to arms that are observing better outcomes, altering the planned total sample size, or refining the patient population based on an identified predictive biomarker.

Fig. 1.
Sample schema for adaptive design

Table 1

Kaplan-Meier overall survival in the EORTC-NCIC C3 trial, including subgroup analysis (Stupp et al., 2009)

	Deaths/ patients	Hazard ratio (95% CI)	Median, <i>months</i> (95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
MGMT unmethylated							
Radiotherapy	54/54	1.0	11.8 (10.0–14.4)	1.8 (0.1–8.6)	0	0	0
Combined	54/60	0.6 (0.4–0.8)	12.6 (11.6–14.4)	14.8 (7.2–25.0)	11.1 (4.7–20.7)	11.1 (4.7–20.7)	8.3 (2.7–18.0)
MGMT methylated ^a							
Radiotherapy	43/46	0.5 (0.3–0.7)	15.3 (13.0–20.9)	23.9 (12.9–36.9)	7.8 (2.2–18.3)	7.8 (2.2–18.3)	5.2 (1.0–15.0)
Combined	37/46	0.3 (0.2–0.4)	23.4 (18.6–32.8)	48.9 (33.7–62.4)	27.6 (15.4–41.4)	22.1 (11.0–35.7)	13.8 (4.5–28.2)

^a Hazard ratio relative to MGMT promoter unmethylated patients who received RT.