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Nomograms for predicting survival of patients with newly diagnosed glioblastoma: Prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3

Abstract

BACKGROUND: A randomised trial published by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group (trial 26981-22981/CE.3) showed that addition of temozolomide to radiotherapy in the treatment of patients with newly diagnosed glioblastoma significantly improved survival. We aimed to undertake an exploratory subanalysis of the EORTC and NCIC data to confirm or identify new prognostic factors for survival in adult patients with glioblastoma, derive nomograms that predict an individual patient's prognosis, and suggest stratification factors for future trials. METHODS: Data from 573 patients with newly diagnosed glioblastoma who were randomly assigned to radiotherapy alone or to the same radiotherapy plus temozolomide in the EORTC and NCIC trial were included in this subanalysis. Survival modelling was done in three patient populations: intention-to-treat population of all randomised patients (population 1); patients assigned temozolomide and radiotherapy (population 2, n=287); and patients assigned temozolomide and radiotherapy who had assessment of MGMT promoter methylation status and who had undergone tumour resection (population 3, n=103). Cox proportional hazards models were fitted with and without O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. Nomograms were developed to predict an individual patient's median and 2-year survival probabilities. No nomogram was developed in the radiotherapy-alone group because combined treatment is now the new standard of care. FINDINGS: Independent of the MGMT promoter methylation status, analysis in all randomised patients (population 1) identified combined treatment with temozolomide, more extensive tumour resection, younger age, Mini-Mental State Examination (MMSE) score of 27 or higher, and no corticosteroid treatment at baseline as independent prognostic factors correlated with improved survival outcome. In patients assigned temozolomide and radiotherapy (population 2), younger age, better performance status, more extensive tumour resection, and MMSE score of 27 or higher were associated with better survival. In patients who had tumours resected, who were assigned temozolomide and radiotherapy, and who had available MGMT promoter methylation status (population 3), methylated MGMT, better performance status, and MMSE score of 27 or higher were associated with improved survival. Nomograms were developed and are available at http://www.eortc.be/tools/gbmcalculator. INTERPRETATION: MGMT promoter methylation status, age, performance status, extent of resection, and MMSE are suggested as eligibility or stratification factors for future trials in patients with newly diagnosed glioblastoma. Stratifying by MGMT promoter methylation status should be mandatory in all glioblastoma trials that use alkylating chemotherapy. Nomograms can be used to predict an individual patient's prognosis, and they integrate pertinent molecular information that is consistent with a paradigm shift towards individualised patient management.

(1) title

NOMOGRAMS FOR PREDICTING SURVIVAL OF PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME : A PROGNOSTIC FACTOR ANALYSIS OF EORTC/NCIC TRIAL 26981-22981/CE.3

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Abstract

Purpose:

To confirm and/or identify new prognostic factors for survival in adult patients with glioblastoma (GBM), derive nomograms predicting an individual patient's prognosis and suggest stratification factors for future trials in newly diagnosed GBM patients.

Patients and Methods

Data from 573 patients with newly diagnosed GBM randomized to EORTC/NCIC trial 26981-22981/CE.3 were included in survival modelling. For 206 patients the methylation status of the MGMT (O6-methylguanine-DNA methyltransferase) gene promoter could be assessed. Cox Proportional Hazards models were fit with and without the MGMT promoter methylation status. Nomograms were developed to predict an individual patient's median and two year survival probabilities.

Results

Independent of the MGMT promoter methylation status, analysis in all randomized patients identified combined treatment with temozolomide (TMZ/RT), tumor resection, younger age, a Mini-Mental State Examination (MMSE) of 27 or higher and no corticosteroids medication at baseline as independent prognostic factors. In resected patients treated by TMZ/RT and available MGMT promoter methylation status assessment, a methylated MGMT, a good performance status and a normal MMSE of 27 or higher were associated with an improved survival.

Conclusions

MGMT promoter methylation status, age, performance status, extent of resection and MMSE are suggested as eligibility or stratification factors for future randomized trials in newly diagnosed GBM. Stratifying by MGMT promoter methylation status should be mandatory in all GBM trials using alkylating agent chemotherapy. Nomograms, electronic versions of which are provided at http://www.eortc.be/tools/gbmcalculator, can be used to predict an individual patient's prognosis. They integrate pertinent molecular patient information in line with a shift in paradigm towards individualized patient management.

Article

Introduction

A randomized trial recently published by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group (EORTC/NCIC trial 26981-22981/CE.3) demonstrated that the addition of temozolomide to radiotherapy for newly diagnosed glioblastoma (GBM) patients significantly improves their survival.(1) Radiotherapy plus concomitant and adjuvant temozolomide has rapidly become the new standard of care in Europe and North America. New strategies are now being developed building on this treatment as the backbone. Despite this progress, the overall outcome of GBM patients remains unsatisfactory, and prognosis is highly variable among various categories of patients. Previous studies have identified several clinical factors that help to explain the variability of outcome in GBM patients. Age, performance status and the extent of surgical resection are the most consistently reported prognostic factors.(2-7) In particular, a recursive partitioning analysis (RPA) carried out by the Radiation Therapy Oncology Group (RTOG) has identified four risk classes for GBM (classes III,IV,V and VI) based on the patient's age, Karnofsky performance status, neurological function, mental status and the extent of surgery.(2, 3) In addition, the impact of the tumor's location has been described by several publications. This concerns especially the unfavourable influence of midline cranial shift involvement, of deep seated tumors and the possible favourable prognosis of a frontal location. (4-10)

The unfavourable prognostic impact of an abnormal mental status was first reported by Curran et al. in the original paper of the RPA classification, although a formal definition of abnormal mental status was not provided.(2) In a recent study on prognosis in high grade gliomas, the Folstein Mini-Mental State Examination (MMSE) was retained together with age and grade in a RPA.(11) Similarly, Brown et al. identified MMSE as a prognostic factor in both low-grade and high-grade glioma patients. In another study, they also suggested increased fatigue as an independent predictor of poorer survival.(12) (13)

A decreased expression of the O6-methylguanine-DNA methyltransferase (MGMT) repair enzyme makes tumors sensitive to alkylating agent chemotherapy. Molecular analysis of the tumor tissue of a large subgroup of patients demonstrated that the benefit of temozolomide chemotherapy might be limited to patients having a silenced *MGMT* gene by promoter methylation. (14,15)

The main objective of this study is to confirm or identify new prognostic factors for survival in GBM patients and to derive nomograms ie graphical representations of statistical models which predict a particular patient's prognosis. They have been utilized in other cancer sites especially urologic oncology but so far have not been applied to neuro-oncology,

Patients and Methods

A total of 573 patients with newly diagnosed GBM (World Health Organization [WHO] astrocytoma grade IV) were randomized in EORTC/NCIC trial 22981/26981/CE.3 .(1) Eligibility criteria included age 18 to 70 years, WHO performance status less than or equal to 2, and no more than 6 weeks since diagnostic surgery or biopsy. Patients received either standard radiotherapy alone or the same radiotherapy plus daily temozolomide followed by up to six cycles of adjuvant temozolomide. Patients were stratified by center, age, performance status and extent of surgical resection. Other available baseline clinical factors were the sex, tumor location, ongoing corticosteroid therapy, MMSE, and the hemoglobin level.

Age was categorized in three classes of almost equal size (≤50, 51-60 and >60). The cut-off for MMSE i.e. normal (27-30) versus impaired (<27), was used as previously reported.(11) For hemoglobin, a value ≥ 120 g/L in females and 130 g/L. in males was considered normal.

Assessment of tumor characteristics was based on the local interpretation of preoperative MRI. Extent of surgical resection was determined perioperatively by the neurosurgeon (macroscopically complete versus partial versus biopsy only).

Survival was calculated as the time from randomization until death from cancer or any cause, or censored at the date of last follow-up. Compared to previous publications (1, 14,16), this study is based on survival data updated in September 2006. Univariate screening was performed using Kaplan-Meier curves (17), the log-rank test for binary variables and the log-rank trend test for ordered categories. In order to identify subgroups of patients with a potentially different survival when treated with TMZ/RT compared to those treated by RT alone, treatment by factor interaction tests were computed. Factors or treatment by factor interactions with a p-value less than an arbitrarily chosen significance level of 10% were candidates for the multivariate analyses. As many factors were ordinal, the association between them was estimated by the Spearman rank correlation coefficient (rho).(18) A coefficient less than 0.30 was considered a poor correlation. The Cox proportional hazards model was used with forward stepwise model selection using a significance level of 5%. (19) The probability of inclusion of a factor in the multivariate model, a criterion for the prognostic importance of the factor, was estimated using the bootstrap resampling technique (see supplemental materials). (20) The variables with a probability of inclusion superior to 60% based on 1000 bootstrap samples were included in the final model. The methylation status of the *MGMT* promoter was determined retrospectively in a representative subset of 206 (36%) patients where sufficient tumor material was available.(14) The subgroup of patients in which the *MGMT* promoter methylation status was assessed was not different from the group of patients without *MGMT* promoter methylation status assessment with respect to known prognostic factors, except for extent of resection. *MGMT* promoter methylation status could not usually be assessed in patients whose tumors were only biopsied due to the lack of a sufficient amount of tumor tissue.

Survival modelling was conducted in three patient populations: population 1) the intent-to-treat (ITT) population of all randomized patients (n=573), population 2) the subgroup of patients treated by TMZ/RT (n=287), population 3) the subgroup of patients who underwent partial or complete resection and were treated by TMZ/RT in the presence of an *MGMT* promoter methylation assessment (n=103). The reasons for performing the analyses in three different populations are the following: 1) it was important to identify main clinical prognostic factors taking into account the treatment 2) the strength and importance of some prognostic factors might differ according to the treatment administered, in particular in TMZ/RT treated patients 3) the impact of *MGMT* promoter methylation status on the prognosis of TMZ/RT treated patients had to be further evaluated.

For the three populations, the R "Design" package was used to develop nomograms which predict the median survival and the probability of survival at 2 years taking into account the patient's characteristics. The accuracy of predictions was assessed by estimating the models' calibration and discrimination measured by the Concprdance index corrected for optimism (C-index). The C-index is the probability that for two patients chosen at random, the patient who had the event first had a higher probability of having the event according to the model. C-index=0.50 represents agreement by chance; c-index=1.0 represents perfect discrimination (21). Ideally, accuracy of a model should be assessed in an independent dataset. If it is no available, the C-index must be corrected for "optimism". The bootstrap technique was used to estimate this correction (see supplemental materials).

Calibration and discrimination of Cox models based on the RPA classification were also assessed and compared to those of our models.

These prognostic factor analyses are exploratory. Their results are therefore limited by their reduced sample sizes, lacks of power and possible selection biases.

All patients provided written informed consent, and the study was approved by the ethics committees of the participating centers.

The clinical study was supported in part by an unrestricted educational grant by Schering-Plough, Kenilworth, NJ, while the study was formally sponsored by EORTC and NCIC. Study design, data collection and analyses, data interpretation, writing of the report, or the decision to submit the paper for publication, were the sole responsibility of the investigators and collaborators of EORTC and NCIC. For the purpose of the current report, only T.G.,the corresponding author, had full access to the raw data in the study and has final responsibility for the decision to submit for publication.

Results

The patient characteristics in population 1 (all randomized patients) are reported in table 1. Overall, MMSE was missing in 22 patients (3.8%). Except for the *MGMT* promoter methylation status, less than 6 patients (1%) had data missing for the other factors. The dataset was found representative of the GBM population so that no imputation technique was used and patients with missing data were excluded from analysis. Table 2 summarizes the univariate survival analyses of each factor by presenting the logrank test p-value. Apart from the hemisphere (left/right), all factors passed the 10% statistical significance criterion. Anemic patients showed a better outcome compared to patients with normal hemoglobin levels (p=0.04). Nevertheless, the hemoglobin level by treatment interaction test was not significant (p=0.11). Both the absence of corticosteroids administration at baseline and the extent of surgery were positively correlated with survival. There wasn't a significant survival difference between frontal, temporal, occipital and parietal locations (data not shown). Tumors with central location or mulltifocal (i.e. present on more than one lobe) had a worse prognosis than unilobar tumors, they also had a complete resection less often (25 vs 201 patients or 24% vs 43%) and such patients more often had an impaired MMSE (42 vs 125 patients or 44% vs 27%). The last column of table 2 shows p-values of the treatment by factor interaction tests. Treatment by performance status was the only interaction test that passed the 10% statistical significance criterion (p=0.06). Kaplan-Meier survival estimates for the most important factors are presented in the supplemental materials (figures 1 to 6).

Significant but poor correlations (rho<0.30) between various factors were found. The extent of surgical resection was found to be positively correlated with a good performance status (rho=0.15), the absence of corticosteroids therapy (rho=0.24), monofocal location (rho=0.17) and a normal mental status (rho=0.16). Younger age was positively associated with a good performance status (rho=0.17) and with a normal mental status (rho=0.25). Good performance status was positively correlated with the absence of corticosteroids therapy (rho=0.13) and a normal mental status (rho=0.25). A negative correlation was found between normal MMSE and mulltifocal or central tumor location (rho=0.13). Anemic patients received corticosteroids at randomization less frequently than did patients with a normal hemoglobin level (81 vs 323 patients or 58% vs 75%) and they more often underwent a complete resection (69 vs 154 patients or 49 % vs 36%). The anemia may thus be due in part to the preceding surgery.

Table 3 presents the results of the multivariate Cox proportional hazards analyses. Factors selected in the final model were treatment, age, extent of surgical resection, MMSE and the use of corticosteroids at baseline. The probabilities of inclusion (ie. of being selected in the Cox model) were 99.6%,82%,96%,98%,85%, respectively. The C-index corrected for optimism was 65.0%. Accuracy was not improved when age and MMSE were entered as continuous factors (C–index corrected for optimism equals 65%). Performance status was not selected and its probability of inclusion was 48%. It was however selected in the absence of MMSE in the Cox model.

For this population, the nomogram is depicted in figure 1 . The patient's median survival and probability of survival at 2 years are obtained by drawing a vertical line from the Total Point axis straight down to the outcome axes (see legend). Alternatively the prognosis can be obtained by summing up the points for each factor in table 4 and reading the median survival and probability of survival at 2 years from figure 4. As an example, a patient treated by RT alone, disregarding *MGMT* promoter methylation and performance status, aged 40 years, with a partially resected tumor, with a MMSE of 30 and not receiving corticosteroids at baseline has a total prognostic score of 132 and is predicted to have a 15 months median survival and 24 % chance of surviving 2 years.

Baseline characteristics of population 2 (TMZ/RT treated patients) were similar to those of RT patients (table 1). Table 2 summarizes the univariate analyses of each factor by presenting the medians with 95% confidence intervals, p-values and hazard ratios with 95% confidence intervals in each of the two treatment groups. For instance, patients with a MMSE less than 27 treated by TMZ/RT had a risk of death of 1.87 times that of patients with MMSE in the range 27 to 30.

Apart from the hemisphere (left/right) and sex, all factors passed the 10% statistical significance criterion. Here also, anemic patients showed a better outcome compared to patients with normal hemoglobin levels (p=0.023).

In multivariate analyses (table 3), factors selected and included in the final model were age (p=0.008, probability of inclusion 80%), performance status (p=0.006, 78%), extent of surgery (p<0.001, 75%) and MMSE (p<0.001, 79%). In this subset, corticosteroids were not selected (p>0.05, 33%). Sex was selected but had a percentage of inclusion in bootstrap simulations less than 60% (p=0.03, 55%) and therefore was excluded from the final model. The C-index corrected for optimism was 63.0%.

Since the performance status by treatment interaction test was significant and this factor was selected in the TMZ/RT population but not in the population of all randomized patients (population 1), a Cox model was also fit in patients treated by RT alone. In this subset, extent of surgery (p=0.007, 80%), MMSE (p<0.0001, 89%) and corticosteroids (p=0.005, 81%) were selected but not age (p>0.05, 29%) or performance status (p>0.05, 8%). Anemic patients did not show a better outcome compared to patients with normal hemoglobin levels (p=0.71).

The resulting nomogram is shown in figure 2. Prognosis can also be obtained from table 4 and figure 5.

As an example, the same patient presented in the all randomized patients population with a performance status 0 has a total prognostic score of 50 and has a predicted 20 months median survival and 42.5% probability of survival at 2 years.

Patients in population 3 (TMZ/RT treated patients, resected tumor and *MGMT* promoter methylation status assessed) were slightly younger (median: 53 [19-70] vs 56 [18-70] yrs), and more often had a frontal tumor (40.8% vs 27.0%). Patients with biopsy only were less likely to have *MGMT* promoter methylation assessed and were not included. With such a high percentage of missing data no substantial benefit was expected from imputation techniques and therefore analyses were performed in the complete dataset.

The *MGMT* promoter methylation status was not found to be correlated with age or with any of the other prognostic factors tested.

Due to the limited sample size and power of the analyses, factors selected in the univariate analyses in the TMZ/RT population were also considered for the multivariate analysis in this population.

The final multivariate Cox model in table 3 included the *MGMT* promoter methylation status (p<0.0001, 92%), performance status (p=0.003, 82%) and MMSE (p=0.008, 81%). The C-index corrected for optimism was 65,5%. The resulting nomogram is shown in figure 3. Prognosis can also be obtained from table 4 and figure 6. As an

example, the patient reported in the previous populations is predicted to have 48.0 compared to 16.9 months median survival and a 66% compared to 32.5% probability of survival at 2 years, in *MGMT* promoter methylated versus unmethylated tumors, respectively.

The nomogram in the population of all randomized patients (population 1) was well calibrated but could not make an accurate prediction for patients with a probability of survival at 2 years superior to 40%. The nomograms in the two other populations could predict patients with a survival probability at 2 years greater than 40% but were less well calibrated and predictions were less accurate (more detail on nomograms' calibration is available at http://www.eortc.be/tools/gbmcalculator/calibration.htm).. We show in supplemental materials that predictions of our nomograms are more accurate than those of models based on the RPA classification. C-index of RPA based models is 58.4%, 58.9% and 55.5% in populations 1, 2 and 3 respectively (see supplementary table 1). Accuracy was particulary low for RPA classes III and V.

Discussion

A proper understanding of prognostic factors is important for the counseling of individual patients, to select patients for specific treatments and for the design and interpretation of clinical trials. EORTC/NCIC trial 26981-22981/CE.3 showed that treatment with concurrent and adjuvant temozolomide in addition to radiotherapy improved the overall outcome as compared to radiotherapy alone.(1) This companion prognostic factor analysis has identified treatment with RT and concomitant and adjuvant treatment with temozolomide, age, extent of surgical resection, *MGMT* promoter methylation status, WHO performance status, neurological function expressed by the MMSE as well as the need for corticosteroids administration after surgery or biopsy as the most relevant independent prognostic factors for the outcome of GBM patients. Although the prognostic significance of some of these factors has been identified before, the significant negative prognostic impact of the presence of corticosteroid treatment at baseline in patients treated by RT alone but not when treated by TMZ/RT, and iWHO performance status and age being significantly correlated with survival in patients treated by TMZ/RT but not when treated by RT alone are novel findings which deserve further investigation.

Corticosteroid use was identified as a poor prognostic factor in an old, small study with a heterogeneous patient population, but has not been assessed in most more recent trials.(22) Its use may identify patients with more severe clinical signs and symptoms prior to surgery, or with larger tumors or tumors that were amenable to a biopsy only. Finally, the efficacy of this therapy seems to be enhanced in patients with a good performance status. In both cases, confirmations in future trials are needed.

Our trial confirmed the presence of a strong relation between outcome and extent of tumor resection; however the interpretation is limited by the fact that the extent of resection was based on perioperative assessment by the neurosurgeon without a mandatory postoperative radiological confirmation. This limits the reliability of the distinction between partially and completely resected patients. The study was not randomized for this issue, and we could not identify the relevance of the extent of resection in the subset of patients with known *MGMT* promoter status. Therefore the relative contribution from attempting maximal resection cannot be assessed. It therefore remains unclear from these data if a more extensive resection improves the outcome. However, in view of the better outcome of resected patients in many studies, all GBM patients should undergo as extensive a resection as is safely possible.(1)

Our trial demonstrated that combined and adjuvant temozolomide treatment improves outcome. It also suggests, although not reaching statistical significance,,that the subset of patients with a methylated *MGMT* promoter particularly benefits from the addition of temozolomide. Even patients not treated with concomitant and adjuvant chemotherapy presented with a better outcome in the presence of a methylated *MGMT* promoter, probably due to a greater efficacy of salvage chemotherapy with alkylating agents administered at the time of recurrence. (14) Earlier studies in which all patients received adjuvant BCNU in addition to radiotherapy also found

alkyltransferase expression of prognostic significance.(23, 24) .We discussed elsewhere the influence of stratifying by this molecular marker in the development of new therapeutic strategies for GBM patients (15).

The present analysis did not show any correlation between age and the *MGMT* promoter methylation status, which implies that the poor prognosis of elderly patients cannot be explained by a lower frequency of *MGMT* promoter methylation. In contrast, in the presence of *MGMT* promoter methylation information, age was no longer retained in the model and the nomogram. This suggests that older patients with methylated *MGMT* promoter might benefit from the new combination therapy despite their age. It cannot be excluded that this might be due to the lack of power in this subgroup analysis. Additional data will be necessary to assess the effect of TMZ/RT in this subgroup.

In a RPA, the RTOG identified 6 prognostic classes of anaplastic gliomas based on clinical factors, in which classes III through VI are applicable to GBMs. However, this system developed and validated in the early 1990's is based on data collected from 1974 to 1994. During the 3 decades since 1974 not only have diagnostic tools, radiotherapy planning and treatment techniques dramatically changed but also the histopathological classification systems have been revised, and molecular factors relevant for outcome have been identified. Within the current clinical context, we have previously shown that RPA prognostic classes still separate prognostic groups after combined chemo-radiotherapy with temozolomide in newly diagnosed GBM. (16,25)

The present analysis adds a new dimension to the previous studies, in that it approaches prognosis from the individual patient's perspective: the nomogram offers a more tailored approach for individual patients taking their individual prognostic factors into account. Investigators might want to use their prediction in groups of patients from small phase II trials investigating innovative adjuvant treatment strategies in order to evaluate if improved outcome is not a consequence of patient selection. As formal comparisons are not possible in phase II trials, this use of nomograms should be limited to guide further research only. We claim that nomograms predictions are more accurate than those based on the RPA classification and therefore better adapted to investigate tailored therapeutic options for individual patients.

This study is exploratory and a limitation of these nomograms is of course that there is no validation yet possible in a large independent set of patients.(3, 26) At present no other large datasets are available on radiotherapy with concurrent and adjuvant temozolomide chemotherapy treated patients including the MMSE score and the *MGMT* promoter methylation status. Some analyses have been performed in sub-groups of patients, in particular in those with sufficient biological materials for MGMT promoter methylation assessment. Validity and generalizability of these nomograms need to be evaluated in prospectively acquired data.

Electronic versions of the nomograms are available at http://www.eortc.be/tools/gbmcalculator.

In future trials of newly diagnosed GBM, the *MGMT* promoter methylation status, age, performance status, extent of resection and MMSE should be considered as eligibility criteria and/or stratification factors. Stratifying by

MGMT promoter methylation status should be mandatory in both adjuvant and recurrent GBM trials that include the administration of alkylating agents. When the *MGMT* promoter methylation status cannot be assessed before randomization, it should be determined after inclusion of the patients and used as a correction factor in the survival analyses.

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Tables and figures

Table 1. Patient demographics and baseline characteristics

Table 2. Univariate analyses of potential survival prognostic factors

Table 3. Cox Proportional Hazards analyses of survival prognostic factors

Table 4: Prognostic scores of each factor in the three nomograms

Figure 1. Nomograms for predicting median survival and probability of survival at 2 years in all randomized patients (population 1),

Figure 2. Nomograms for predicting median survival and probability of survival at 2 years in patients treated by TMZ/RT (population 2)

Figure 3. Nomograms for predicting median survival and probability of survival at 2 years in patients treated by TMZ/RT who underwent complete or partial resection in presence of MGMT promoter methylation status assessment (population 3).

Legend: First, choose the patient's treatment on the Treatment axis. Draw a line straight upwards to the points axis and record by how many points survival outcome is affected when the patient receives the treatment. This process must be repeated for the other axes. For each predictor, points must be summed and the sum must be located on the Total Point axis. A line straight down must be drawn to get an estimate of the patient's median survival and 24 months probability of survival at 2 years.

Figure 4. Prognostic plots for the nomograms in all randomized patients (population 1).

Figure 5. Prognostic plots for the nomograms in patients treated by TMZ/RT (population 2).

Figure 6. Prognostic plots for the nomograms in patients treated by TMZ/RT who underwent complete or partial resection in presence of MGMT promoter methylation status assessment (population 3).

Legend: Median survival in months (dashed line, left y-axis) and probability of survival at 2 years (solid line, right y-axis) are plotted as a function of the total prognostic score.

Conflict of interest statement

We declare that we have no conflict of interest

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Supplemental materials to the manuscript by Gorlia T et al

➢ Methods

- **Development of nomograms**
- **What is the bootstrap technique ?**
- **Measuring nomograms predictions' accuracy**
- **Comparison of accuracy of predictions based on our nomograms and on those of Cox models based on the RPA classification**

➢ Results

- **Supplementary Figure 1.** Kaplan Meier estimates of Overall Survival according to age .
- **Supplementary Figure 2**. Kaplan Meier estimates of Overall Survival according to the extent of surgery .
- **Supplementary Figure 3.** Kaplan Meier estimates of Overall Survival according to the Mini-Mental State Examination .
- **Supplementary Figure 4.** Kaplan Meier estimates of Overall Survival according to the administration of Corticosteroids at baseline.
- **Supplementary Figure 5.** Kaplan Meier estimates of Overall Survival according to the WHO performance status.
- **Supplementary Figure 6**. Kaplan Meier estimates of Overall Survival according to the *MGMT* promoter methylation status in the population of resected patient.
- **Comparison of accuracy between predictions of nomograms and those of Cox models based on the RPA classification**
- **Supplementary Table 1.** Concordance index adjusted for optimism of the nomograms and Cox models based on the RPA classification in the three study populations.

Supplementary methods

Development of nomograms

The main goals of staging systems like nomograms are to provide as accurate as possible predictions for specified endpoints. To be useful in the clinic, they must be sufficiently practical and must include easily available and measured parameters (1,2). We claim that our nomograms fulfill these conditions.

In this study, three multivariate Cox's proportional hazards models for overall survival were fit in three different populations with a set of prognostic factors initially screened by univariate analyses (3). Coefficients of the three Cox regression models were utilized to generate nomograms that predict for individual patient's median survival for those patients with similar characteristics and probability of survival at 2 years. For each nomogram and patient, the Cox regression linear predictor function (LP_j) was obtained by summing up the products between the characteristic i of patient j (X_{ij}) and corresponding Cox coefficient (β_i):

$$LP_j = \sum_i \beta_i * X_{ij}$$

Baseline value LP_j equals 0 and corresponds to the best prognosis patients.

For each factor, prognostic scores presented in table 4 of the manuscript are given by the following formula:

$$\text{Prognostic score for each value of characteristic i} = \frac{\beta_i * X_{ij}}{B} * 100$$

Where B is the Cox coefficient corresponding to the factor with the maximum product $\beta_i * X_{ij}$

The formula for median survival taking into account the patient's characteristics:

$$\text{Median Survival}_j = \text{minimum}\{t : H_0 \geq u_j\} \text{ where } u_j = -\ln(0.5) * e^{-LP_j}$$

It is the smallest time (t) corresponding to a value of the baseline cumulative hazard (H0) superior or equal to u_j. When LP_j=0, it provides the median survival of the best prognosis patients.

The probability of survival at 2 years is given by the following formula:

$$\text{Probability of survival at 2 years}_j = S_0^{e^{LP_j}}$$

Where, S_0 is the probability of survival at 2 years for patients with the best prognosis.

What is the bootstrap technique and what does it do ?

The bootstrap is a simulation technique first described by Bradley Efron (4). The idea is that the original dataset is a random sample of patients representative of a general population. Bootstrapping means generating a large number of datasets each of which with the same sample size as the original one by resampling with replacement (ie. an already selected patient may be selected again). From these replicated datasets, uncertainties around estimates or inferences can be measured.

Measuring and comparing nomograms predictions' accuracy

Accuracy is defined as the degree of conformity with a standard or a true value or the degree of correctness attained in a measure. Accuracy is useful to quantify the utility of a predictor or model, diagnose for model overfitting or lack of fit. Accuracy of competing models can be compared. Accuracy can be assessed by two parameters: discrimination and calibration (5).

Discrimination measures a predictor's ability to separate patients with different prognosis. It is quantified by the Concordance Index (Harrel's C-index) which is the proportion of all usable patient pairs in which the predictions and observations are in agreement; i.e. the probability that for two patients chosen at random, the patient who had the event first had a higher probability of having the event according to the model. It ranges from 0.5 (agreement by chance) to 1.0 (perfect discrimination ability).

Calibration refers to the ability to provide unbiased survival predictions in groups of similar patients. This ability is assessed by visual examination of calibration plots. In our calibration plots (see supplementary figures 7-12), horizontal axis is prediction (provided by our nomograms or Cox models based on the RPA classification) for the probability of survival at 2 years. Vertical axis is the observed proportion of patients surviving 2 years. Dashed line represents a perfectly calibrated nomogram. Solid line is current prediction model performance with 95% confidence intervals. ○ represents subgroups of patients with different predicted probability of surviving 2 years. × represents the bootstrap-corrected estimate of nomogram performance (see below for more details on the use of the bootstrap technique).
A prediction model was considered "well calibrated" if the difference between predictions and observations in all groups of similar patients was close to 0 (perfect calibration). Any large deviation (eg. >5%) indicated lack of calibration.

Measuring the accuracy of a multivariate model in the training dataset provides generally too optimistic estimates. Ideally, accuracy should be assessed in an independent dataset from the same population. In this study, no large validation dataset including both the MGMT promoter methylation status and MMSE was available. As a substitute, the bootstrap technique was used to best estimate the likely external validation accuracy of our models. Corrections for optimism were calculated for the calibration plots and the C-index. The bootstrap technique was also used for each factor to estimate its probability of being selected into a Cox model and to assess its importance for the prediction. Cox models were fit on 1000 bootstrap resampling and the probability of inclusion of each factor was estimated by the proportion of samples with the factor included in the set of prognosticators selected by the stepwise method.

The R “Design” package used to assess these parameters is a program developed by Harell FE in the R language. It can be downloaded from the URL: http://cran.cnr.berkeley.edu/src/contrib/Descriptions/Design.html

Accuracy comparison of predictions based on our nomograms and on those of Cox models based on the RPA classification:

Mirimanoff RO et al (6) showed in a previous report based on the same dataset that RPA classification retained its prognostic significance in Glioblastoma patients treated by irradiation with or without Temozolomide. RPA classes had to be adapted because performance status and mental status scales were different from those used in the original RTOG study. We used the same definitions in this study. Accuracy of predictions based on our nomograms and on those of Cox models with the RPA class entered as an ordered factor (called RPA models) was compared with the calibration and discrimination parameters.

Supplementary results

Supplementary Figure 1. Kaplan Meier estimates of Overall Survival according to age (all randomized patients: population 1, n=573) .

Supplementary Figure 2. Kaplan Meier estimates of Overall Survival according to the extent of surgery (all randomized patients: population 1, n=573) .

Supplementary Figure 3. Kaplan Meier estimates of Overall Survival according to the Mini-Mental State Examination (all randomized patients: population 1, n=573) .

Supplementary Figure 4. Kaplan Meier estimates of Overall Survival according to the administration of Corticosteroids at baseline (all randomized patients: population 1, n=573) .

Supplementary Figure 5. Kaplan Meier estimates of Overall Survival according to the WHO performance status (all randomized patients: population 1, n=573) .

Supplementary Figure 6. Kaplan Meier estimates of Overall Survival according to the *MGMT* promoter methylation status in the population of resected patient (all randomized patients with tumor resection and MGMT promoter methylation status assessed, n=199) .

Comparison of accuracy of predictions based on our nomograms and on those of Cox models based on the RPA classification:

Discrimination

The C-indexes corrected for optimism were lower in all three RPA models compared to nomograms (58.4% vs 65.0%, supplementary table 1). The discrimination of the RPA model in the population of TMZ/RT treated patients, resected tumor and MGMT promoter methylation status assessed was particularly low (55.5% versus 65.5%).

Supplementary table 1. Concordance Indexes corrected for optimism of the nomograms and RPA classification in the three study populations.

Calibration

More detail on nomograms' calibration is available at http://www.eortc.be/tools/gbmcalculator/calibration.htm.

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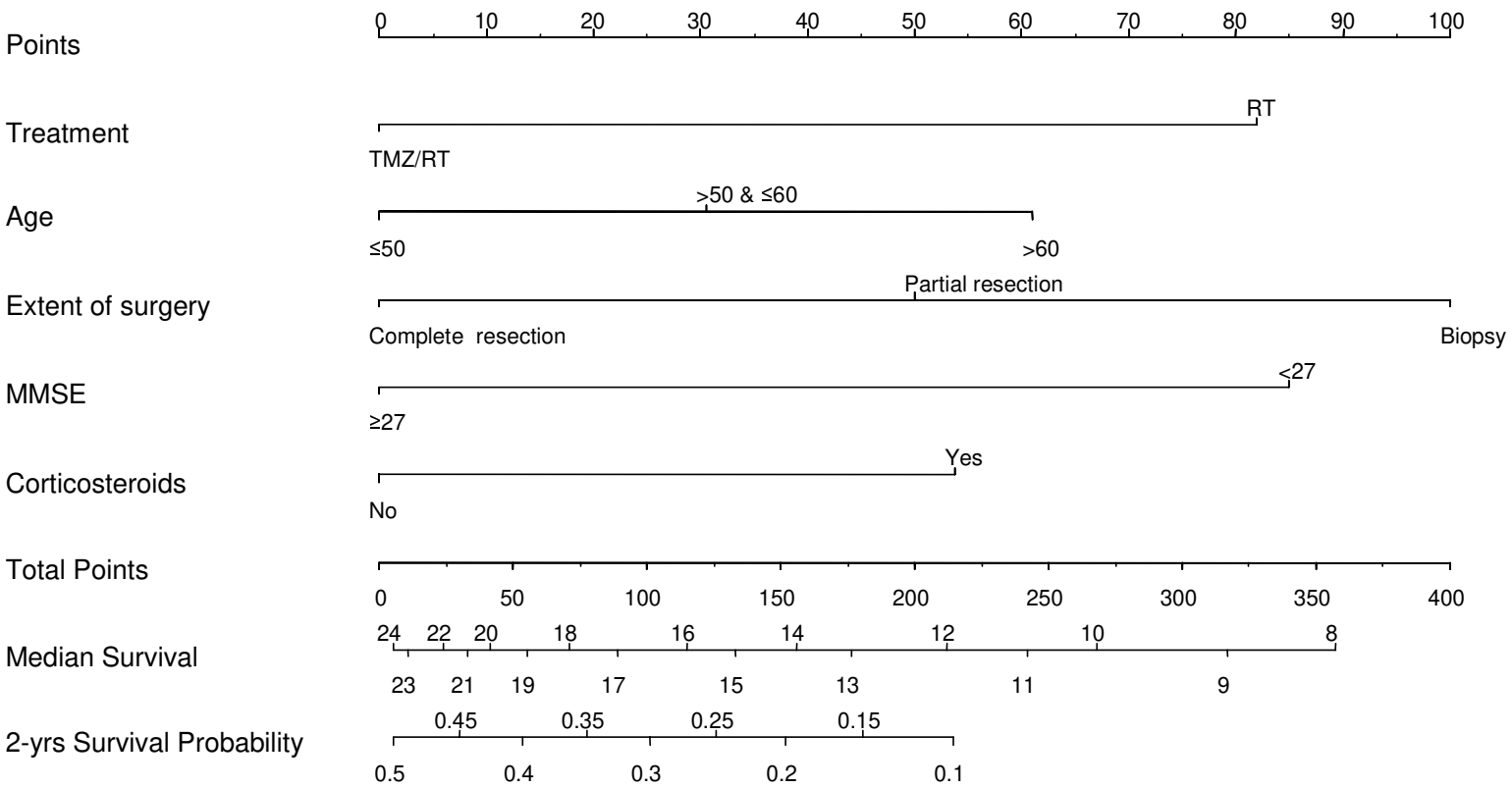
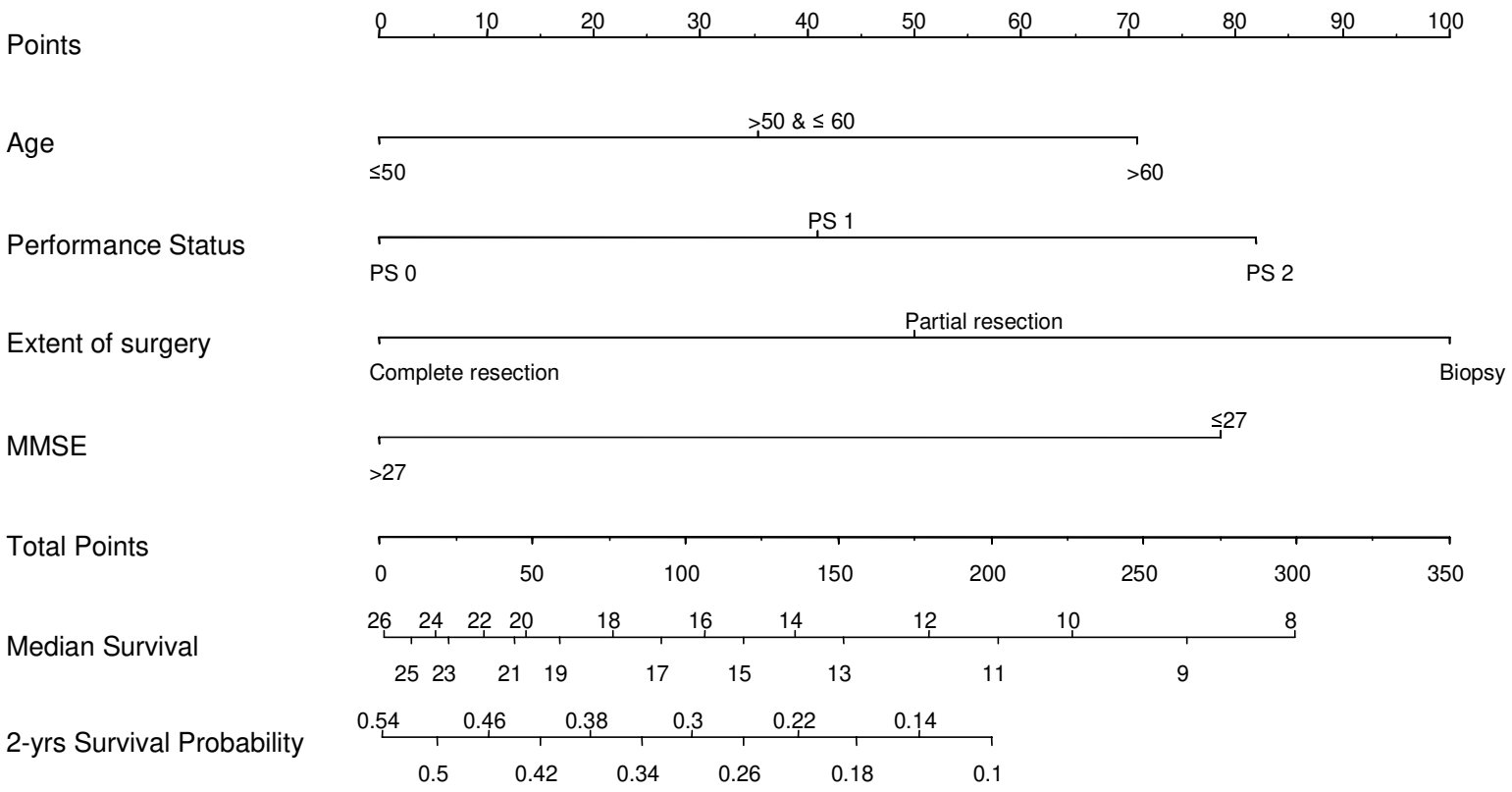
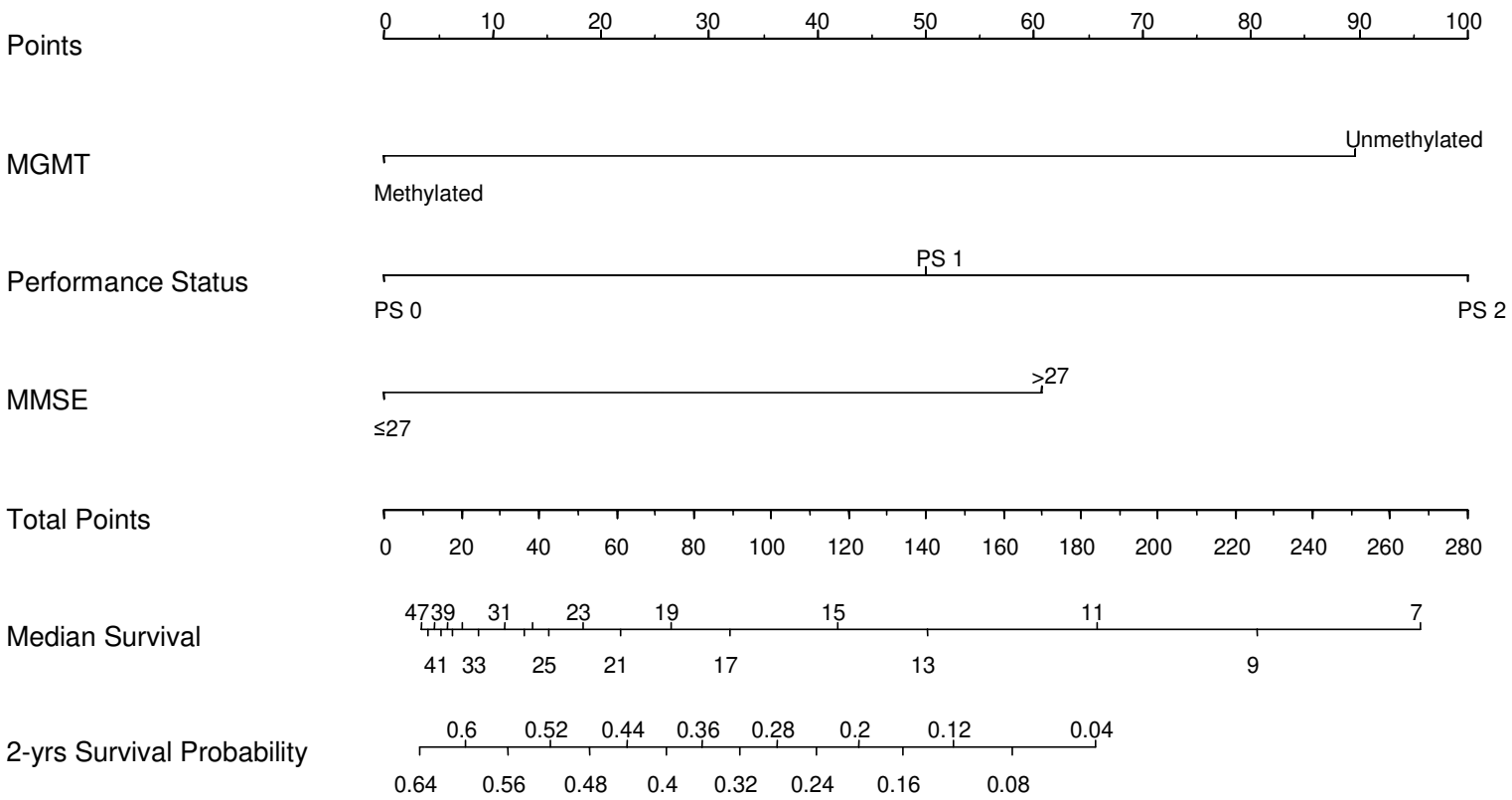
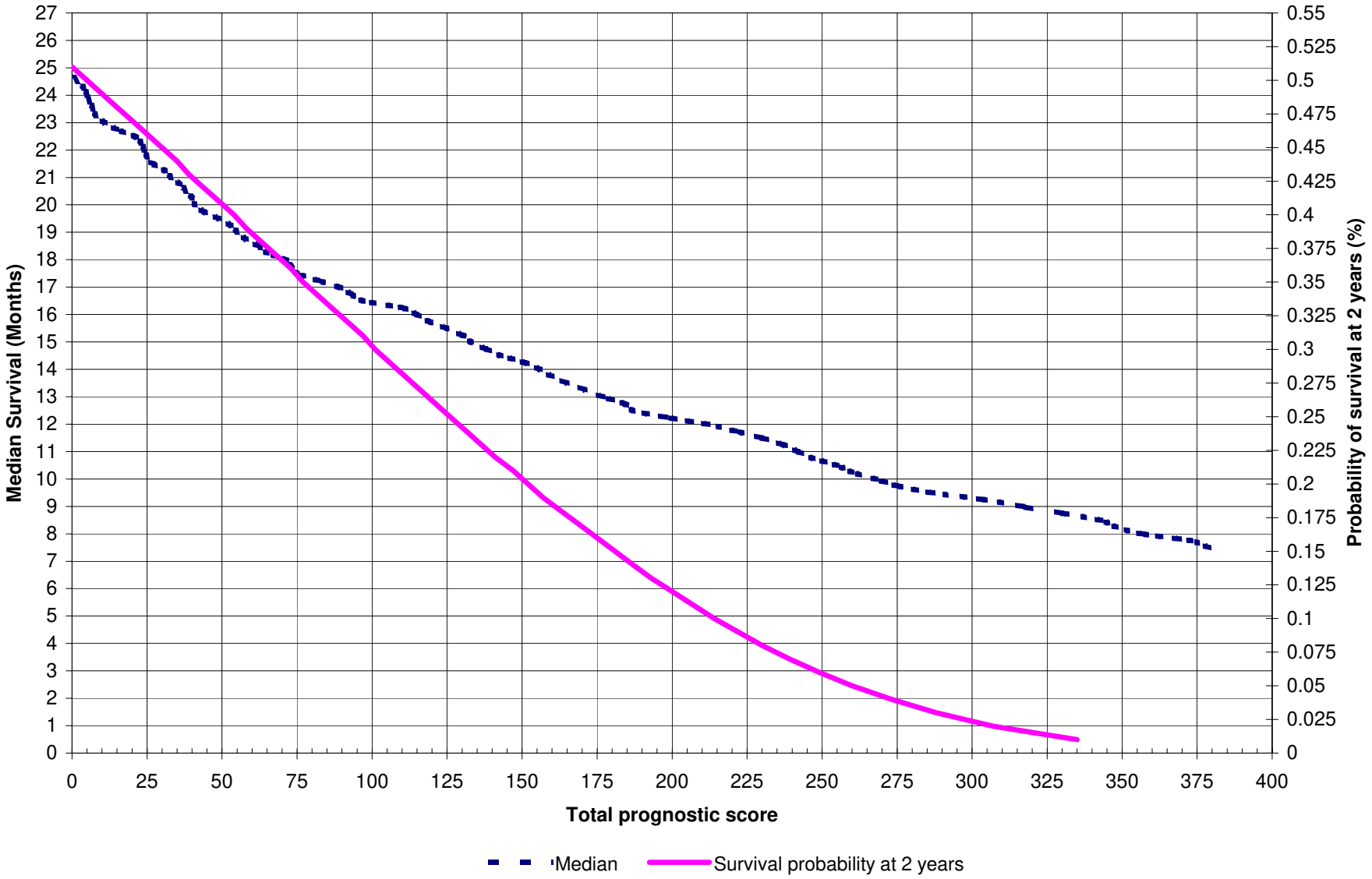
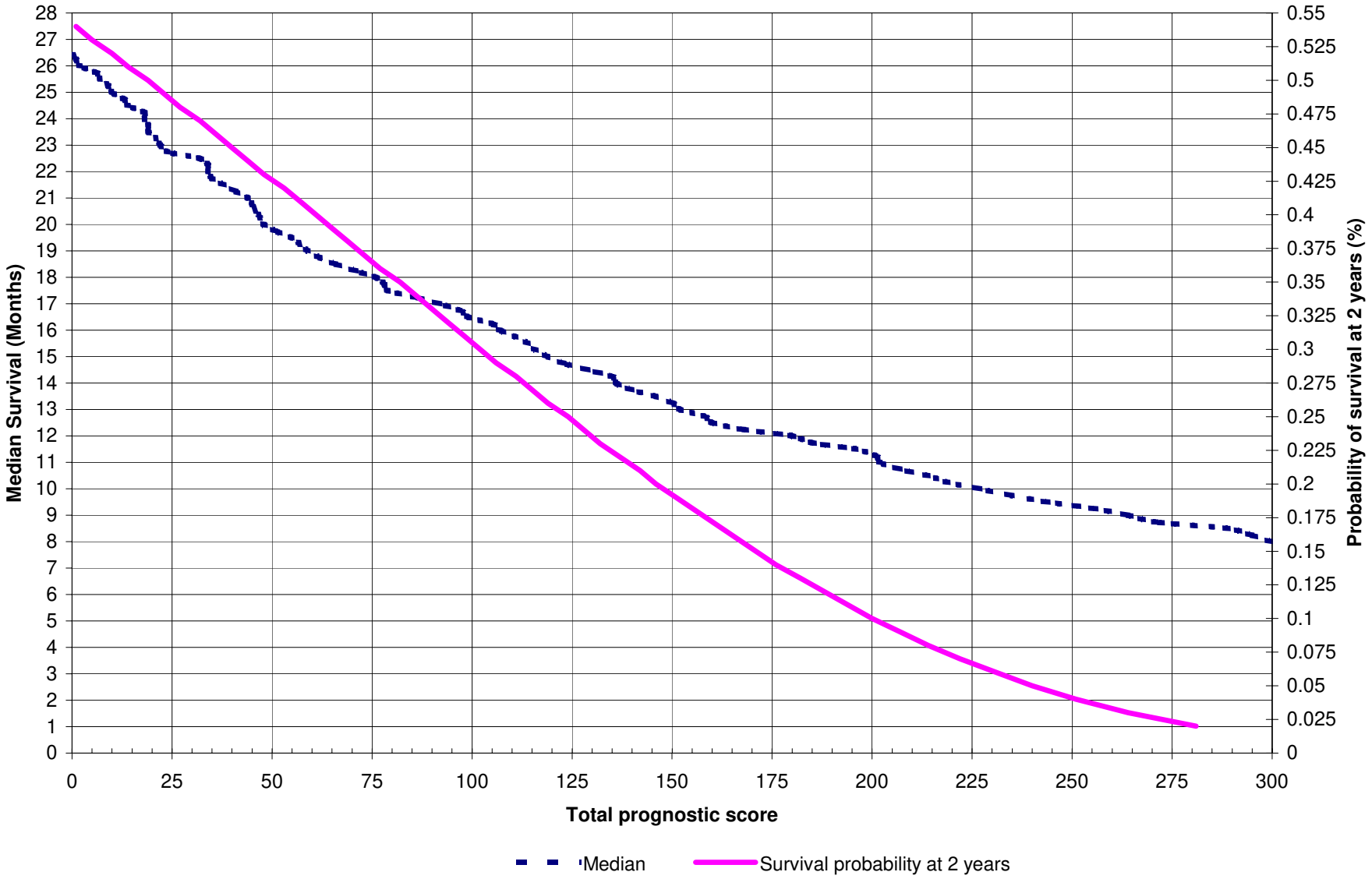

Points
0 10 20 30 40 50 60 70 80 90 100
Treatment
RT
TMZ/RT
Age
>50 & ≤60
≤50
>60
Extent of surgery
Partial resection
Complete resection
Biopsy
MMSE
<27
≥27
Corticosteroids
Yes
No
Total Points
0 50 100 150 200 250 300 350 400
Median Survival
24 22 20 18 16 14 12 10 8
23 21 19 17 15 13 11 9
2-yrs Survival Probability
0.45 0.35 0.25 0.15
0.5 0.4 0.3 0.2 0.1


Points
0
10
20
30
40
50
60
70
80
90
100
Age
>50 & ≤ 60
≤50
>60
Performance Status
PS 1
PS 0
PS 2
Extent of surgery
Partial resection
Complete resection
Biopsy
MMSE
≤27
>27
Total Points
0
50
100
150
200
250
300
350
Median Survival
26
24
22
20
18
16
14
12
10
8
25
23
21
19
17
15
13
11
9
2-yrs Survival Probability
0.54
0.46
0.38
0.3
0.22
0.14
0.5
0.42
0.34
0.26
0.18
0.1


Points
0 10 20 30 40 50 60 70 80 90 100
MGMT
Unmethylated
Methylated
Performance Status
PS 1
PS 0
PS 2
MMSE
>27
≤27
Total Points
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280
Median Survival
47 39 31 23 19 15 11 7
41 33 25 21 17 13 9
2-yrs Survival Probability
0.6 0.52 0.44 0.36 0.28 0.2 0.12 0.04
0.64 0.56 0.48 0.4 0.32 0.24 0.16 0.08


Median Survival (Months)
Probability of survival at 2 years (%)
Total prognostic score
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400
Median
Survival probability at 2 years


Median Survival (Months)
Probability of survival at 2 years (%)
Total prognostic score
0
25
50
75
100
125
150
175
200
225
250
275
300
Median
Survival probability at 2 years

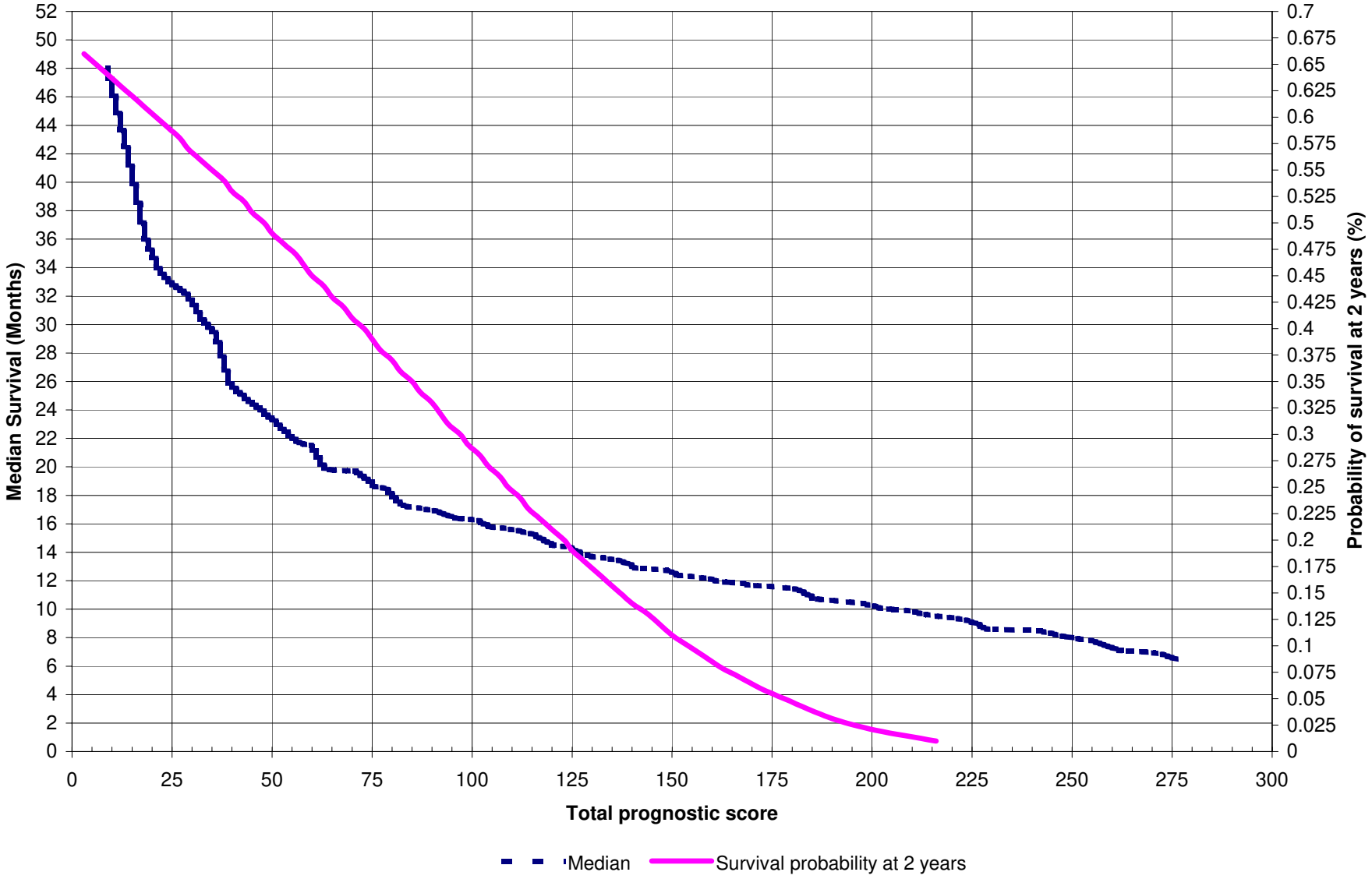

Median Survival (Months)
Probability of survival at 2 years (%)
Total prognostic score
0
25
50
75
100
125
150
175
200
225
250
275
300
Median
Survival probability at 2 years

Table 1. Patient demographics and baseline characteristics

Factor	Population 1 ‡ (n=573) No. of Patients (%)	RT alone patients (n=286) No. of Patients (%)	Population 2 ‡ (n=287) No. of Patients (%)	Population 3 ‡ (n=103) No. of Patients (%)	Not in population 3 ‡ (n=470) No. of Patients (%)
Extent of surgery					
Biopsy	93 (16.2)	45 (15.7)	48 (16.7)	0 (0.0)	93 (19.8)
Partial	254 (44.3)	128 (44.8)	126 (43.9)	56 (54.4)	198 (42.1)
Complete	226 (39.4)	113 (39.5)	113 (39.4)	47 (45.6)	179 (38.1)
Age					
≤50 years	183 (31.9)	88 (30.8)	95 (33.1)	44 (42.7)	139 (29.6)
51-60 years	220 (38.4)	111 (38.8)	109 (38.0)	40 (38.8)	180 (38.3)
>60 years	170 (29.7)	87 (30.4)	83 (28.9)	19 (18.4)	151 (32.1)
WHO performance status					
0	223(38.9)	110 (38.5)	113 (39.4)	42 (40.8)	181 (38.5)
1	277 (48.3)	141 (49.3)	136 (47.4)	49 (47.6)	228 (48.5)
2	73 (12.7)	35 (12.2)	38 (13.2)	12 (11.7)	61 (13.0)
Sex					
Male	360 (62.8)	175(61.2)	185 (64.5)	65 (63.1)	295 (62.8)
Female	212 (37.0)	110 (38.5)	102 (35.5)	38 (36.9)	174 (37.0)
Not recorded	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Corticosteroids at randomization					
No	164 (28.6)	70 (24.5)	94 (32.8)	31 (30.1)	133 (28.3)
Yes	408 (71.2)	215 (75.2)	193 (67.2)	72 (69.9)	336 (71.5)
Missing	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
MMSE					
27-30	167 (29.1)	86 (30.1)	81 (28.2)	24 (23.3)	143 (30.4)
<27	384 (67.0)	188 (65.7)	196 (68.3)	75 (72.8)	309 (65.7)
Missing	22 (3.8)	12 (4.2)	10 (3.5)	4 (3.9)	18 (3.8)
Lobe					
Frontal	169 (29.5)	82 (28.7)	87 (30.3)	42 (40.8)	127 (27.0)
Temporal	160 (27.9)	79 (27.6)	81 (28.2)	30 (29.1)	130 (27.7)
Parietal	101 (17.6)	54 (18.9)	47 (16.4)	10 (9.7)	91 (19.4)
Occipital	37 (6.5)	17 (5.9)	20 (7.0)	8 (7.8)	29 (6.2)
Central	20 (3.5)	7 (2.4)	13 (4.5)	1 (1.0)	19 (4.0)
Multifocal	79 (13.8)	40 (14.0)	39 (13.6)	12 (11.7)	67 (14.3)
Other	4 (0.7)	4 (1.4)	0 (0.0)	0 (0.0)	4 (0.9)
Missing	3 (0.5)	3 (1.0)	0 (0.0)	0 (0.0)	3 (0.5)
Hemisphere					
Right	297 (51.8)	146 (51.0)	151 (52.6)	57 (55.3)	240 (51.1)
Left	269 (46.9)	135 (47.2)	134 (46.7)	46 (44.7)	223 (47.4)
Both	5 (0.9)	3 (1.0)	2 (0.7)	0 (0.0)	5 (1.1)
Missing	2 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.4)
Hemoglobin level					
Anemia	140 (24.4)	72 (25.2)	68 (23.7)	24 (23.3)	116 (24.7)
Normal	429 (74.9)	214 (74.8)	215 (74.9)	77 (74.8)	352 (74.9)
Missing	4 (0.7)	0 (0.0)	4 (1.4)	2 (1.9)	2 (0.4)
MGMT **promoter methylation status**					
Methylated	92 (16.1)	46 (16.1)	46 (16.0)	45 (43.7)	47 (10.0)
Unmethylated	114 (19.9)	54 (18.9)	60 (20.9)	58 (56.3)	56 (11.9)
Unknown	367 (64.0)	186 (65.0)	181 (63.1)	0 (0.0)	367 (78.1)

Legend: ‡ population 1: all randomized patients (ITT), population 2 : all patients treated by TMZ/RT, population 3: patients who underwent partial or complete resection treated by TMZ/RT with MGMT assessment available, not in population 3: RT alone patients or with biopsy or without MGMT promoter methylation status assessed

Table 2. Univariate analyses of potential survival prognostic factors

	RT alone patients (n=286)			**Population 2 ‡ (n=287)**			**Population 1 ‡ (n=573)**		**Treatment Interaction test**
	Median survival/95% CI (months)	HR-95%CI	p-value	Median survival /95% CI (months)	HR-95%CI	p-value	HR-95%CI	p-value	p-value
Treatment Temozolomide and radiotherapy Radiotherapy	N/A	N/A	N/A	N/A	N/A	N/A	1 1.57 [1.32-1.87]	<0.0001	N/A
Extent of surgery µ Complete resection Partial resection Biopsy	14.2 (13.0-16.2) 11.7 (9.7-13.1) 7.9 (6.4-10.6)	1.45(1.22-1.73)	<0.0001	18.8 (16.4-22.9) 13.5 (11.9-16.4) 9.4 (7.5-13.6)	1.46(1.22-1.74)	<0.0001	1.44[1.27-1.63]	<0.0001	0.41
Age µ ≤50 years 51-60 years >60 years	13.6 (11.6-15.6) 12.0 (10.0-14.2) 11.8 (10.5-12.8)	1.16(1.00-1.36)	0.054	17.4 (15.3-21.5) 14.6 (13.6-17.9) 11.3 (9.4-15.1)	1.34 (1.14-1.57)	0.0004	1.26 [1.13-1.41]	<0.0001	0.17
WHO performance status µ 0 1 2	13.3 (11.8-15.7) 11.9 (10.0-13.2) 10.5 (8.5-13.0)	1.19 (1.00-1.42)	0.050	17.4 (15.7-21.2) 14.1 (12.5-17.0) 9.9 (6.9-12.1)	1.47 (1.21-1.79)	0.0001	1.33 [1.17-1.51]	<0.0001	0.06
Sex									

Female Male	12.6 (11.9-16.1) 11.4 (10.5-12.9)	1.24(0.97-1.59)	0.08	16.3 (13.4-20.4) 14.4 (12.4-16.4)	1.16(0.89-1.51)	0.26	1.17 [0.98-1.40]	0.09	0.87
Corticosteroids at randomization No Yes	16.3 (14.4-17.3) 11.0 (9.7-12.1)	1.70 (1.29-2.25)	0.0002	19.7 (16.4-24.9) 13.6 (11.9-14.9)	1.47(1.12-1.94)	0.005	1.60 [1.32-1.95]	<0.0001	0.92
MMSE 27-30 <27	13.3 (12.2-14.8) 9.3 (7.9-11.7)	1.78 (1.37-2.31)	<0.0001	17.1 (15.3-19.1) 10.3 (8.6-12.9)	1.87 (1.43-2.46)	<0.0001	1.81 [1.50-2.19]	<0.0001	0.41
Lobe Unilobal Central & multilobal	12.5 (12.0-14.1) 9.5 (7.5-11.7)	1.40(1.02-1.91)	0.03	16.3 (14.4-18.3) 11.3 (9.2-14.0)	1.76 (1.28-2.42)	0.0004	1.58 [1.26-1.96]	<0.0001	0.20
Hemisphere Right Left	13.0 (11.9-14.4) 11.4 (10.0-12.3)	1.07 (0.84-1.36)	0.28	15.7 (13.9-18.1) 14.4 (12.4-17.0)	.00 (0.80-1.30)	0.92	1.05 [0.88-1.24]	0.62	0.89
Hemoglobin level Anemia Normal	11.4 (10.0-13.3) 12.2 (11.4-13.5)	1.05 (0.80-1.39)	0.71	18.6 (15.7-25.9) 13.5 (12.2-15.5)	1.41 (1.05-1.89)	0.023	1.24 [1.01-1.52]	0.04	0.11
***MGMT* promoter methylation** Methylated	15.3 (13.0-20.9)	2.40 (1.53-	0.0001	21.7 (18.6-N)	2.24 (1.43-	0.0003	2.10 [1.54-2.85]	<0.0001	0.31

Unmethylated	11.8 (10.0-14.4)	3.78)		12.4 (11.6-14.4)	3.51)				

μ : For ordered categorical factors, the first value is the reference. HR = 1.x% means that death rate is increased by x% on average between patients belonging to adjacent groups. E.g. For age in population 1, HR= 1.16 indicates a death rate increase of 16% between age <=50 and 51-60 and the same increase between class 51-60 and >60.

Table 3. Cox Proportional Hazards analyses of survival prognostic factors

	Population 1 * (n=573, # used=547, # deaths=498)		**RT alone patients (n=286, #used=274, # deaths=263)**		**Population 2 * (n=287, # used=273,# deaths=235)**		**Population 3 * (n=103,# used=97, # deaths=77)**	
	Hazard Ratio (95% CI)	P(% inclusion)	Hazard Ratio (95% CI)	P(% inclusion)	Hazard Ratio (95% CI)	P(% inclusion)	Hazard Ratio (95% CI)	P(% inclusion)
Treatment assignment **Temozolomide and Radiotherapy** **Radiotherapy**	1 1.60 (1.34-1.91)	<0.0001 (99.6)	NI	NI	NI	NI	NI	NI
***MGMT* promoter** **Methylated** **Unmethylated**	NI	NI	NI	NI	NI	NI	2.75 (1.68-4.49)	<0.0001(92)
Age µ ≤50 years 51-60 years >60 years	1.19(1.06-1.34)	0.003 (82)	1.12 [0.95-1.32]	NS (29)	1.26 (1.06-1.48)	0.008(80)	1.32 [0.95-1.84]	NS(37)
Performance status µ 0 1 2	1.12 [0.98-1.28]	NS(48)	0.98 [0.82-1.19]	NS (8)	1.32 (1.08-1.60)	0.006(78)	1.76 (1.21-2.55)	0.003(82)
Interaction term between performance status & Treatment	0.99 [0.82-1.19]	NS(40)	NI	NI	NI	NI	NI	NI
Extent of surgery µ Complete resection Partial resection Biopsy	1.33 (1.17-1.52)	<0.0001(96)	1.29 (1.07-1.55)	0.007 (80)	1.37 (1.14-1.63)	<0.001(75)	1.03 [0.64-1.64]	NS(7)†
Tumor location Unilobal Central & multilobal	1.17 [0.92-1.50]	NS(30)	0.94 [0.66-1.33]	NS (13)	1.40 [0.99-1.97]	NS(52)	1.62 [0.80-3.29]	NS(41)
MMSE 27-30 <27	1.63 (1.34-1.98)	<0.0001(98)	1.71(1.31-2.24)	<0.0001 (89)	1.66 (1.25-2.19)	<0.001 (79)	1.98 (1.20-3.28)	0.008(81)
Corticosteroids No Yes	1.36 (1.11-1.67)	0.003(85)	1.52 (1.13-2.03)	0.005 (81)	1.19 [0.89-1.59]	NS(33)	1.17 [0.70-1.97]	NS(12)

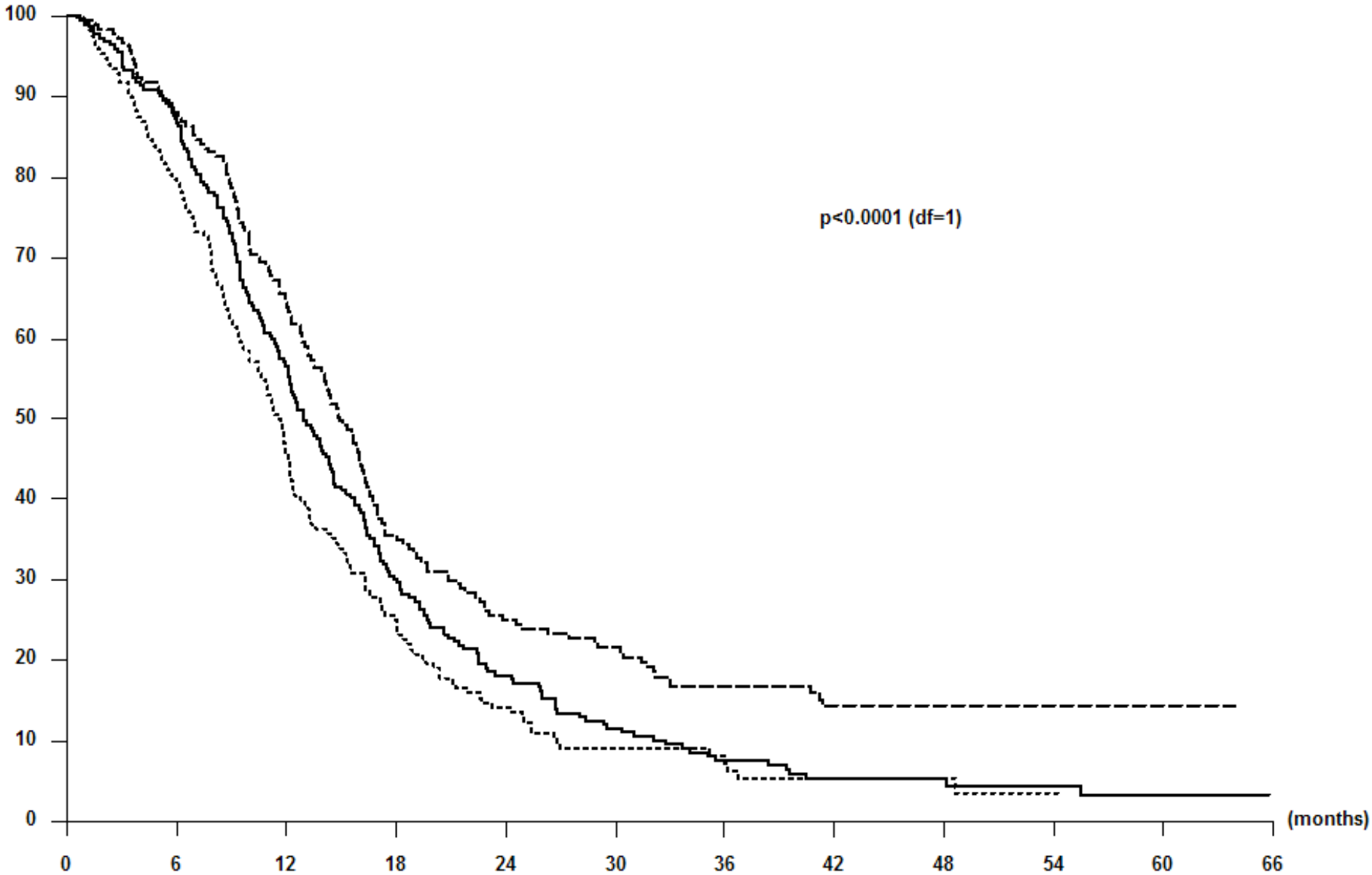
Sex Female Male	1.16 [0.97-1.40]	NS(51)	1.13 [0.88-1.46]	NS (22)	1.30 [0.99-1.70]	0.03‡(55)	1.10 [0.69-1.77]	NS(10)
Hemoglobin level Anemia Normal	1.06 [0.86-1.31]	NS(9)	0.96 [0.72-1.28]	NS (9)	1.33 [0.98-1.81]	NS(36)	1.44 [0.85-2.46]	NS(21)
C-Index corrected for otimism	65%		NI		63%		65.5%	

µ : For ordered categorical factors, the first value is the reference. HR = 1.x% means that death rate is increased by x% on average between patients belonging to adjacent groups. E.g. For age in population 1, HR= 1.19 indicates a death rate increase of 19% between age <=50 and 51-60 and the same increase between class 51-60 and >60.

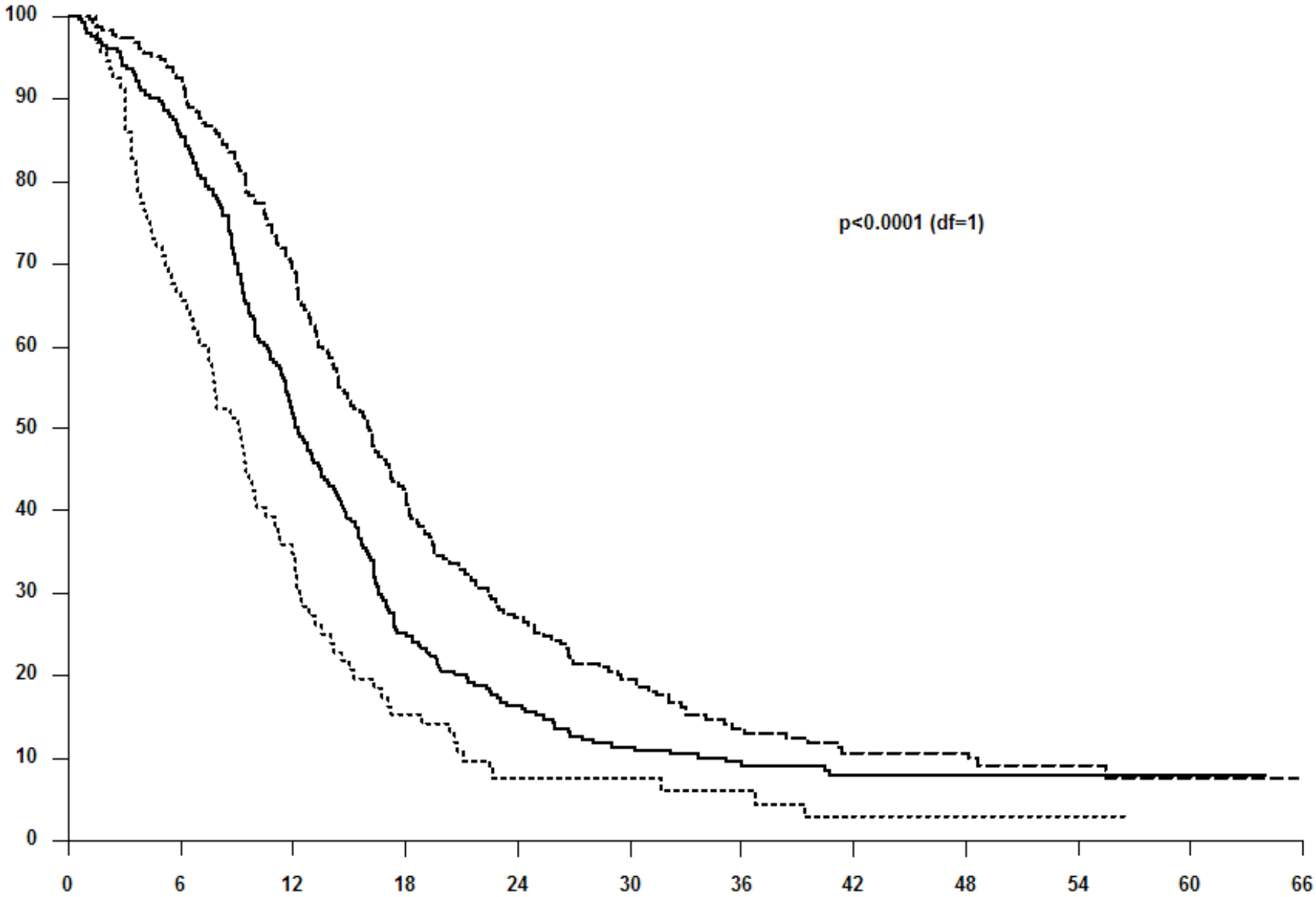
Table 4: Prognostic scores of each factor in the three nomograms

Factor	**Population 1 ‡ (n=573)**	**Population 2 ‡ (n=287)**	**Population 3 ‡ (n=103)**
Treatment			
TMZ/RT	0	N/A	N/A
RT alone	82		
MGMT promoter			
Methylated	NI	NI	0
Unmethylated			90
Age (years)			
≤50	0	0	NI
51-60	31	35	
>60	61	71	
Extent of surgery			
Total	0	0	NI
Partial	50	50	
Biopsy	100	100	
WHO performance status			
0	NI	0	0
1		41	50
2		82	100
MMSE			
27-30	0	0	0
<27	85	78	61
Corticosteroids			
No	0	NI	NI
Yes	54		
Total Points	0-382	0-331	0-251

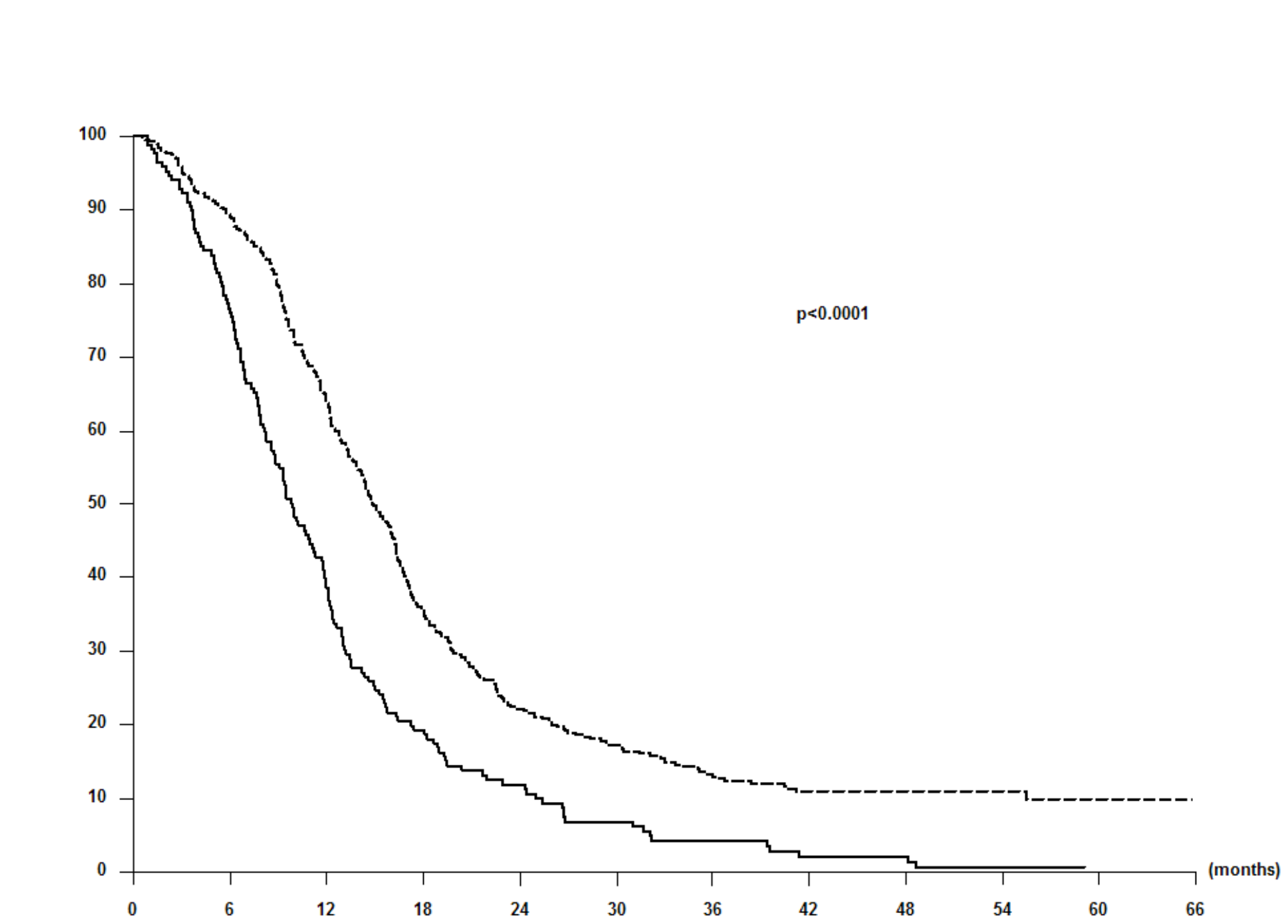
Legend: N/A : not applicable. NI Not included: factor was not included in the final model. Points must be summed-up to obtain a total prognostic score. Good prognoses have a low total prognostic score. ‡ population 1: all randomized patients (ITT), population 2 : all patients treated by TMZ/RT, population 3: patients who underwent partial or complete resection treated by TMZ/RT with MGMT assessment available.



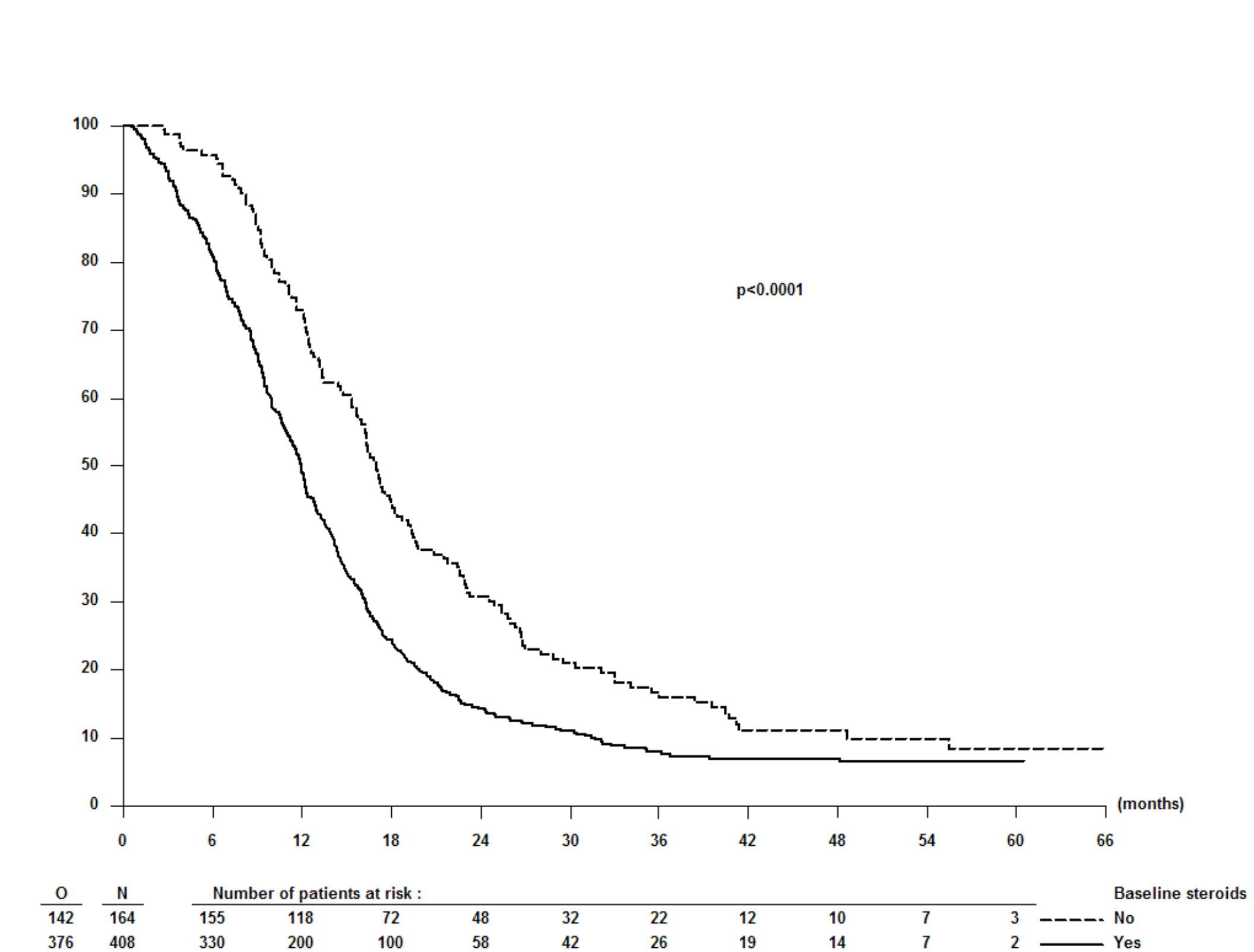
O	N	Number of patients at risk :										Age (class)
154	183	161	118	65	45	36	25	17	15	8	3	<=50 yrs
207	220	191	124	66	39	24	15	10	6	5	2	>50 & <=60 yrs
157	170	134	77	42	23	14	8	4	3	1	0	>60 yrs

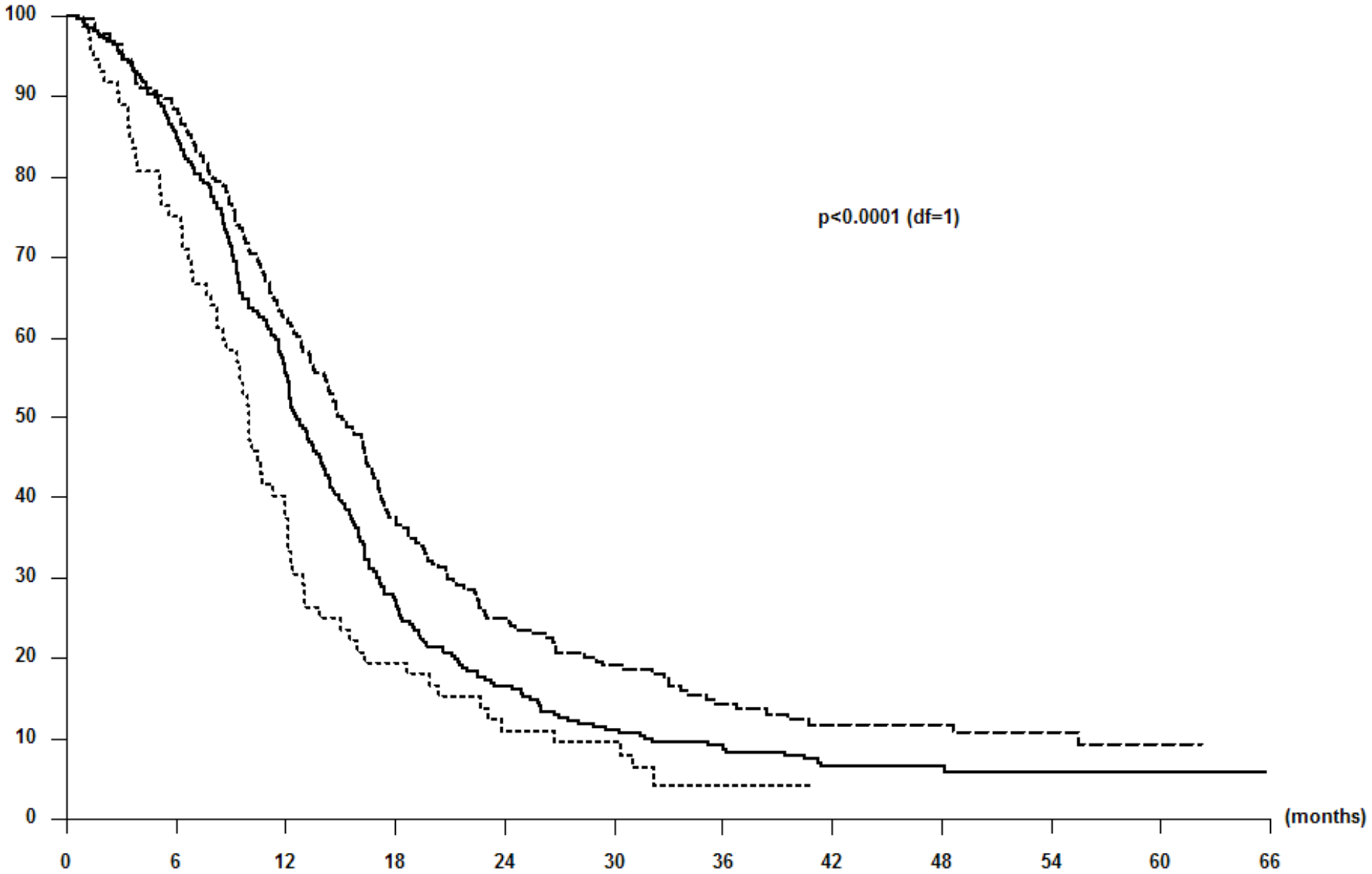


O	N	Number of patients at risk :										Extent of resection
200	226	208	156	95	60	41	25	18	15	6	3	Complete
230	254	217	131	64	40	27	19	11	7	6	2	Partial
88	93	61	32	14	7	6	4	2	2	2	0	Biopsy only

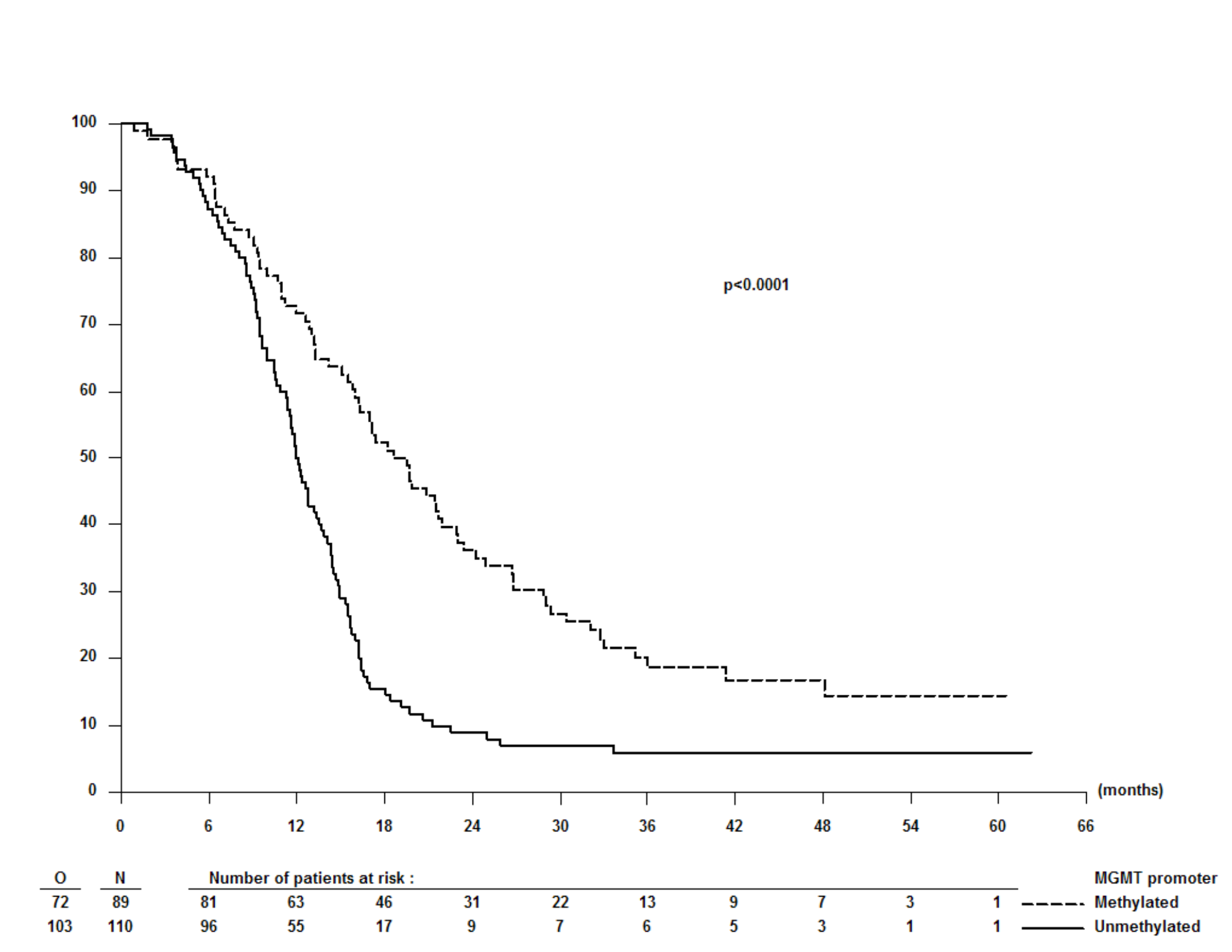


O	N	Number of patients at risk :										MMSE
336	384	341	245	136	83	61	40	28	21	13	5	27-30
163	167	127	64	32	19	11	7	3	3	1	0	<27


100
90
80
70
60
50
40
30
20
10
0
p<0.0001
(months)
0
6
12
18
24
30
36
42
48
54
60
66
O
N
Number of patients at risk :
142
164
155
118
72
48
32
22
12
10
7
3
376
408
330
200
100
58
42
26
19
14
7
2
Baseline steroids
No
Yes



O	N	Number of patients at risk :										Performance statu
194	223	197	139	84	53	38	25	16	13	7	2	PS 0
256	277	235	153	75	46	30	22	15	11	7	3	PS 1
68	73	54	27	14	8	6	1	0	0	0	0	PS 2


100
90
80
70
60
50
40
30
20
10
0
p<0.0001
(months)
0
6
12
18
24
30
36
42
48
54
60
66
O
N
Number of patients at risk :
72
89
81
63
46
31
22
13
9
7
3
1
103
110
96
55
17
9
7
6
5
3
1
1
MGMT promoter
Methylated
Unmethylated

Supplementary table 1. Concordance Indexes corrected for optimism of the nomograms and RPA classification in the three study populations.

Concordance-index corrected for optimism	Population 1 ‡	Population 2 ‡	Population 3 ‡
RPA classification	58.4%	58.9%	55.5%
Nomograms	65.0%	63.0%	65.5%

Legend: ‡ Population 1: all randomized patients (ITT), population 2 : all patients treated by TMZ/RT, population 3: patients who underwent partial or complete resection treated by TMZ/RT with MGMT assessment available.