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ORIGINAL REPORT

Radiotherapy and Temozolomide for Newly Diagnosed Glioblastoma: Recursive Partitioning Analysis of the EORTC 26981/22981-NCIC CE3 Phase III Randomized Trial

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ABSTRACT

Purpose

The European Organisation for Research and Treatment of Cancer and National Cancer Institute of Canada trial on temozolomide (TMZ) and radiotherapy (RT) in glioblastoma (GBM) has demonstrated that the combination of TMZ and RT conferred a significant and meaningful survival advantage compared with RT alone. We evaluated in this trial whether the recursive partitioning analysis (RPA) retains its overall prognostic value and what the benefit of the combined modality is in each RPA class.

Patients and Methods

Five hundred seventy-three patients with newly diagnosed GBM were randomly assigned to standard postoperative RT or to the same RT with concomitant TMZ followed by adjuvant TMZ. The primary end point was overall survival. The European Organisation for Research and Treatment of Cancer RPA used accounts for age, WHO performance status, extent of surgery, and the Mini-Mental Status Examination.

Results

Overall survival was statistically different among RPA classes III, IV, and V, with median survival times of 17, 15, and 10 months, respectively, and 2-year survival rates of 32%, 19%, and 11%, respectively ($P < .0001$). Survival with combined TMZ/RT was higher in RPA class III, with 21 months median survival time and a 43% 2-year survival rate, versus 15 months and 20% for RT alone ($P = .006$). In RPA class IV, the survival advantage remained significant, with median survival times of 16 *v* 13 months, respectively, and 2-year survival rates of 28% *v* 11%, respectively ($P = .0001$). In RPA class V, however, the survival advantage of RT/TMZ was of borderline significance ($P = .054$).

Conclusion

RPA retains its prognostic significance overall as well as in patients receiving RT with or without TMZ for newly diagnosed GBM, particularly in classes III and IV.

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INTRODUCTION

Until recently, the outcome of glioblastoma (GBM), the most common and most malignant brain tumor in adults, has not improved greatly. Postoperative radiotherapy (RT) is recognized as standard therapy based on six randomized studies published between 1976 and 1991,[1] whereas the addition of chemotherapy to radiotherapy has been a more controversial issue—a meta-analysis based on 12 randomized trials suggests only a small benefit.[2] Indeed, many studies in the past decade have demonstrated that pretreatment prognostic factors have more impact on outcome than any new and potentially active therapy or treatment strategy.[3-6] The development of a set of classes on high-grade glioma from a recursive partitioning model of treatment- and pretreatment-related prognostic variables by Curran et al[4] proved useful and was tested and validated in a number of subsequent trials.[5,7-17] The recursive partitioning analysis (RPA) classification was developed to compare survival categories and to obtain homogenous subsets of patients.[4] It can be useful in refining stratification and the design of phase III randomized studies, and its judicious use and interpretation in phase II studies could avoid the undertaking of phase III studies based on false expectations.[5] In large randomized trials, RPA also

has the potential to determine if a particular category of patients will benefit most from newer approaches and if some may be spared unnecessary treatment.

The recent trial by the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) Clinical Trials Group (EORTC 26981/22981-NCIC CE3) was the first study to demonstrate unequivocally that the addition of temozolomide (TMZ) to RT early in the course of GBM provides a statistically significant and clinically meaningful survival benefit.[18] We present RPA of the EORTC/NCIC trial to determine if RPA classes III through V retained their prognostic value in the overall population and if the advantage of the combined treatment of RT/TMZ remains beneficial in all RPA classes.

PATIENTS AND METHODS

Trial Summary

EORTC 26981/22981-NCIC CE3 enrolled 573 patients from 85 institutions between August 2000 and March 2002. Details of the trial methods and the main results were published elsewhere.[18] Patients from 18 to 70 years of age with newly diagnosed and histologically confirmed GBM; a WHO performance status of 0 to 2; and adequate hematologic, renal, and hepatic function were eligible. Patients were randomly assigned to standard focal RT alone or to the same RT plus concomitant daily TMZ followed by adjuvant TMZ. Conformal RT with three-dimensional planning was administered for a total daily dose of 60 Gy at 2 Gy/fraction on 5 days a week for 6 weeks, with a linear accelerator. Concomitant chemotherapy consisted of TMZ at a daily dose of 75 mg/m^2 on 7 days a week from the first until the last day of RT, up to 49 days. After a 4-week break, patients received up to six cycles of adjuvant TMZ for 5 days every 28 days. The dose was 150 mg/m^2 for the first adjuvant cycle and was increased to 200 mg/m^2 beginning with the second cycle, provided there were no hematologic toxicities. Prophylaxis against *Pneumocystis carinii* with either pentamidine or trimethoprim-sulfamethoxazole was mandatory during concomitant RT/TMZ.[15] The primary end point was overall survival; secondary end points were progression-free survival, safety, and quality of life.

Recursive Partitioning Analysis

Patients were classified according to modified Radiation Therapy Oncology Group (RTOG) RPA classification.[4] Only patients with GBM (not including anaplastic astrocytomas) were eligible for the EORTC/NCIC trial. Performance status and mental status scales differed between the previous

Table 1. Original and Adapted RTOG/EORTC RPA Class III-V

RPA Class	RTOG (original)	EORTC (adapted)
III		
Age, years	< 50	< 50
Tumor type	Anaplastic astrocytomas	Glioblastoma multiforme
Mental status	Abnormal	
Performance status		WHO PS 0
or		
Age, years	< 50	
Tumor type	Glioblastoma multiforme	
Performance status	KPS 90-100	
IV		
Age, years	< 50	< 50
Tumor type	Glioblastoma multiforme	Glioblastoma multiforme
Performance status	KPS < 90	WHO PS 1-2
or		
Age, years	≥ 50	≥ 50
Tumor type	Anaplastic astrocytomas	Glioblastoma multiforme
Performance status	KPS 70-100	
Treatment status	≤ 3 from time of first symptom to start of treatment	Complete/partial surgery
Mental status		MMSE ≥ 27
or		
Age, years	≥ 50	
Tumor type	Glioblastoma multiforme	
Mental status	Good neurologic function	
Treatment status	Surgical resection	
V		
Age, years	≥ 50	≥ 50
Tumor type	Glioblastoma multiforme	Glioblastoma multiforme
Performance status	KPS 70-100	
Mental status	Neurologic function that inhibits the ability to work	MMSE < 27
Treatment status	Surgical resection or biopsy only followed by at least 54.4 Gy radiotherapy	Biopsy only
or		
Age, years	≥ 50	
Tumor type	Glioblastoma multiforme	
Performance status	KPS < 70	
Mental status	Normal	

RTOG, Radiation Therapy Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; RPA, recursive partitioning analysis; PS, performance status; KPS, Karnofsky performance status; MMSE, Mini-Mental Status Examination.

Table 2. Baseline Patient Demographics

Characteristic	RT (N = 286)		RT + TMZ (N = 287)	
	No.	%	No.	%
Age, years				
< 50	81	28	90	31
≥ 50	205	72	197	69
Sex				
Male	175	61	185	64
Female	111	39	102	36
WHO PS				
0	110	38	113	39
1	141	49	136	47
2	35	12	38	13
Extent of surgery				
Biopsy	45	16	48	17
Partial resection	128	45	126	44
Complete resection	113	40	113	49
Corticosteroid therapy	215	75	193	67
Baseline MMSE				
30	92	32	100	35
27-29	97	34	96	33
≤ 26	86	30	81	28
Missing	12	4	10	3
EORTC RPA class				
III	39	14	42	15
IV	150	52	152	53
V	97	34	93	32

Abbreviations: RT, radiotherapy; TMZ, temozolomide; PS, performance status; MMSE, Mini-Mental Status Examination; EORTC, European Organisation for Research and Treatment of Cancer; RPA, recursive partitioning analysis.

RTOG studies and the current trial. Therefore, we adapted the class definitions. Both the original and adapted definitions are presented in Table 1. The most important differences are as follows: EORTC classes III through V include GBM only, whereas RTOG classes III and IV include both anaplastic astrocytomas (WHO grade 3) and GBM; EORTC uses WHO performance status, whereas RTOG uses the Karnofsky index; and neurologic function in the RTOG RPA classification is defined as either "good" in RPA III or "neurologic function that inhibits the ability to work" in RPA IV, and mental status is described as "normal" or "abnormal," whereas the EORTC classification uses the Mini-Mental Status Examination (MMSE).[19] The MMSE is a brief, standardized tool used to grade cognitive function. It contains an assessment of orientation to place and time, a memory test, a substraction test, and an aphasia and apraxia evaluation. The maximum score that can be achieved is 30 points. In an analysis of a North Central Cancer Treatment Group trial, an abnormal MMSE score was characterized as ≤ 26, and these patients had a significantly worse prognosis.[20]

Statistical Analysis

The prognostic value for survival, independent of treatment received, according to the RPA classification was estimated using the Kaplan-Meier method.[21] This technique was also used to assess the efficacy of RT with or without TMZ in the three classes. The trend test was used to assess the ordering of the classes. The log-rank test was used for each treatment comparison. The interaction tests (heterogeneity and trend tests) were also computed.

RESULTS

Patient Demographics

Patient characteristics are presented in Table 2. RT and RT/TMZ treatment arms were well balanced for the repartition of RPA classes, with 14% and 15% of patients in class III, 52% and 53% in class IV, and 34% and 32% in class V, respectively. The percentage of patients receiving corticosteroids at the time of random assignment was slightly higher in the RT group than in the RT/TMZ group.

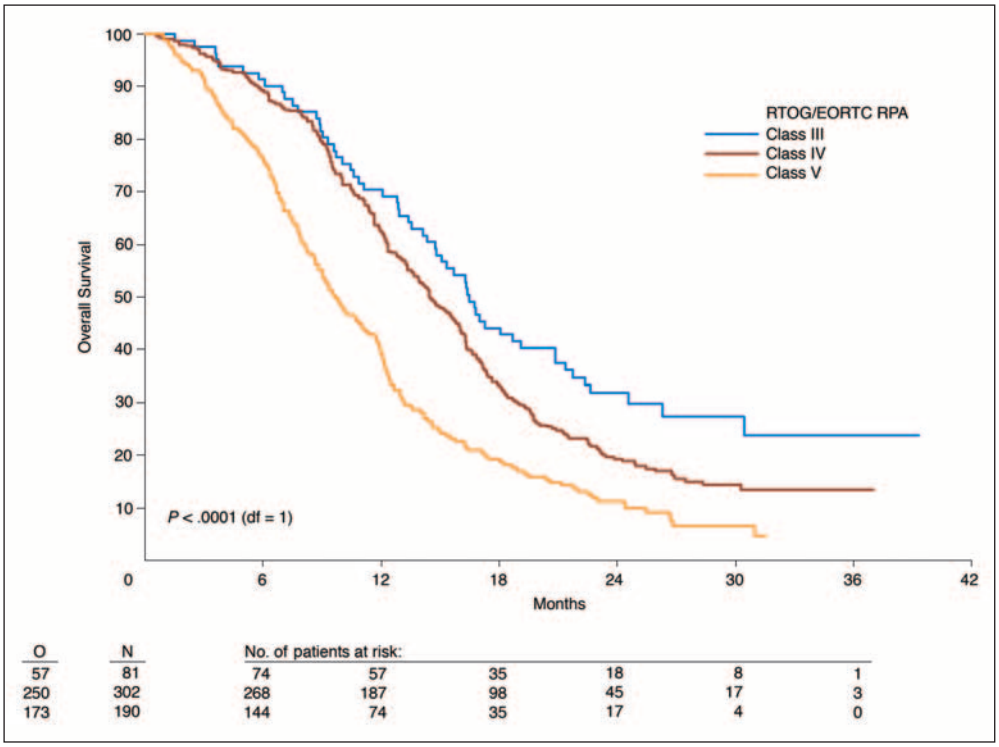

Fig 1. Kaplan-Meier estimates of overall survival according to Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) class.

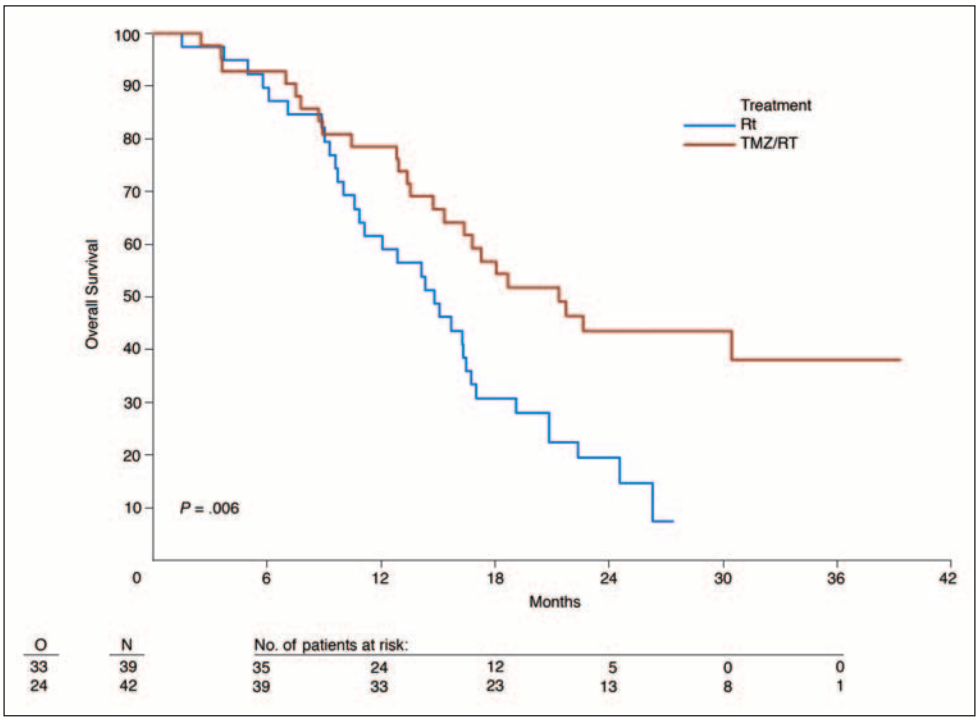

Fig 2. Kaplan-Meier estimates of overall survival according to the treatment in Radiation Therapy Oncology Group (RTOG)/ European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) class III.

Overall Study Results

The median follow-up for all patients was 28 months. Among patients still alive after 28 months, the median follow-up was 27 months (minimum 13, maximum 39 months). Two hundred nineteen patients in the RT/TMZ arm and 261 in the RT-only arm died, with a median survival time of 15 *v* 12 months, respectively, and a 2-year survival rate of 27% *v* 10%, respectively ($P < .001$).[18]

Validation of RPA Classes

The overall population survival was analyzed according to EORTC RPA classes. Median survival times were 17 months (range,

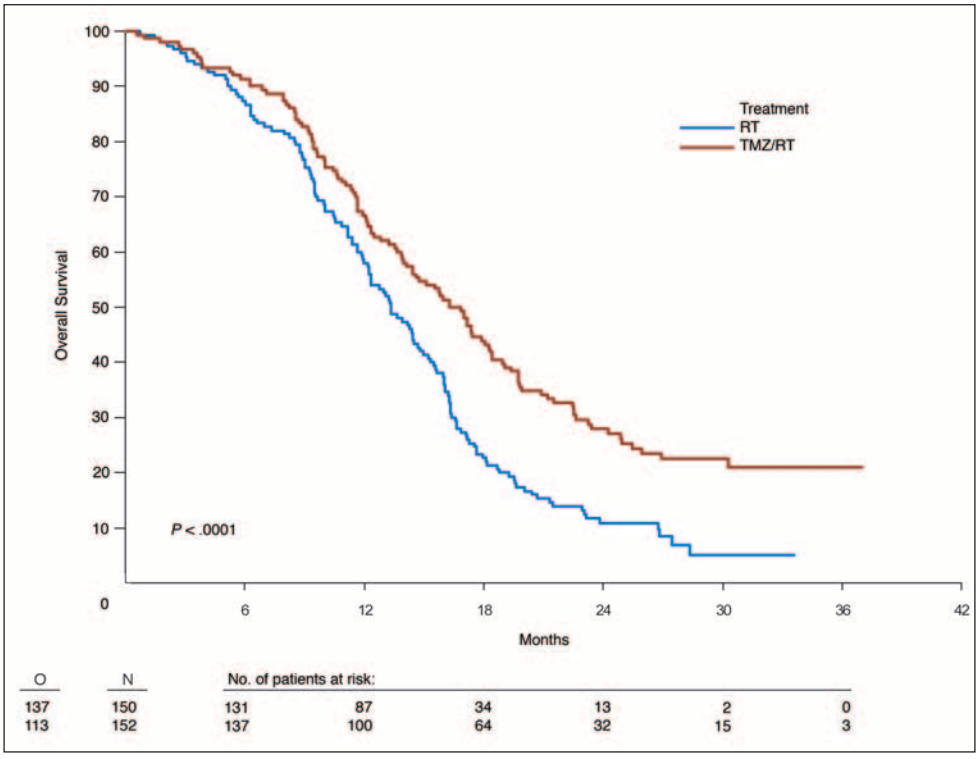

Fig 3. Kaplan-Meier estimates of overall survival according to the treatment in Radiation Therapy Oncology Group (RTOG)/ European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) class IV.

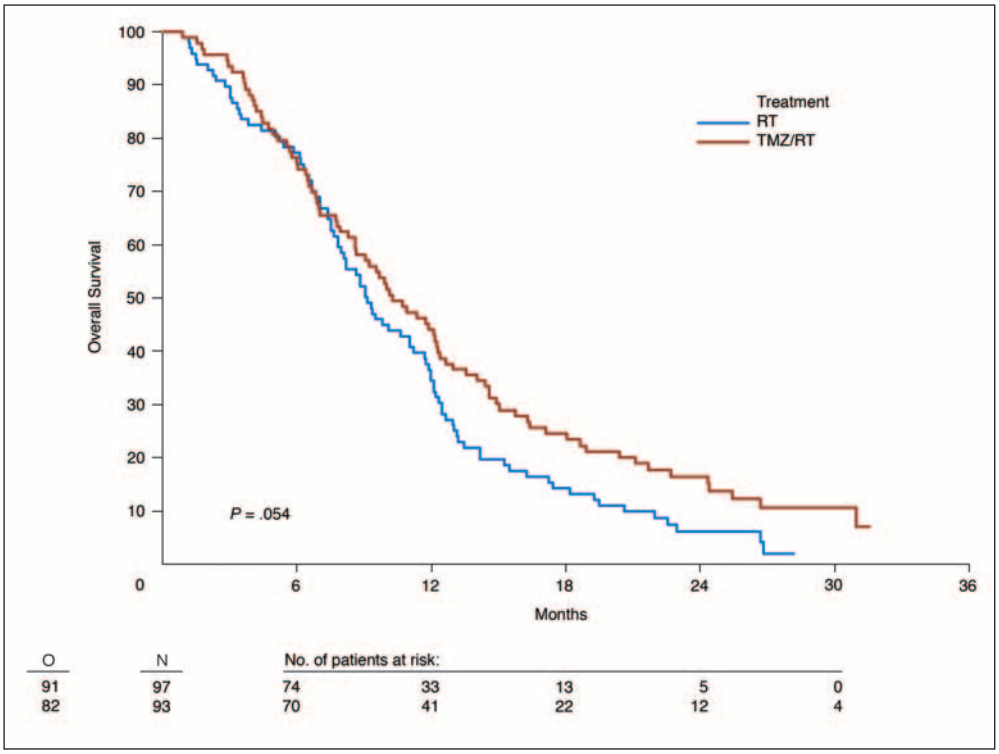

Fig 4. Kaplan-Meier estimates of overall survival according to the treatment in Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) class V.

15 to 21 months), 15 months (range, 13 to 16 months), and 10 months (range, 9 to 12 months), and the corresponding 2-year survival rates were 32% (range, 21% to 42%), 19% (range, 15% to 24%), and 11% (range, 7% to 16%) for classes III, IV, and V, respectively ($P < .0001$; Fig 1 and Table 3).

Overall Survival by Treatment Arm in RPA Classes III Through V

The survival benefit of combined treatment was highest in RPA class III, with a median survival time of 21 *v* 15 months and a 2-year survival rate of 43% *v* 20%, respectively (hazard ratio [HR], 0.48; $P = .006$; Fig 2). In RPA class IV, the advantage remained highly significant, with a median survival time of 16 *v* 13 months and a 2-year survival rate of 28% *v* 11%, respectively (HR, 0.61; $P = .0001$; Fig 3). For patients in RPA class V, however, the difference between the two treatment arms was small and of borderline significance, with a median survival time of 10 *v* 9 months and a 2-year survival rate of 17% *v* 6%, respectively (HR, 0.74; $P = .054$; Fig 4). This trial did not have enough power to definitively identify a difference in treatment efficacy among the three classes based on interaction tests (heterogeneity, $P = .28$; trend, $P = .12$).

DISCUSSION

The recently published results of our EORTC/NCIC randomized study have shown unequivocally that the addition of TMZ to RT confers a meaningful survival advantage compared with postoperative RT alone in GBM.[18] However, for decades, pretherapeutic prognostic factors—in particular their regrouping in RPA classes—had a much more powerful impact on survival than any adjuvant treatment.[3-6,13] For this reason, RPA analysis within the framework of our positive EORTC/NCIC trial is particularly important. RPA analysis can be used as a tool to identify patients from a phase II trial who could benefit from a particular and novel treatment. This technique was tested in numerous phase II trials in GBM.[7-12,14-17,22] However, when compared with patients from the RTOG database using RPA analysis, none of the new treatments appeared superior to previously tested therapies.

At EORTC, we have used RPA analysis in strategic decisions on whether to embark on phase III randomized trials in GBM. The first example is the Accelerated Radiotherapy with Carbogen and Nicotinamide (ARCON) protocol, based on promising preclinical data.[23,24] In our phase I/II EORTC Radiotherapy Group ARCON trial for GBM, 115 patients were treated with carbogen, nicotinamide, and accelerated RT in three steps.[16] The overall median survival time was 11 months. However, survival times by RPA class were quite comparable with those of the RTOG database, and we concluded that the results do not support the development of a randomized trial.[16] Therefore, no further study on ARCON in GBM was undertaken by the EORTC.

In contrast, the second example was our phase II study on concomitant RT/TMZ followed by adjuvant TMZ.[15] The median

Table 3. Overall Survival Rates by RPA Class

RPA Class	Median Survival		2-Year Survival	
	Months	95% CI	%	95% CI
III*	17	15 to 21	32	21 to 42
IV	15	13 to 16	19	15 to 24
V	10	9 to 12	11	7 to 16

Abbreviation: RPA, recursive partitioning analysis.
*Overall trend test ($df = 1$), $P < .0001$.

Table 4. Comparison of Survival Data Among RPA Classes in the RTOG Database and in Two Trials Using TMZ

	Phase II Survival With RT/TMZ (15)		Phase III Survival* (18)		RTOG Database (4,5)	
RPA Class	Median, Months	2-Year, %	Median, Months	2-Year, %	Median, Months	2-Year, %
III	24+	51	21.4	43.4	17.9	35
IV	13.8	32	16.3	27.9	11.1	15
V	9.2	0	10.3	16.5	8.9	6

Abbreviations: RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group; TMZ, temozolomide; RT, radiation therapy.
*EORTC 26981/22981-NCIC CE3 study, RT/TMZ arm.

survival time for the 64 enrolled patients was 16 months. Median survival time was 24+ months for Class III, 14 months for Class IV, and 9 months for Class V, which compared quite favorably with the RTOG database results.[15] These promising results represented a strong incentive at EORTC to undertake the EORTC/NCIC randomized phase III trial.[18]

Table 4 shows median and 2-year survival values in the phase II RT/TMZ trial,[15] the TMZ arm of the phase III trial,[18] and the RTOG database[4,5] by RPA class. Results of the phase II and phase III trials appear fairly similar and consistently superior to those of the RTOG database across all RPA classes.

One objective of the present analysis was to verify whether the EORTC RPA classification retained its overall value within the phase III randomized EORTC/NCIC trial, in which a fairly large difference was observed between the two treatment arms. Our results with the 573 patients show that the overall median and 2-year survival values differed among RPA classes III, IV, and V and this was highly statistically different ($P < .001$), confirming the distinction among these three prognostic classes.

We also used RPA methodology to evaluate the effect of combined therapy in each of the three RPA classes of the EORTC/NCIC randomized study. The highest treatment effect on survival was observed in RPA class III, with a gain in the median survival time of 7 months and in the 2-year survival rate of 24% with RT/TMZ ($P = .006$). For this category of patients, the addition of TMZ to RT provided a 43% probability of survival at 2 years. The EORTC/NCIC RPA system excludes the more favorable grade 3 gliomas, so these results appear promising for such a devastating disease. The combination of TMZ/RT in RPA class IV still offers a significant and useful advantage, more than doubling the 2-year survival rate compared with RT alone($P = .0001$). In the worst prognostic category, RPA V, the gain appeared smaller ($P = .054$).

Within the framework of the EORTC/NCIC trial, 06-methylguanine-DNA methyltransferase (MGMT) methylation in GBM was an independent favorable prognostic factor. Among patients with methylated MGMT, a large survival benefit was observed when TMZ was added to RT.[25] We analyzed the impact of MGMT status in each RPA class. However, the subsets were too small to draw any meaningful conclusions.

It appears from our trial that simple clinical (RPA) or sophisticated laboratory (MGMT) tools can be used to predict individual patient outcome and should also be considered for stratification procedures in future protocols, in which novel therapies will be added to RT and TMZ.

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