

Adjuvant Procarbazine, Lomustine, and Vincristine Improves Progression-Free Survival but Not Overall Survival in Newly Diagnosed Anaplastic Oligodendrogliomas and Oligoastrocytomas: A Randomized European Organisation for Research and Treatment of Cancer Phase III Trial

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A B S T R A C T

Purpose

Anaplastic oligodendrogliomas are more responsive to chemotherapy than high-grade astrocytomas. We investigated, in a multicenter randomized controlled trial, whether adjuvant procarbazine, lomustine, and vincristine (PCV) chemotherapy improves overall survival (OS) in newly diagnosed patients with anaplastic oligodendrogliomas or anaplastic oligoastrocytomas.

Patients and Methods

The primary end point of the study was OS; secondary end points were progression-free survival (PFS) and toxicity. Patients were randomly assigned to either 59.4 Gy of radiotherapy (RT) in 33 fractions only or to the same RT followed by six cycles of standard PCV chemotherapy (RT/PCV). 1p and 19q deletions were assessed with fluorescent in situ hybridization.

Results

A total of 368 patients were included. The median follow-up time was 60 months, and 59% of patients have died. In the RT arm, 82% of patients with tumor progression received chemotherapy. In 38% of patients in the RT/PCV arm, adjuvant PCV was discontinued for toxicity. OS time after RT/PCV was 40.3 months compared with 30.6 months after RT only ($P = .23$). RT/PCV increased PFS time compared with RT only (23 v 13.2 months, respectively; $P = .0018$). Twenty-five percent of patients were diagnosed with combined 1p/19q loss; 74% of this subgroup was still alive after 60 months. RT/PCV did not improve survival in the subgroup of patients with 1p/19q loss.

Conclusion

Adjuvant PCV chemotherapy does not prolong OS but does increase PFS in anaplastic oligodendroglioma. Combined loss of 1p/19q identifies a favorable subgroup of oligodendroglial tumors. No genetic subgroup could be identified that benefited with respect to OS from adjuvant PCV.

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INTRODUCTION

Phase II studies in the mid-1990s on recurrent anaplastic oligodendrogliomas and anaplastic mixed oligoastrocytomas showed that 60% to 70% of these tumors respond to chemotherapy consisting of procarbazine, lomustine, and vincristine (PCV).^{1,2} One of the questions that these studies raised was whether adjuvant PCV chemotherapy would increase survival in anaplastic oligodendroglial tumors. Although classical adjuvant nitrosourea-

based chemotherapy in high-grade glioma results in only a modest increase of 5% in 24-month survival, the high response rates in recurrent oligodendroglioma suggest that patients with newly diagnosed oligodendroglial tumors might have a more substantial benefit from adjuvant chemotherapy.³ To answer this question, in 1995, the European Organisation of Research and Treatment of Cancer (EORTC) initiated a randomized study (EORTC 26951) that investigated the value of six cycles of adjuvant PCV chemotherapy after 59.4 Gy of radiotherapy (RT) in

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anaplastic oligodendroglioma. The control arm received only RT, with the recommendation to administer chemotherapy at the time of tumor progression. Because the first chemotherapy reports on recurrent oligodendroglial tumors noted similar response rates in anaplastic oligodendrogliomas and anaplastic mixed oligoastrocytomas, the study design included both tumor types. This study was supported by the Medical Research Council Clinical Trials Group.

After the initiation of the study, it became clear that a specific subgroup of patients with oligodendroglial tumors, those with combined loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), is particularly sensitive to chemotherapy. In several studies, oligodendroglial tumors with combined 1p/19q loss were shown to have an almost 100% response rate to chemotherapy, in contrast to a 25% response rate in tumors without 1p/19q loss.^{4,5} In view of this observation, loss of 1p and 19q was analyzed with fluorescent in situ hybridization (FISH) using locus-specific probes, which allows assessment of chromosomal losses and gains in paraffin-embedded tissue samples. The current report describes the overall outcome of the study on the intent-to-treat population and in relation to 1p/19q status.

PATIENTS AND METHODS

Patients were eligible for this study if they had been diagnosed by the local pathologist with an anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma with at least 25% oligodendroglial elements; had at least three of five anaplastic characteristics (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation, and necrosis); were between 16 and 70 years old; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; had provided written informed consent; had not undergone prior chemotherapy or RT to the skull; had no diseases interfering with follow-up; and had adequate hematologic, renal, and hepatic function (WBC count $\geq 3.0 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, serum creatinine $< 120 \mu\text{mol/L}$, and serum bilirubin $< 25 \mu\text{mol/L}$). All centers had to obtain approval of the study design from their local ethical board before study activation.

Treatment

RT was to begin within 6 weeks from surgery and consisted of a dose of 45 Gy to be delivered to the planning target volume (PTV-1) in 25 daily fractions of 1.8 Gy, 5 fractions a week. Thereafter, a boost of 14.4 Gy (up to a cumulative dose of 59.4 Gy) was delivered to the PTV-2 in eight fractions of 1.8 Gy, 1 fraction a day, 5 fractions a week. PTV-1 was defined as the low-density area on preoperative computed tomography (CT) scanning and/or the high-density area on preoperative T2-weighted magnetic resonance imaging (MRI) scan with a margin of 2.5 cm. The PTV-2 was to include the nonenhancing tumor area and/or the enhancing area as visible on the postoperative CT scan with contrast with a 1.5-cm margin; in case of an unenhancing tumor on CT scan, a postoperative MRI scan with and without gadolinium was recommended to further define the tumor volume.⁶

PCV chemotherapy consisted of six cycles of standard PCV chemotherapy and had to start within 4 weeks after the end of RT. Each cycle consisted of lomustine 110 mg/m² orally on day 1 with antiemetics (domperidone or metoclopramide, and if necessary, ondansetron or a similar agent), procarbazine 60 mg/m² orally on days 8 to 21, and vincristine 1.4 mg/m² intravenous on days 8 and 29 (with a maximum dose of 2 mg). Cycles were to be repeated every 6 weeks, with dose reductions as previously described.²

During the entire treatment period, corticosteroids were to be kept at the lowest possible dose. Treatment at the time of progression was left to the discretion of the local investigators, but the protocol advised the treating physicians to consider PCV chemotherapy.

Follow-Up

At baseline and every 3 months, the protocol requested the following assessments: assessment of the disease with a neurologic examination and MRI

or CT scans (the same imaging modality was to be used throughout the entire study), ECOG PS, Mini-Mental Status Examination (which is a short bedside assessment of cognitive function), and the EORTC Quality of Life Questionnaire C30 in combination with the disease-specific Brain Cancer Module, which addresses 20 topics relevant for brain tumors. The patients were to be observed every 3 months until progression; thereafter, they were to be observed every 3 months for survival, at which time only the ECOG PS and data on further treatments were collected. Progression was defined according to Macdonald's criteria and was assessed by the local investigator.⁷ For comparison, the post-RT scan showing the smallest residual lesion had to be used. The day of recurrence was considered as the day of the diagnostic scan or the day necessitating neuroradiologic evaluation, whichever was first. The quality-of-life analysis will be reported separately.

Pathology Review

Central pathology review was part of the study and was carried out by J.M.K. Centers were required to submit paraffin-embedded blocks or 10 to 15 unstained slides for review and further research. This report presents all patients who were included based on the local pathology diagnosis

Assessment of 1p and 19q Status

Amendment 3 of the study (dated 3/21/2001) described the assessment of chromosomal loss of 1p and 19q within the study, with the predefined objectives to assess the relation between 1p/19q loss and both progression-free survival (PFS) and overall survival (OS). For the assessment of 1p and 19q status, FISH was used, as described previously.⁵ For 1p, probes to 1p36 (D1S32) and centromere 1 (pUC1.77) were used. For the assessment of 19q, probes were used directed to 19p (equivalent amounts of BAC 959O6, 95711, and 153P24) and 19q (BAC 426G3). A Zeiss Axioplan microscope (Zeiss, Jena, Germany) equipped with single-, dual-, and triple-pass filters (4,6-diamidino-2-phenylindole [DAPI]; fluorescein isothiocyanate [FITC]; tetramethylrhodamine isothiocyanate [TRITC]) was used to count the number of FISH signals for each locus-specific FISH probe. Sixty nonoverlapping nuclei were enumerated per hybridization. Ratios were calculated for 1p versus centromere 1 or 19q versus 19p by dividing the number of signals of the marker by the number of signals of the reference; a ratio of less than 0.80 was considered as allelic loss. If a borderline ratio was obtained (0.75 to 0.90), spots in 200 nuclei were counted.

Statistical Design

Assuming a median duration of survival in the control group of approximately 2 years, a total of 192 deaths was necessary to detect an increase of 1 year in the median duration of survival with a two-sided type I error of 0.05 and

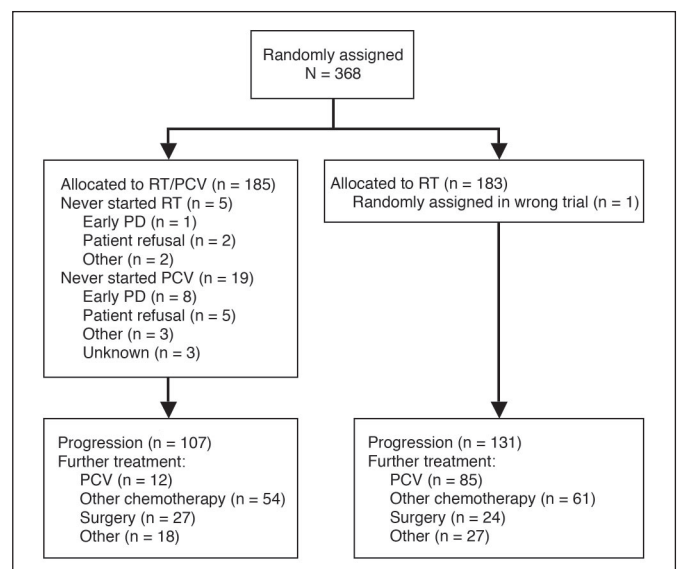


Fig 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; PD, progressive disease.

a power of 80%. Assuming 4 years of recruitment and 2 years of follow-up after closing the trial to patient entry, 292 patients (146 in each treatment arm) had to be randomly assigned. In March 2000, analysis of the pathology review on the first 150 patients showed disagreement with the local diagnosis in 25 patients (17%). Considering an additional 3% of patients to take into account losses to follow-up or drop out, the study sample was increased by 20% (58 patients). Therefore, 350 patients had to be included in the study to assure that at least 292 patients with an anaplastic oligodendroglial tumor at central pathology review (as originally expected) were randomly assigned. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Random Assignment Procedure

Patients were randomly assigned, after verification of eligibility, directly by the EORTC Data Center computer, 24 hours a day, 7 days a week, through the INTERNET network. Alternatively, registration was performed by telephone to the EORTC Data Center from 9:00 AM to 5:00 PM on Monday through Friday. Patients were stratified by age (≤ 40 v > 40 years), extent of resection (biopsy v resection), WHO ECOG PS (0 or 1 v 2), and possible prior surgery for a low-grade oligodendroglioma (yes v no). Treatment was assigned using the minimization technique of Simon and Pocock to ensure balance with respect to the stratification factors.

Table 1. Baseline Characteristics of the Two Treatment Groups

| Characteristic | Radiotherapy Plus PCV (n = 185) | | Radiotherapy Only (n = 183) | |
|--|---------------------------------|----|-----------------------------|----|
| | No. of Patients | % | No. of Patients | % |
| Age, years | | | | |
| Median | 48.6 | | 49.8 | |
| Range | 18.6-68.7 | | 19.2-68.7 | |
| Sex | | | | |
| Male | 102 | | 110 | |
| Female | 83 | | 73 | |
| WHO performance status | | | | |
| 0-1 | 155 | 84 | 153 | 84 |
| 2 | 30 | 16 | 30 | 16 |
| Previous resection for low-grade tumor | | | | |
| Yes | 27 | 15 | 25 | 14 |
| No | 156 | 84 | 157 | 86 |
| Enhancement of the tumor | | | | |
| Yes | 144 | 78 | 140 | 77 |
| No | 33 | 18 | 29 | 16 |
| Tumor localization | | | | |
| Frontal | 89 | 48 | 84 | 47 |
| Elsewhere | 96 | 52 | 98 | 53 |
| MMSE score | | | | |
| 27-30 | 116 | 63 | 14 | 62 |
| < 27 | 46 | 25 | 53 | 29 |
| Extent of resection* | | | | |
| Biopsy | 27 | 15 | 25 | 14 |
| Partial resection | 100 | 54 | 83 | 45 |
| Total resection | 58 | 31 | 75 | 41 |
| Pathology | | | | |
| Oligodendroglioma | 139 | 75 | 126 | 69 |
| Oligoastrocytoma | 44 | 24 | 56 | 31 |
| Missing | 2 | 1 | 1 | 1 |
| 1p/19q determined | 155 | | 156 | |
| 1p/19q loss | 42 | 27 | 36 | 23 |
| 1p loss | 24 | 15 | 24 | 15 |
| 19q loss | 18 | 12 | 20 | 13 |
| No loss | 71 | 46 | 76 | 49 |

Abbreviations: PCV, procarbazine, lomustine, and vincristine; MMSE, Mini-Mental State Exam.
*The extent of resection as assessed by the neuro surgeon.

Table 2. Cumulative No. of Cycles in the Patients Who Started Adjuvant PCV Chemotherapy (N = 161)

| Cumulative No. of Cycles of PCV Chemotherapy | No. of Patients | % |
|--|-----------------|----|
| 1 | 18 | 11 |
| 2 | 35 | 22 |
| 3 | 28 | 17 |
| 4 | 20 | 12 |
| 5 | 11 | 7 |
| 6 | 49 | 30 |

Abbreviation: PCV, procarbazine, lomustine, and vincristine.

RESULTS

This report is based on the data as of March 30, 2005. Between August 13, 1996 and March 3, 2002, 368 patients were randomly assigned by 40 institutions; 183 patients were assigned to the control arm (RT only), and 185 were assigned to RT plus PCV (RT/PCV; Fig 1). The median follow-up time was 62.6 months in the RT/PCV arm and 59 months in RT arm. Table 1 lists the patient characteristics of the two treatment groups; no significant baseline differences were observed.

Treatment

Ninety-five percent of patients received at least 59 Gy of RT. The calculated dose-intensity was more than 90% in 88.5% of patients, without differences between the two treatment groups. From the 185 patients randomly assigned to RT/PCV, 161 patients started PCV. Reasons for not starting PCV were progression during or before RT (n = 6), patient refusal (n = 8), other (n = 4), and unknown (n = 4). The total number of administered PCV cycles was 601 cycles; the median number of cycles administered was three. Of the 161 patients who started PCV, 37% completed at least five cycles, and 30% completed six cycles (Table 2). Reasons for premature discontinuation of PCV were hematologic toxicity in 33% of patients, nonhematologic toxicity in 5%, tumor progression in 24%, patient refusal in 5%, and other reasons in 4%. Table 3 lists the observed grade 3 and 4 toxicities during PCV chemotherapy, which were mainly hematologic.

Salvage Treatment

At the time of this report, 107 patients in the RT/PCV arm and 131 patients in the RT arm were diagnosed with disease progression.

Table 3. Grade 3 and 4 Toxicity in the Patients Who Started PCV Chemotherapy (N = 161)

| Toxicity | Grade 3 | | Grade 4 | |
|--------------------------|-----------------|----|-----------------|----|
| | No. of Patients | % | No. of Patients | % |
| WBC count | 43 | 27 | 5 | 3 |
| Neutrophils | 39 | 24 | 13 | 8 |
| Platelets | 23 | 14 | 11 | 7 |
| Hemoglobin | 10 | 6 | 1 | 1 |
| Any hematologic toxicity | 51 | 32 | 23 | 14 |
| Nausea | 9 | 6 | — | — |
| Vomiting | 10 | 6 | — | — |
| Polyneuropathy | 3 | 2 | — | — |
| Allergic skin reactions | 2 | 1 | — | — |

Abbreviation: PCV, procarbazine, lomustine, and vincristine.

Table 4. Further Treatments Administered at the Time of Progression

| Further Treatment | RT/PCV (n = 107) | | RT (n = 131) | |
|--------------------|------------------|----|-----------------|----|
| | No. of Patients | % | No. of Patients | % |
| Surgery | 27 | 25 | 24 | 18 |
| Any chemotherapy | 59 | 55 | 107 | 82 |
| Salvage PCV | 12 | 11 | 85 | 65 |
| Other chemotherapy | 54 | 51 | 61 | 47 |
| Temozolomide | 46 | 43 | 49 | 37 |
| Other | 18 | 17 | 27 | 21 |

Abbreviations: RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine.

In 95% of patients, the diagnosis of progression was based on findings at neuroimaging. Table 4 lists further treatment in these patients at the time of progression. In the RT arm, 82% of the patients with disease progression received some kind of chemotherapy, and 65% received PCV chemotherapy. Temozolomide was slightly more often used in the RT/PCV arm compared with the RT arm (43% v 37% of patients, respectively).

Outcome

At the time of analysis, 103 patients in the RT/PCV arm (55.7%) and 114 patients in the RT arm (62.3%) had died; 70.7% of patients had either died or experienced progression. Table 5 lists the OS and PFS in both treatment groups. Median OS time in the RT arm was 30.6 months; in the RT/PCV arm, median OS time was 40.3 months (hazard ratio = 0.85; 95% CI, 0.65 to 1.11; $P = .23$; Fig 2). PFS time in the RT/PCV arm was significantly better compared with the RT arm (median PFS time, 23.0 v 13.2 months, respectively; hazard ratio = 0.68; 95% CI, 0.53 to 0.87; $P = .0018$; Fig 3).

1p/19q Analysis

For 311 patients (85%), sufficient tissue was available to assess 1p and 19q status. Survival in patients in whom 1p/19q status was assessed was similar to the survival in patients without 1p/19q assessment (data not shown). Combined 1p and 19q loss was observed in 78 patients (25.1%); 1p loss without 19q loss was observed in 48 patients (15.4%); and 19q loss without 1p loss was observed in 12%. The presence of chromosomal losses was balanced between the two treatment groups. Table 6 lists median and 5-year OS and PFS. Both were significantly better in patients with combined 1p/19q loss, but in none of the subgroups did RT/PCV provide a better outcome compared with RT only (Figs 4 and 5).

Predictive Factor Analysis

The results from a predictive factor analysis including the stratification factors, the presence of the five anaplastic features according to the review pathology, 1p/19q loss, treatment, and treatment in relation to 1p/19q loss are listed in Table 7. Age, extent of surgery, previous surgery for a low-grade tumor, 1p/19q loss, PS, endothelial proliferation, and necrosis were found to be related to survival. The presence of 1p/19q loss was found to be the most important factor, with a hazard ratio of 0.27.

DISCUSSION

This trial on 368 patients with anaplastic oligodendroglioma compared adjuvant PCV chemotherapy with PCV chemotherapy at the time of recurrence. More than 80% of the patients who experienced progression and who were randomly assigned to the RT only arm indeed received chemotherapy at the time of progression. The outcome shows that, although adjuvant PCV chemotherapy improves PFS, it does not affect OS. Most likely, the absence of a benefit in OS is a result of the efficacy of chemotherapy at the time of recurrence. Therefore, the primary conclusion that can be drawn from the present data is that, provided chemotherapy is administered, the timing of chemotherapy is less relevant with regard to OS. PCV chemotherapy was only moderately well tolerated; more than one third of patients who started PCV discontinued treatment because of (usually asymptomatic) cumulative myelosuppression before reaching the intended six cycles of adjuvant treatment. As a consequence, the achieved dose-intensity was much less than what was intended by the protocol. In this respect, PCV differs from temozolomide, which is increasingly being used for both recurrent and newly diagnosed glioma. As a rule, this drug is better tolerated, with most patients receiving more than 90% of the intended dose-intensity.⁸

Several reports published during the past decade have shown a considerable interobserver variation in the histologic diagnosis of oligodendroglial tumors and an increasing tendency among pathologists to diagnose oligodendroglial tumors.^{9,10} This shift is at least partly a result of the absence of objective diagnostic criteria for oligodendroglioma and the presence of mixed oligoastrocytomas, which, by definition, contain elements of both astrocytomas and oligodendrogliomas.¹¹ The presence of 25% oligodendroglial elements, which both we and others have used as a criterion for inclusion onto trials on oligodendroglioma, is also subjective and prone to interobserver variation.¹² Well after the initiation of the study, it became clear that the

Table 5. Overall Survival and Progression-Free Survival

| Survival | RT | | RT/PCV | | RT | | RT/PCV | |
|-------------------------|------------------|--------------|------------------|--------------|---------------------------|--------------|---------------------------|--------------|
| | Overall Survival | 95% CI | Overall Survival | 95% CI | Progression-Free Survival | 95% CI | Progression-Free Survival | 95% CI |
| Median survival, months | 30.6 | 21.9 to 45.3 | 40.3 | 28.7 to 68.2 | 13 | 9.2 to 19.4 | 23 | 17.6 to 43.8 |
| 12-Month survival, % | 80 | 74.6 to 86.1 | 81 | 75.8 to 87.1 | 52 | 44.7 to 59.2 | 65 | 58.2 to 72.0 |
| 24-Month survival, % | 55 | 47.9 to 62.4 | 62 | 55.1 to 69.2 | 39 | 32.3 to 46.4 | 50 | 42.4 to 56.9 |
| 60-Month survival, % | 37 | 29.6 to 44.8 | 44 | 35.9 to 51.1 | 23 | 16.2 to 29.2 | 37 | 29.8 to 44.6 |

Abbreviations: RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine.

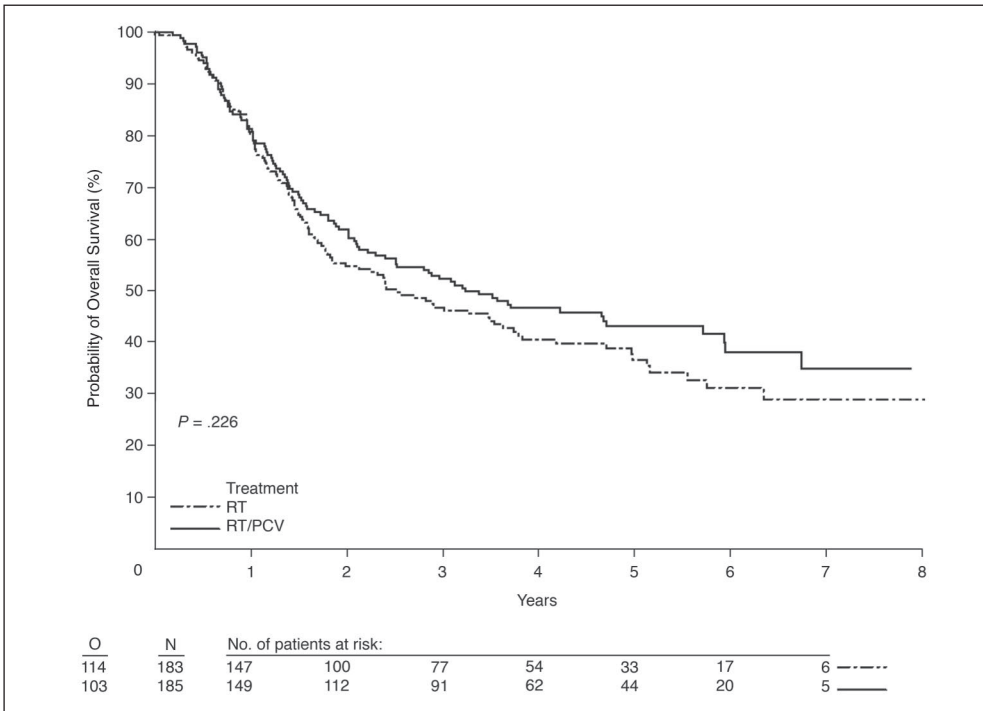


Fig 2. Overall survival in both treatment arms. RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; O, observed events; N, total number of events.

subset of patients with oligodendroglial tumors with combined loss of 1p and 19q is particularly sensitive to PCV chemotherapy, with almost 100% of patients responding.^{4,5} Today, genotyping allows much more reliable diagnosis of patients with chemotherapy-sensitive oligodendroglial tumors compared with classical histology. In this study, only 25% of the samples available for analysis had combined 1p and 19q loss. Thus, only a minority of our

patients carried the chemotherapy-sensitive 1p/19q loss oligodendroglial tumor subtype, which represents the subgroup of tumors that this trial was originally aiming to study. Still, even in this subgroup, the survival curves of the two treatment groups are overlapping, without any suggestion of OS benefit of early chemotherapy for the patients with chemotherapy-sensitive tumors. Obviously, the small number of patients with 1p/19q loss limits the

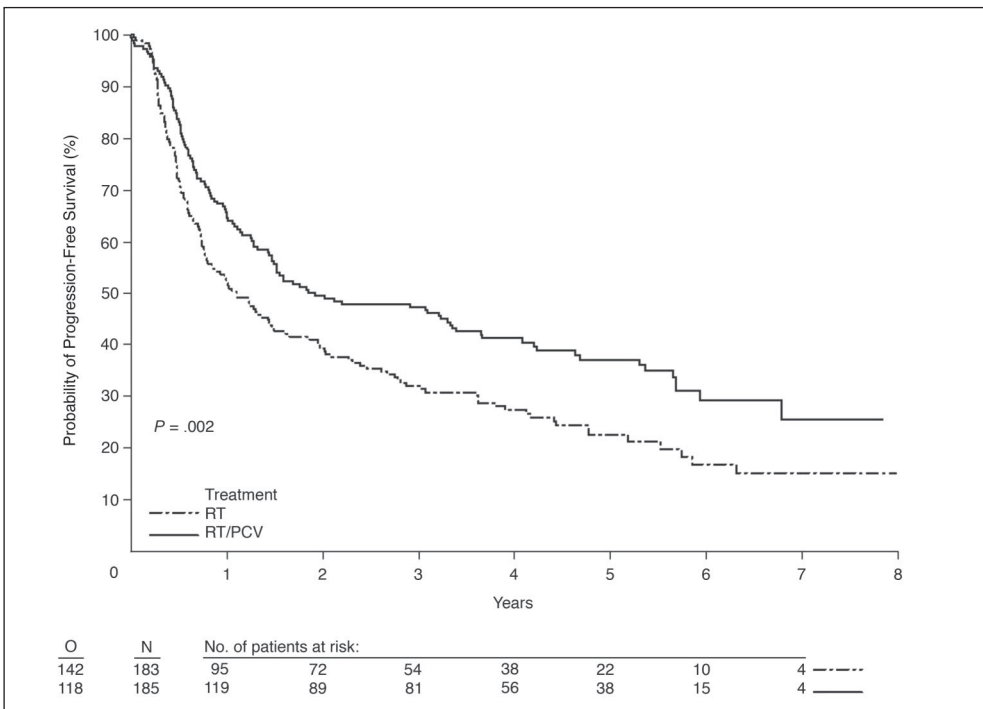


Fig 3. Progression-free survival in both treatment arms. RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; O, observed events; N, total number of events.

Table 6. Median and 5-Year Progression-Free Survival and Overall Survival According to Combined 1p/19q Loss Status

| Chromosomal Loss | Progression-Free Survival | | | | | | | | Overall Survival | | | | | | | |
|-------------------------|---------------------------|-----------------|-----------------|-----------------|------------|--------------|------------|--------------|------------------|-----------------|-----------------|-----------------|------------|--------------|------------|--------------|
| | RT/PCV | | RT | | RT/PCV | | RT | | RT/PCV | | RT | | RT/PCV | | RT | |
| | Median (months) | 95% CI (months) | Median (months) | 95% CI (months) | 5-Year (%) | 95% CI (%) | 5-Year (%) | 95% CI (%) | Median (months) | 95% CI (months) | Median (months) | 95% CI (months) | 5-Year (%) | 95% CI (%) | 5-Year (%) | 95% CI (%) |
| Combined 1p/19q loss | NR | NR | 62.2 | 43.4 to NR | 69.5 | 52.4 to 81.5 | 50.2 | 32.3 to 65.7 | NR | NR | NR | NR | 74.0 | 56.9 to 85.1 | 74.7 | 54.8 to 86.9 |
| No combined 1p/19q loss | 15.3 | 11.8 to 23.0 | 8.9 | 7.1 to 14.8 | 26.8 | 18.6 to 35.6 | 13.7 | 7.9 to 21.0 | 25.2 | 18.9 to 42.6 | 21.4 | 17.6 to 30.0 | 33.5 | 24.4 to 42.8 | 27.5 | 19.2 to 36.4 |

Abbreviations: RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; NR, not reached.

power to detect clinical differences in this subset of patients, but from the present data, no benefit of early adjuvant chemotherapy in the 1p/19q loss patients can be concluded.

In this study, 1p and 19q loss was the most important predictive factor for outcome. Although it is usually assumed that 1p/19q loss predicts, in particular, a better outcome to chemotherapy, the present study shows that PFS after RT only in patients harboring 1p/19q loss tumors is also much better. After a median follow-up time of 60 months, median survival time in patients with tumors without 1p/19q loss is less than 2 years, whereas it was not reached in patients with 1p/19q loss. This improved outcome has also been observed in retrospective studies on heterogeneously treated patients with 1p/19q loss.^{9,13} Clearly, tumors with 1p/19q loss are a completely different biologic entity and should be kept apart in future studies on glioma. Vice versa, trials on anaplastic glioma can include tumors with oligodendroglial morphology having no 1p/19q loss. These tumors have a similar prognosis as anaplastic astrocytoma, and until new molecular

markers are identified, there is no reason to keep them apart based on rather subjective histologic criteria.

Simultaneously with our study, the North American Radiation Therapy Oncology Group (RTOG) has carried out a similar study (RTOG 94-02), which differed in only the following few aspects: chemotherapy was administered before RT, patients received intensified PCV, and patients with two of five anaplastic characteristics were allowed as long as frequent mitosis or endothelial proliferation were present.¹⁴ The conclusions of that study are similar to ours; an increased PFS after neoadjuvant PCV was observed, but there was no difference in OS. Interestingly, in contrast to our study, the RTOG study observed an increase in PFS only in patients with 1p/19q loss but not in patients with intact 1p/19q. It is tempting to speculate that this is a result of the different sequence of treatments; 1p/19q-intact tumors are less sensitive to chemotherapy, and historical trials on high-grade glioma have shown that RT is more effective for this disease than chemotherapy.¹⁵ Another striking difference is

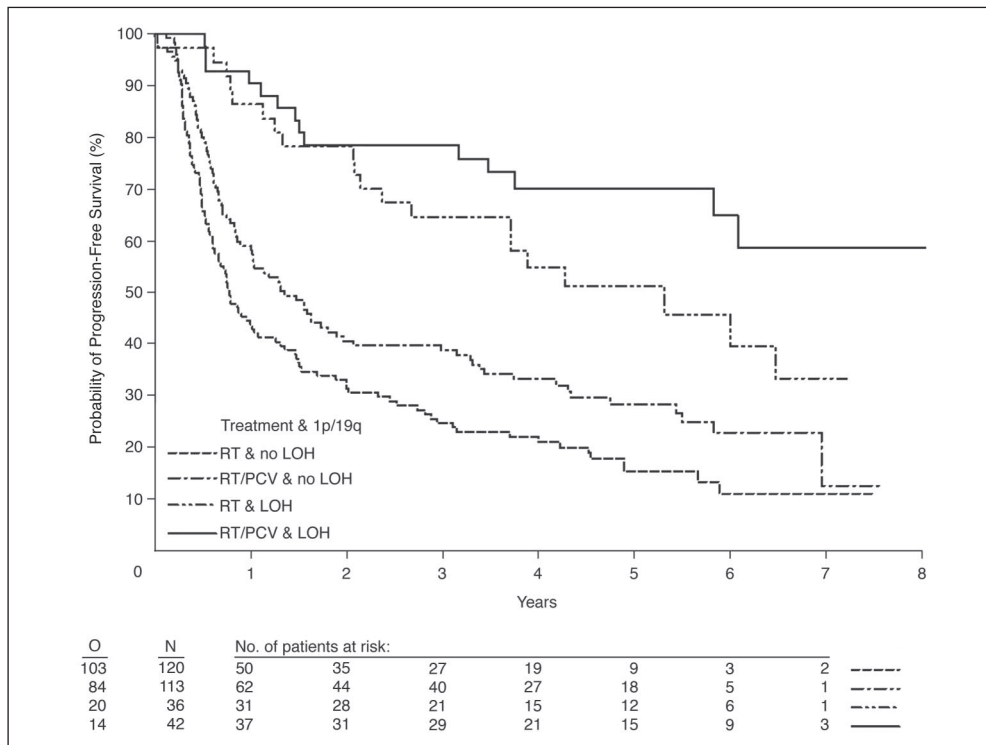


Fig 4. Progression-free survival in both treatment arms in the groups with and without combined 1p/19q loss. RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; LOH, loss of heterozygosity of both 1p and 19q; O, observed events; N, total number of events.

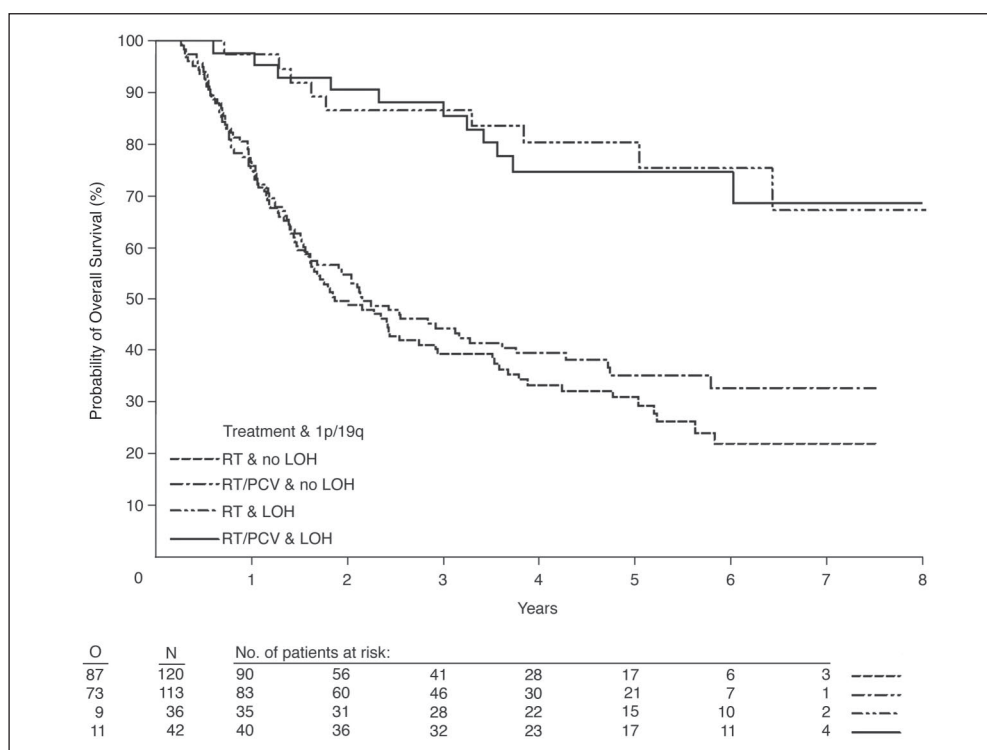


Fig 5. Overall survival in both treatment arms in the groups with and without combined 1p/19q loss. RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; LOH, loss of heterozygosity of both 1p and 19q; O, observed events; N, total number of events.

the higher rate of patients with 1p/19q loss (46%) in the RTOG study and the better OS (median OS time was almost 5 years). The longer survival may be explained by the higher percentage of patients with 1p/19q loss in the RTOG trial and by the inclusion of tumors with only two anaplastic features. The considerable difference in the percentage of tumors with 1p/19q loss between the European and the North American trials points to differences among pathologists and further stresses the need to classify these tumors according to their genetic profile.

It is rather confusing to see that two trials on adjuvant chemotherapy in oligodendroglioma, which is a chemotherapy-sensitive subset of tumors, failed to demonstrate improved OS, whereas the recent EORTC trial on concurrent and adjuvant temozolomide demonstrated an improved survival in glioblastoma multiforme, which is a chemotherapy-resistant disease.⁸ One explanation for this surprising finding could be that, in the trial on glioblastoma, temozolomide chemotherapy was administered daily during RT, which is an approach that has not been tried before in glioma and which is not

Table 7. Results of the Analyses With the Cox Proportional Hazards Model in Patients in Whom 1p/19q Status Was Assessed (N = 311)

| Variable | No. of Patients | % | Predictive-Factor Model | | |
|--|-----------------|----|-------------------------|--------------|--------------|
| | | | P | Hazard Ratio | 95% CI |
| 1p and 19q LOH and PCV plus RT v no 1p and 19q LOH or RT | 42 | 14 | .93 | 1.04 | 0.39 to 2.76 |
| RT/PCV v RT | 155 | 50 | .85 | 1.03 | 0.75 to 1.43 |
| 1p and 19q LOH v no 1p and 19q LOH | 78 | 25 | < .001 | 0.27 | 0.13 to 0.56 |
| Age ≥ 50 v < 50 years | 145 | 47 | < .001 | 1.69 | 1.24 to 2.31 |
| Surgery, resection v biopsy | 271 | 87 | .005 | 0.57 | 0.38 to 0.84 |
| Performance score* | | | < .001 | 1.54 | 1.23 to 1.91 |
| 0 | 113 | 37 | | | |
| 1 | 144 | 47 | | | |
| 2 | 49 | 16 | | | |
| Previous resection for low-grade glioma, yes v no | 43 | 14 | .02 | 0.46 | 0.24 to 0.88 |
| Frontal location v other location | 147 | 47 | .02 | 0.68 | 0.49 to 0.95 |
| Endothelial abnormalities, present v absent† | 253 | 82 | .007 | 2.32 | 1.26 to 4.26 |
| Necrosis, present v absent† | 184 | 60 | < .001 | 2.04 | 1.41 to 2.97 |

Abbreviations: LOH, loss of heterozygosity; RT, radiotherapy; PCV, procarbazine, lomustine, and vincristine; NR, not reached.

*As reported on the study form; for five patients, no performance score was available.

†Assessment performed by the central pathologist.

feasible with nitrosourea-based chemotherapy like PCV. The study on concurrent chemoirradiation with temozolomide in glioblastoma multiforme also identified a subset of patients with tumors showing methylation of the promoter gene *MGMT* to be the patients who profited most from combined-modality treatment.¹⁶ Determination of *MGMT* status in a subset of patients from this study is ongoing.

Several studies on glioma and on brain metastases have now shown that early chemotherapeutic or radiotherapeutic treatment postpones progression without affecting OS.^{17,18} These studies show that, by postponing adjuvant treatment, OS is not jeopardized if effective salvage treatment is available. However, none of these studies have determined whether patients deteriorate at

the time of progression. If that is the case, postponing progression becomes a target because it will help to maintain the patients in a better condition. Instruments must be developed that allow the objective assessment of neurologic deterioration-free survival in trials.

What conclusions should be drawn from this trial? First, the trial shows that the timing of chemotherapy is of little relevance with regard to survival if it is administered sequentially with RT and using a classical adjuvant approach. Second, future studies on anaplastic oligodendroglioma should keep the patients with 1p/19q loss tumors apart. Third, the high attrition rate in patients treated with PCV suggests that this is not an optimal regimen for adjuvant treatment.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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