

## Practice changing mature results of RTOG study 9802: another positive PCV trial makes adjuvant chemotherapy part of standard of care in low-grade glioma

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The long-term follow-up of the RTOG 9802 trial that compared 54 Gy of radiotherapy (RT) with the same RT followed by adjuvant procarbazine, CCNU, and vincristine (PCV) chemotherapy in high-risk low-grade glioma shows a major increase in survival after adjuvant PCV chemotherapy. Median overall survival increased from 7.8 years to 13.3 years, with a hazard ratio of death of 0.59 (log rank:  $P = .002$ ). This increase in survival was observed despite the fact that 77% of patients who progressed after RT alone received salvage chemotherapy. With this outcome, RT + PCV is now to be considered standard of care for low-grade glioma requiring postsurgical adjuvant treatment. Unfortunately, studies on molecular correlates associated with response are still lacking. This is now the third trial showing benefit from the addition of PCV to RT in grade II or III diffuse glioma. The optimal parameter for selecting patients for adjuvant PCV has not yet been fully elucidated, but several candidate markers have so far emerged. It is still unclear whether temozolomide can replace PCV and whether initial management with chemotherapy only is a safe initial treatment. Potentially, that may adversely affect overall survival, but concerns for delayed RT-induced neurotoxicity may limit acceptance of early RT in patients with expected long term survival. The current evidence supports that in future trials, grades II and III tumors with similar molecular backgrounds should be combined, and trials should focus on molecular glial subtype regardless of grade.

**Keywords:** chemotherapy, low grade glioma, PCV, temozolomide.

The mature results of the Radiation Therapy Oncology Group (RTOG) trial 9802, “Phase III study of radiation therapy with or without procarbazine, CCNU, and vincristine (PCV) in low grade glioma,” as presented by Jan Buckner at the American Society of Clinical Oncology (ASCO) 2014 meeting (and in the presence of Ed Shaw, the principal investigator of the study), by all means qualify for “practice changing.”<sup>1</sup> This trial, conducted by RTOG in collaboration with the North Central Cancer Treatment Group, the Eastern Cooperative Oncology Group (ECOG), and the SWOG cooperative group, randomized so-called high-risk patients (defined as either >40 y and/or with less than total resection) to 54 Gy of radiotherapy (RT) only or the same RT followed by 6 cycles of PCV chemotherapy (RT + PCV). The outcome was a striking and clinically significant increase in overall survival (OS) after RT + PCV. These results were already anticipated at the time of the first publication in 2012, which was based on the results presented at ASCO 2008.<sup>2,3</sup> At that time 35% of the 251 patients in the study had died. Now, with still only 55% of patients having died, the addition of PCV to RT increased median progression-free

survival (PFS) from 4.0 years to 10.4 years, and median OS from 7.8 years to 13.3 years. The hazard ratio for OS was 0.59, mirrored by a statistically highly significant  $P$ -value. In a risk-adjusted multivariate analysis, patients treated with PCV, those with oligodendroglial histology, and females had better survival. Moreover, the increasing follow-up duration increasing separation of the survival curves tells us that with further passage of time, the difference in OS will become even larger. Of note (and similar to the adjuvant PCV trials on anaplastic oligodendroglioma), no less than 71 of the 92 relapsed patients (77%) in the RT-only arm received chemotherapy at progression. Thus, the message is that initial treatment with RT + PCV is far superior to sequential treatment: initial RT and further chemotherapy at the time of relapse. Buckner concluded that the toxicity profile of the PCV schedule is manageable and comparable to that of other chemotherapy combination regimens. Indeed, the study once again documents the (mainly hematological) toxicities of PCV, but the present update in OS shows that advantages of the addition of PCV to RT by far exceed the added toxicities.

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### Three Positive Adjuvant PCV Trials

RTOG 9802 represents the third trial showing survival benefit of (neo-)adjuvant PCV chemotherapy in at least subsets of diffuse grade II and grade III glioma, and the first ever trial to show OS benefit of a particular treatment in grade II glioma. This trial together with the 2 trials on adjuvant PCV chemotherapy in newly diagnosed anaplastic oligodendroglial tumors show a similar phenomenon: initially overlapping survival curves, which somewhere between 3 and 5 years start to separate.<sup>4,5</sup> That phenomenon accounts for the absence of an OS benefit in the initial publication of all 3 trials, despite the increase in PFS that was already present at that time.<sup>2,6,7</sup>

The report presented at ASCO was still not complete, though. No analysis by histology was presented, apparently because the subgroups became too small to allow definitive conclusions. This implies that at present the OS benefit from adjuvant PCV in low-grade glioma must be assumed to be present in all histologies. Whether this is truly a loss is debatable. The interobserver variation in the distinction between grades II and III is notoriously large, adding to the notion of a lack of relevance of the World Health Organization (WHO) grading scale in individual glioma patients. And that brings us to a more serious issue: no molecular correlates with outcome were presented, which was a huge disappointment. The 2 randomized trials on anaplastic oligodendroglial tumors have offered the possibility of a more personalized strategy for grade III tumors. They have given evidence that molecular features offer a better way to select patients for adjuvant chemotherapy compared with classical histology. Despite some of the unresolved issues, both of these trials have shown a benefit to 1p/19q codeleted tumors by the addition of PCV to RT. Both have also indicated that a larger population than patients with 1p/19q codeleted tumors alone benefited from adjuvant PCV chemotherapy, although the optimal identification of this population is still not clearly defined. The currently suggested marker of benefit is either the presence of isocitrate dehydrogenase (IDH) mutations, tumors positive for cytosine-phosphate-guanine island methylated phenotype (CIMP), or even good old O<sup>6</sup>-DNA methylguanine-methyltransferase (MGMT) promoter methylation.<sup>8,9</sup> The existing data do not, however, provide a definitive answer, and despite claims of the predictive value of IDH mutational status for benefit to PCV, statistical tests for interaction remained negative in RTOG 9402. MGMT promoter methylation assessed by the Illumina methylation array appeared to be the most predictive factor in the European Organisation for Research and Treatment of Cancer (EORTC) 26951 trial, but that trial has enrolled a conceivable number of glioblastoma. Moreover, these factors are all interrelated, and the optimal predictive test remains to be identified. The RTOG 9802 trial could be a major contribution to this analysis, but apparently the collection of tissue samples was not part of the original trial design. Most likely, only a limited number of samples will be available for molecular studies, making it questionable whether enough samples will be available for a meaningful analysis of this most important aspect. Every effort should therefore be made to make missing samples available for correlative molecular studies—in fact, this should already have been done years ago.<sup>3</sup> In addition, no substantial data on quality of survival have been presented. Buckner presented 5-year follow-up data on the Mini-Mental State Examination (MMSE), suggesting absence of decline over time (and no

difference between the 2 treatment groups). Similar data were earlier this year published on the initial OS dataset.<sup>10</sup> However, and as recognized by the authors, the MMSE is a scale designed to screen for dementia and is not an appropriate tool to assess RT and brain tumor–induced cognitive deterioration. Although a baseline is missing, formal neuropsychological evaluation would help us to understand what physical and cognitive restraints the long-term surviving patients of RTOG 9802 are facing. With the current inclination of many clinicians to postpone RT as long as possible, this type of information is of high clinical relevance. The evidence is currently limited to one long-term follow-up report, which shows a rather mixed result (see section Quality of Survival).<sup>11</sup> Obviously, more data would be very useful, and RTOG 9802 provides an excellent opportunity to acquire them.

### Selection of Patients for Adjuvant Chemotherapy

What are the remaining questions? There are many. First, this trial addressed high-risk low-grade glioma patients, defined as either over the age of 40 or having undergone a less than gross total resection. Should RT + PCV only be given to those patients? The “high risk” classification, however, by no means represents exact science. Previously, RTOG published the results of the “low-risk” low-grade glioma patients from the same trial, describing the outcome of 111 patients between 18 and 39 years of age who had undergone a less than gross total resection.<sup>12</sup> PFS at 5 years in this group was 48%, whereas in the “high-risk” group treated in RTOG 9802, PFS was 44% after RT only and 61% after RT + PCV. In the “low-risk” cohort of RTOG 9802, three prognostic factors predicted decreased PFS: (i) preoperative tumor diameter  $\geq 4$  cm; (ii) astrocytoma or oligoastrocytoma histological subtype; and (iii) residual tumor  $\geq 1$  cm on MRI. So, with half of the patients having progressed in the “low-risk” group at 5 years, the outcome was not that favorable, and some “low-risk” low-grade gliomas are clearly more “low-risk” than others. The EORTC 22033 trial, comparing RT with temozolomide (TMZ), used different criteria to define grade of glioma requiring treatment.<sup>13</sup> Here, at least one of the following criteria needed to be present: age  $\geq 40$  years, radiologically proven progressive lesion, new or worsening neurological symptoms other than seizures only (focal deficits, signs of raised intracranial pressure, mental deficits), or the presence of intractable seizures. A recent meta-analysis on the 4 large randomized trials from the pre-molecular era (including RTOG 9802) showed 4 factors related to worse OS: the presence of baseline neurological deficits, a shorter time since first symptoms ( $< 30$  wk), an astrocytic tumor type, and tumors larger than 5 cm in diameter.<sup>14</sup> Clearly, “high-risk” low-grade glioma patients can be defined in many different ways. The more fundamental question is whether it is rational to base the choice for or against RT + PCV on specific risk factors associated with poor OS. It appears more rational to base this on expected benefit to chemotherapy, and that benefit may in fact be present or more pronounced in patients with more favorable outcome. From a more practical perspective, the decision to treat with adjuvant PCV should be based on the consideration that following surgery some type of adjuvant treatment is required, at whatever point in the course of the disease. This timing of adjuvant treatment in low-grade glioma has been a controversial topic for decades, but the present

data give guidance that once adjuvant treatment is indicated, it should be RT and PCV. That leaves undisputed that for many who risk low-grade glioma, a watch-and-wait policy is appropriate, provided the patients are well monitored.

## PCV or Temozolomide?

Which leads to the next question: does it have to be RT followed by PCV or can PCV be replaced by TMZ? This very same question was raised when the long-term follow-up data on adjuvant PCV in anaplastic oligodendroglioma were presented. Historically, the PCV schedule was developed in the mid-1980s based on assumptions regarding the effects of drugs on tumor cells in various phases of the cell cycle.<sup>15</sup> The schedule became popular when high response rates were demonstrated in recurrent oligodendroglial tumors.<sup>16</sup> Over the past decade, PCV has been gradually replaced by TMZ, with its more easy schedule and better tolerance. It needs to be stated, though, that no similar long-term benefit data exist from clinical trials on TMZ in diffuse grade II or grade III glioma. One may assume that TMZ will be equally effective, but in the absence of data, that remains speculative. Another drawback of the PCV schedule is that it is based on old cytotoxic drugs, which because of manufacturing issues have been temporarily unavailable in certain regions of the world over the past years. On top of this is the debate over whether TMZ should be given in an adjuvant setting or as combined chemoradiotherapy (as, for instance, in the ECOG trial E3F05). Again, no data exist, but the risk of an aggravation of RT side effects has been pointed to once RT is combined with TMZ. Although recent papers have demonstrated the development of novel mutations in early TMZ-treated low-grade glioma patients, whether this has any impact on outcome of patients is completely unclear.<sup>17</sup> As long as this is unclear, it is only a laboratory finding. Of note, similar molecular studies on patients relapsing after RT only are lacking, but in the past it has been assumed that early RT might induce earlier malignant dedifferentiation. That assumption was never proven.

## Quality of Survival

That brings us to the issue of quality of survival, whether RT is really needed as part of the initial adjuvant treatment and whether RT can be safely postponed by administering upfront chemotherapy. The wish, held by many to delay RT in low-grade glioma patients, is based on concerns of adverse effects of RT on cognition, which has resulted in a growing tendency to treat with chemotherapy first. It took a major Dutch study a rather prolonged follow-up to find some evidence of decreased functioning of low-grade glioma patients who underwent early RT.<sup>18,19</sup> Well-designed prospective studies are unfortunately lacking, which is no surprise, as they would require a follow-up of more than a decade. This leaves the effect size of adverse events of early RT on cognition at least unclear. So far, delaying RT has not been an issue, as a previous EORTC trial on low-grade glioma indeed has shown that a delay in RT after surgery does not affect survival.<sup>20</sup> Therefore RT is usually only given once adjuvant treatment is indicated. We now have a trial that shows improved OS after early RT + PCV, and indeed at a moment in time when many clinicians postpone RT in lieu of chemotherapy only with the objective to

postpone RT-induced cognitive changes. What matters here is whether early aggressive treatment (RT + PCV) improves outcome without jeopardizing quality of survival, and whether an effective treatment (RT) can be safely postponed without jeopardizing survival in order to maintain quality of survival. Data on the quality of long-term survival in RT + PCV-treated patients are scarce, and such datasets on patients receiving chemotherapy only are lacking. It was already mentioned that in RTOG 9802, cognitive assessment with MMSE did not show differences between the 2 treatment arms of the study and no decline in the first 5 years of follow-up, but the MMSE is not a sensitive tool for the assessment of RT-induced cognitive complaints.<sup>10</sup> In a unique cohort of long-term survivors of EORTC 26951, patients were given full neuropsychological evaluation.<sup>11</sup> Unfortunately, baseline testing of these patients is not available. The results in progression-free patients ( $n = 27$ ) were highly variable: 44% had no cognitive impairments and 30% showed severe cognitive impairments; 41% were still employed and 81% could live independently. Also, the few patients<sup>5</sup> in this cohort who had relapsed suffered from more severe cognitive impairments. Thus, indeed, quality of survival is an issue in brain tumor patients. Whether poor functioning in a subset of patients is by and large indeed the result of RT is less clear. The tumor itself, surgery, seizures, and anti-seizure medication also contribute to this, but effects of RT are likely to be part of decreased cognitive functioning. These concerns about the impact of RT on quality of survival will undoubtedly have an impact on the acceptance of the results of this trial by both patients and clinicians. Since any new phase III question will take another 2 decades to deliver results, this controversy is unlikely to be solved at a more evidence-based level.

## Delay Radiotherapy and Use Chemotherapy Alone?

What are the data that we can safely postpone RT and treat with upfront chemo alone? In view of 3 trials that showed prolonged OS when RT was combined with PCV chemotherapy, can we indeed expect to use upfront TMZ to postpone RT without the risk of decreased survival? In other words, how long is upfront TMZ only going to postpone RT? And can we expect that salvage RT with second-line chemotherapy will be equally effective? Two phase III trials have investigated upfront chemotherapy in newly diagnosed grades II and III glioma: the German NOA-04 study (PCV or TMZ) on anaplastic glioma<sup>21</sup> and EORTC 22033 (TMZ) on low-grade glioma.<sup>13</sup> In both trials the OS data were still immature at the time of initial reporting; and with passage of time, results may still change. Median PFS in EORTC 22033 was 39 months for all patients, 30 months for patients with 1p/19q intact tumors, and 55 months for patients with 1p/19q codeleted tumors.<sup>13</sup> In NOA-04, median PFS in the chemotherapy arm was 31 months, with a PFS of 18.2 months for anaplastic astrocytoma patients and 52.7 months for patients with a tumor with an oligodendroglial component.<sup>21</sup> Of note, median PFS for all patients in the RT arm was 4.0 years in RTOG 9802, 30.6 months in NOA-04, and 46 months in EORTC 22033. None of these figures is even close to the PFS of 10.4 years in the RT + PCV arm of RTOG 9802. Thus, there is a major increase in PFS with combined treatment, which in fact preceded the OS benefit after more long-term follow-up. The fundamental question is whether salvage

treatment at the time of relapse following upfront chemotherapy alone will bring the same OS, which is to be demonstrated. All 3 RT + PCV trials have given evidence of superior outcome of adjuvant treatment compared with sequential treatment, with RT first and chemotherapy given at progression. The available historical data of either second-line PCV or second-line TMZ after failure of the other regimen tend to show a decreased response rate and PFS in comparison with first-line PCV or TMZ.<sup>22–28</sup> This appears to hold true for 1p/19q codeleted tumors as well, although data are limited and mostly derived from salvage studies.<sup>29</sup> Still, it shows that it is by no means guaranteed that initial chemotherapy and RT with second-line chemotherapy at the time of relapse will be equally effective as initial combined treatment. Obviously, PFS is not an endpoint in itself in this slowly progressive disease in which many patients remain asymptomatic for many years. PFS is a radiological endpoint and in itself clinically irrelevant unless accompanied by clinical signs and symptoms or reflecting OS. The present data, however, point to PFS being predictive for OS—at least PFS benefit has predicted OS benefit in all 3 trials. Plus, several studies have documented that at progression, cognition may decline, although that may be more of an issue in high-grade tumors.<sup>30</sup>

## Diffuse Glioma: Does Grade Still Matter?

Last but not least, with the current data the question has arisen whether it is still relevant to continue with distinguishing between WHO tumor grades. In particular in grade II and grade III tumors, the classical typing and grading of glioma are subject to a major interobserver variation, which questions the foundation of this classification.<sup>31</sup> The similar results of the 3 RT + PCV trials support the notion that there is only a gradual distinction between diffuse grades II and III glioma. The similarities in outcome and treatment sensitivity between grade II and grade III tumors of the same lineage appear more striking than the modest difference in OS between grade II and grade III tumors of the same lineage. The currently identified molecular factors that may predict benefit to the addition of PCV to RT—1p/19q, IDH, CIMP, MGMT—are present in the majority of both grade II and grade III glioma, and the so-called triple negative low-grade glioma most likely represents an entirely different breed.<sup>32</sup> The time has come to develop common treatment strategies for grades II and III tumors, based on their molecular characteristics. On the molecular level, grades II and III tumors differ only in some increase in number of chromosomal lesions, but the basic tumor-driving alterations are the same. At the same time, these basic alterations are correlated to both prognosis and benefit to the addition of PCV. The original WHO grading system was built on similarities in survival, which indeed differ between grades II and III tumors. However, if we now know that OS in 1p/19q codeleted anaplastic oligodendroglioma is well beyond 12 to 14 years and much longer in comparison with low-grade astrocytoma, what is the rationale to mix in studies low-grade 1p/19q codeleted tumors with non-1p/19q codeleted tumors? Entering both low- and high-grade codeleted tumors into one trial will bring together tumors with a similar molecular background without discussion of arbitrary cutoffs and will make trials on codeleted tumors feasible. It will fuel new discussions, like the optimal RT dosage for 1p/19q codeleted anaplastic tumors in such trials, but that is a question that

merits consideration anyway. Grade will continue to carry prognostic information, but more so in molecularly defined classes. It must be admitted, though, that the data on grades II and III astrocytic tumors and the predictive role of IDH mutations are less solid. The use of TMZ in grade III tumors without 1p/19q loss is the subject of the ongoing CATNON trial (Phase III Trial on Concurrent and Adjuvant Temozolomide Chemotherapy in Non-1p/19q Deleted Anaplastic Glioma). Although that trial is approaching the end of its accrual, it will take (again) many years for this trial to mature. With its RT-only arm, the CATNON trial will further help us to understand the molecular factors associated with benefit to chemotherapy in 1p/19q intact tumors. Equally important, it will be the first trial to answer the adjuvant TMZ chemotherapy question.

## Conclusion

To conclude, RTOG 9802 brings adjuvant chemotherapy to the last group of diffuse glioma patients, for which RT + PCV is now part of standard of care. Over the past 3 years, a major role of adjuvant chemotherapy in grades II and III glioma has emerged from old trials designed in the 1990s, and adjuvant chemotherapy is now part of standard of care for a significant proportion of diffuse glioma patients. A still missing piece of information in the spectrum of chemotherapy for diffuse glial tumors is its role in non-1p/19q codeleted tumors. Concerns about RT-associated delayed neurotoxicity are likely to remain, however, and may limit the acceptance of RT as part of the initial adjuvant treatment in patients who need adjuvant treatment. Also, RTOG 9802 investigated a chemotherapy regimen that is considered today by many as too toxic, and many clinicians will be inclined to use TMZ instead of PCV. To answer these relevant questions, however, new trials are needed, which would take another 2 decades to complete. With those conclusions we must also realize that to further improve outcome, new active agents are desperately needed, preferably with better safety profiles. And we must give credit to the many investigators who have been motivated to pursue these long-lasting academic trials. Their efforts have significantly improved the outcome of our patients.

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