Prospective clinical trials of intracranial low-grade glioma in adults and children

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Over the last decade, the results of 5 prospective clinical trials of intracranial low-grade glioma (LGG) have been published, 4 in adults with supratentorial LGG and 1 in children with infra- and supratentorial LGG. The data from the more than 1600 patients treated on these studies are summarized herein. European Organization for Research and Treatment of Cancer study 22845 randomized 311 adults to postoperative observation or radiation therapy (RT). There was no difference in the 5-year overall survival (OS) rate between the 2 arms. Irradiated patients had a significantly improved 5-year progression-free survival (PFS) rate. European Organization for Research and Treatment of Cancer study 22844 randomized 379 adults to low-dose (45 Gy) versus high-dose (59.4 Gy) RT. Similarly, an intergroup study conducted by the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group randomized 203 adults to low-dose (50.4 Gy) versus high-dose (64.8 Gy) RT. There was no difference in the 5-year OS or PFS rates between the 2 dose groups in either study. A Southwest Oncology Group study randomized 54 adults with incompletely resected LGG to RT alone or RT plus CCNU (lomustine) chemotherapy. There was no difference in outcome between the 2 treatment arms. Important prognostic factors for OS in these 4 adult trials included extent of surgical resection, histology, tumor size, and age. An intergroup study of the Children's Cancer Group and Pediatric Oncology Group enrolled 660 pediatric patients with management based on the extent of surgical resection: Children who underwent gross total tumor resection were observed postoperatively, whereas those who had subtotal resection or biopsy were either observed or administered RT at the discretion of their physician. Survival was most impacted by several prognostic factors, primarily extent of resection. Besides extent of resection, other prognostic factors that were consistent in predicting survival in these 5 clinical trials included patient age and tumor location, size, and histology. The data from these 5 studies indicate that for intracranial LGG in adults, postoperative RT is associated with improved 5-year PFS but not OS rates compared to postoperative observation. Radiation doses of 45 to 54 Gy result in 5-year OS and PFS rates that are similar to those for higher doses. The strategies of chemotherapy alone and RT plus chemotherapy are under investigation. For pediatric LGG, extent of surgical resection is the most important prognostic factor associated with favorable 5-year OS and PFS. Radiation therapy and chemotherapy are generally used in the settings of incomplete resection and recurrent disease, and these strategies are being investigated in prospective clinical trials. The schemata from recently completed and ongoing studies in both adult and pediatric intracranial LGG are reviewed. *Neuro-Oncology 5, 153–160, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-060, May 09, 2003. URL http://neuro-oncology.mc.duke.edu;*
DOI: 10.1215/S1152 8517 02 00060 1)

Received December 16, 2002; accepted January 8, 2003.

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[2] Abbreviations used are as follows: EORTC, European Organization for Research and Treatment of Cancer; LGG, low-grade glioma; OS, overall survival; PFS, progression-free survival; RT, radiation therapy.

Prior to 1993, the only data available in the medical literature regarding management strategies for adults and children with intracranial low-grade glioma (LGG)[3] was retrospective in nature. In the 1980s and 1990s, 5 prospective clinical trials were conducted ad-

dressing the important issues related to radiation therapy (RT), including timing of treatment, radiation dose, and chemotherapy plus RT. The data from the more than 1600 patients treated on these studies are summarized in this review article. In addition, the schemata from recently completed and ongoing studies are reviewed.

Summary of Completed and Published Clinical Trials

European Organization for Research and Treatment of Cancer Study 22845 (Karim et al., 2002)

This European Organization for Research and Treatment of Cancer (EORTC) study randomized patients to postoperative observation or RT. Eligibility criteria included age between 16 and 65 years, supratentorial LGG (astrocytoma, oligodendroglioma, and mixed oligoastrocytoma), Karnofsky performance status ⩾60, and either no or minor to moderate neurologic deficit. Patients were stratified by histology (astrocytoma vs. oligodendroglioma vs. mixed oligoastrocytoma), extent of surgical resection (biopsy vs. more extensive surgery), and institution. Patients randomized to RT received 54 Gy to localized treatment fields encompassing the tumor with a 1- to 2-cm margin, the RT treatment starting ⩽8 weeks postoperatively. Between 1986 and 1997, 311 patients were randomized, of whom 290 were eligible/analyzable. The 5-year overall survival (OS) rate was 66% with observation and 63% with RT ($P = 0.49$) (Fig. 1). The 5-year progression-free survival (PFS) rate was 37% with observation and 44% with RT ($P = 0.02$). Similarly, the median time to progression was significantly longer with, compared to without, postoperative RT (4.8 vs. 3.4 years, respectively). Information on the impact of prognostic factors on OS, PFS, or time to progression was not presented.

European Organization for Research and Treatment of Cancer Study 22844 (Karim et al., 1996)

This EORTC study randomized patients to low-dose versus high-dose RT. It was conducted during the same time period as EORTC 22845. "Believers" in postoperative RT entered their patients on 22844, whereas RT "nonbelievers" entered patients on 22845. Eligibility criteria and stratification factors were the same as for EORTC study 22845. Patients randomized to low-dose RT received 45 Gy to localized treatment fields encompassing the tumor with a 2-cm margin. Those randomized to high-dose RT received a 14.4-Gy "boost" to the tumor with a 1-cm margin, for a total dose of 59.4 Gy. Between 1986 and 1997, 379 patients were randomized, of whom 343 were eligible/analyzable. The 5-year OS rate was 58% with low-dose and 59% with high-dose RT ($P = 0.73$) (Fig. 2). The 5-year PFS rate was 47% with low-dose and 50% with high-dose RT ($P = 0.94$). Of the multiple prognostic factors analyzed for their effect on OS, the extent of surgical resection had the greatest impact (Fig. 3).

North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group Intergroup Study (Shaw et al., 2002)

This study is similar to EORTC study 22844 in that it also randomized patients to low-dose versus high-dose RT. Eligibility criteria included age ⩾18 years and supratentorial LGG (astrocytoma, oligodendroglioma, and mixed oligoastrocytoma). Patients were stratified by tumor grade (Kernohan grade 1 vs. 2), histology (astrocytoma or astrocytoma-dominant mixed glioma vs. oligodendroglioma or oligodendroglioma-dominant mixed glioma), extent of surgical resection (gross total vs. subtotal vs. biopsy), preoperative tumor diameter (<5 cm vs. ⩾5 cm), and institution. Patients randomized to low-dose RT received 50.4 Gy to localized treatment fields encompassing the tumor with a 2-cm margin. Those random-

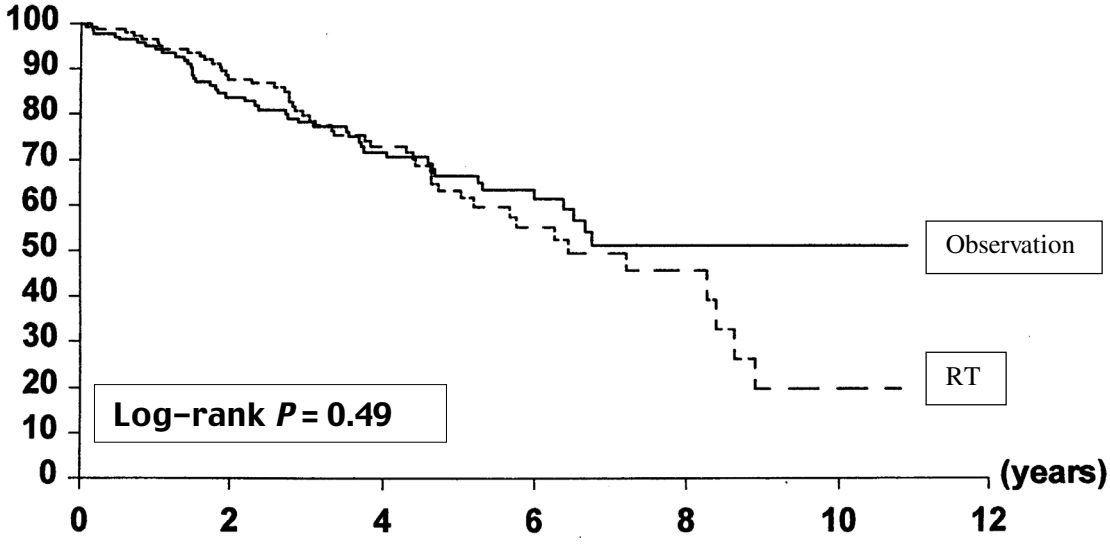

Fig. 1. Survival curves for EORTC study 22845 (from Karim et al., 2002)

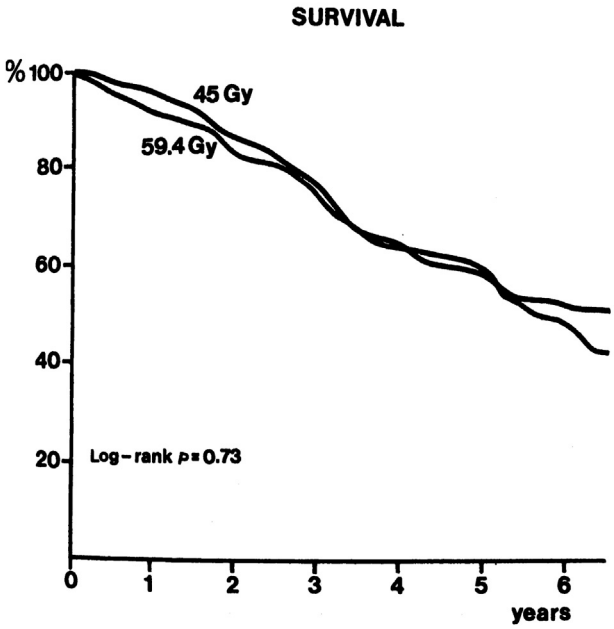

Fig. 2. Survival curves for EORTC study 22844 (from Karim et al., 1996)

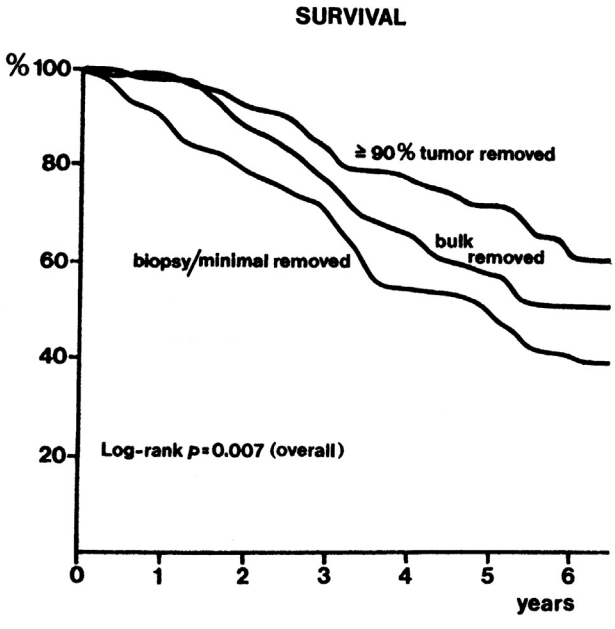

Fig. 3. Survival curves by extent of surgical resection for EORTC study 22844 (from Karim et al., 1996)

ized to high-dose RT received a 14.4-Gy "boost" to the tumor with a 1-cm margin, for a total dose of 64.8 Gy. Between 1986 and 1994, 211 patients were randomized, of whom 203 were eligible/analyzable. The 5-year OS rate was 72% with low-dose and 65% with high-dose RT ($P = 0.48$) (Fig. 4). The 5-year PFS rate was 55% with low-dose and 52% with high-dose RT ($P = 0.65$). Of the multiple prognostic factors analyzed for their effect on OS, histology, tumor size, and age had the greatest impact (Figs. 5–7). The 5-year actuarial incidence of severe or worse neurotoxicity (i.e., radionecrosis) was 2% with low-dose RT (50.4 Gy in 28 fractions of 1.8 Gy each) and 10% with high-dose RT (64.8 Gy in 36 fractions of 1.8 Gy each) (Fig. 8).

Southwest Oncology Group Study (Eyre et al., 1993)

This study randomized patients to postoperative RT alone or with chemotherapy. Eligibility criteria included age ⩾18 years and a subtotally resected or biopsied supratentorial LGG (astrocytoma, oligodendroglioma, and mixed oligoastrocytoma). Patients were stratified by extent of surgical resection (biopsy vs. subtotal resection) and performance status (0–1 vs. 2–4). Patients randomized to RT alone received 55 Gy to localized treatment fields. Those randomized to RT plus chemotherapy received up to 2 years of lomustine (CCNU) given at a dose of 100 mg/m^2 every 6 weeks. Sixty patients were randomized between 1980 and 1985 (1:2 randomization; that is, for every patient randomized to RT alone, 2 were randomized to RT plus CCNU), of whom 54 were eligible/analyzable. The median survival time was 4.45 years for RT alone compared to 7.4 years for RT plus CCNU; however, the 10-year survival rate was 40% for RT alone versus 20% for RT plus CCNU ($P = 0.7$). Of the multiple prognostic factors analyzed for their effect on OS, age and performance status had the greatest impact..

Children's Cancer Group and Pediatric Oncology Group Study (Sanford et al., 2002)

This prospective but nonrandomized clinical trial assigned or allowed physician choice of treatment based on the extent of surgical resection, which was determined from the operative report and a postoperative imaging study (CT or MRI scan) of the brain. Eligible LGG histologies included diffuse fibrillary astrocytoma, juvenile pilocytic astrocytoma, oligodendroglioma, mixed oligoastrocytoma, and ganglioglioma. Children who had a gross total resection or a near total resection (<1.5 cm^3 residual tumor) were observed. Those who had a subtotal resection (⩾1.5 cm^3 residual tumor) were either observed or administered localized RT at the discretion of their physician. Between 1991 and 1996, 660 children were accrued, of whom 516 were eligible/analyzable. Early data on the impact of various prognostic factors on OS and PFS have been published in abstract form (Sanford et al., 2002). The 5-year OS rate was 99% with gross total resection, 95% with <1.5 cm^3 residual disease, 94% with 1.5–2.9 cm^3 residual, and 87% with ⩾3 cm^3 residual ($P = 0.0004$). The 5-year PFS rate was 90% with gross total resection and 45–65% with any volume (<1.5 to ⩾3 cm^3) of residual disease ($P < 0.0001$) (Fig. 9). Other prognostic factors that significantly impacted PFS were tumor location and histology (Figs. 10 and 11).

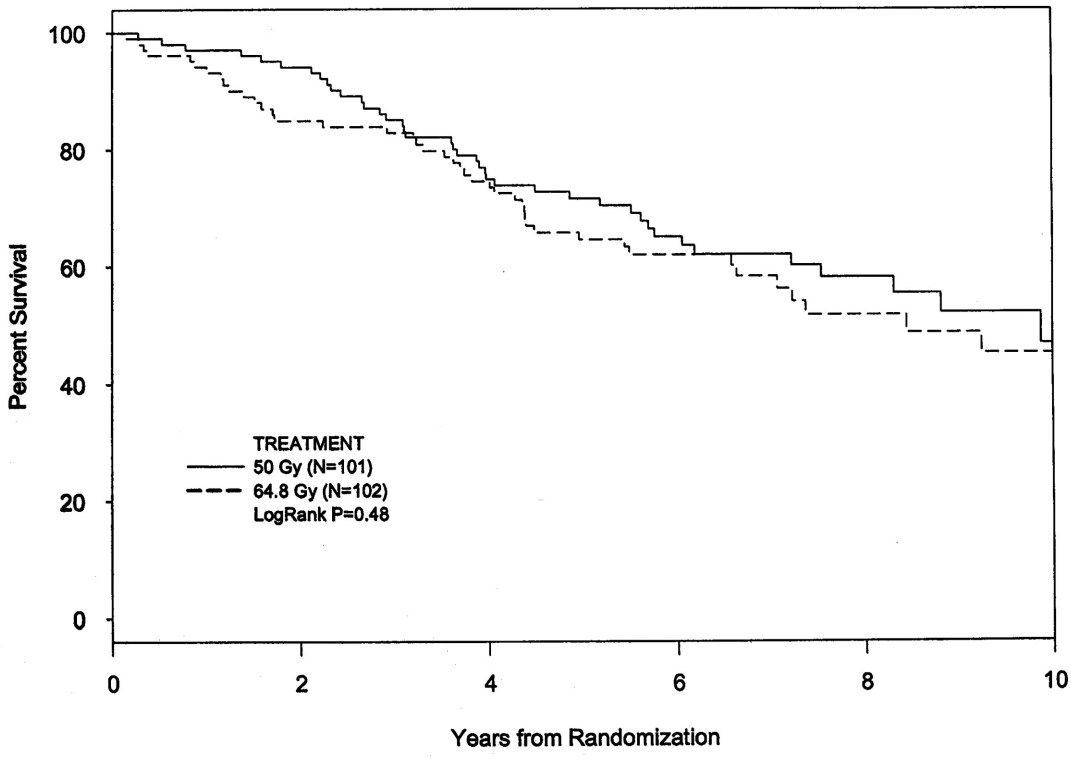

Fig. 4. Survival curves for the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group Intergroup Study (from Shaw et al., 2002)

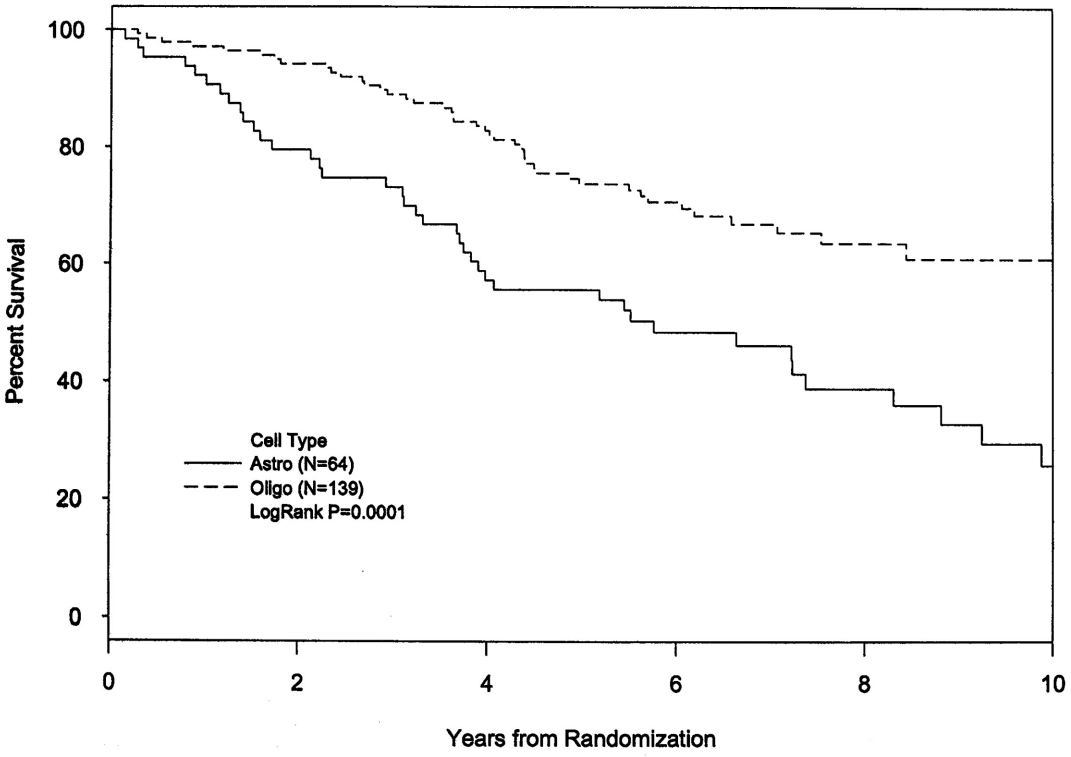

Fig. 5. Survival curves by histology for the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group Intergroup Study (from Shaw et al., 2002)

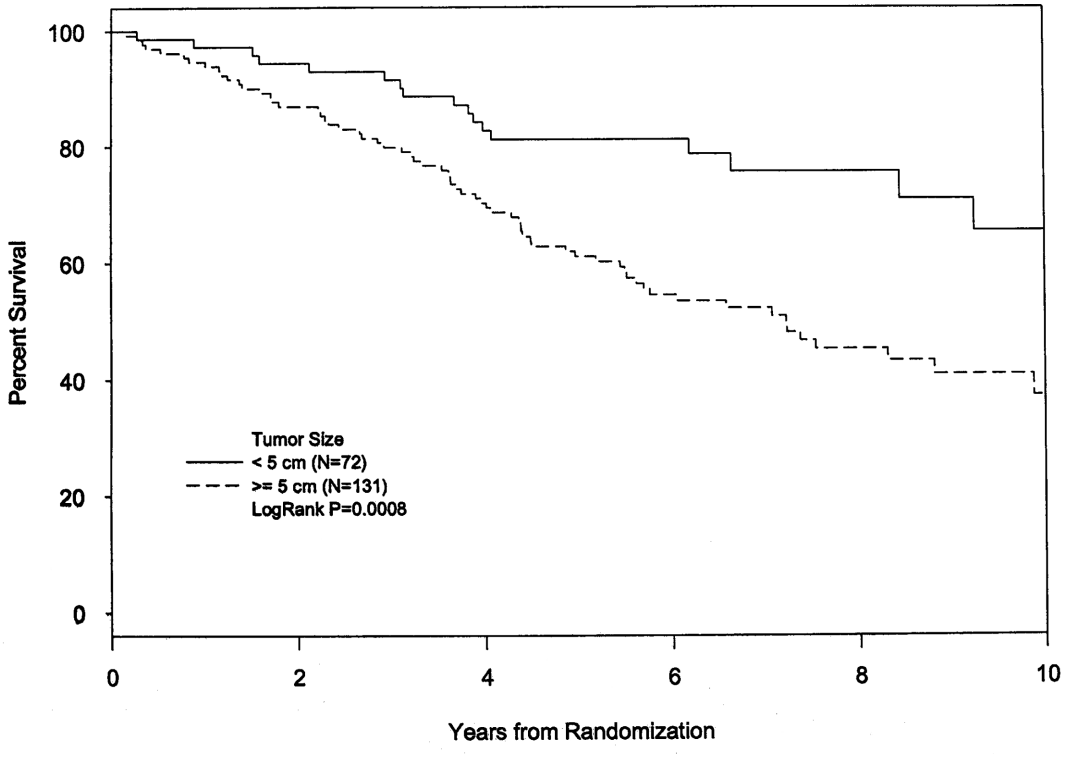

Fig. 6. Survival curves by tumor size for the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group Intergroup Study (from Shaw et al., 2002)

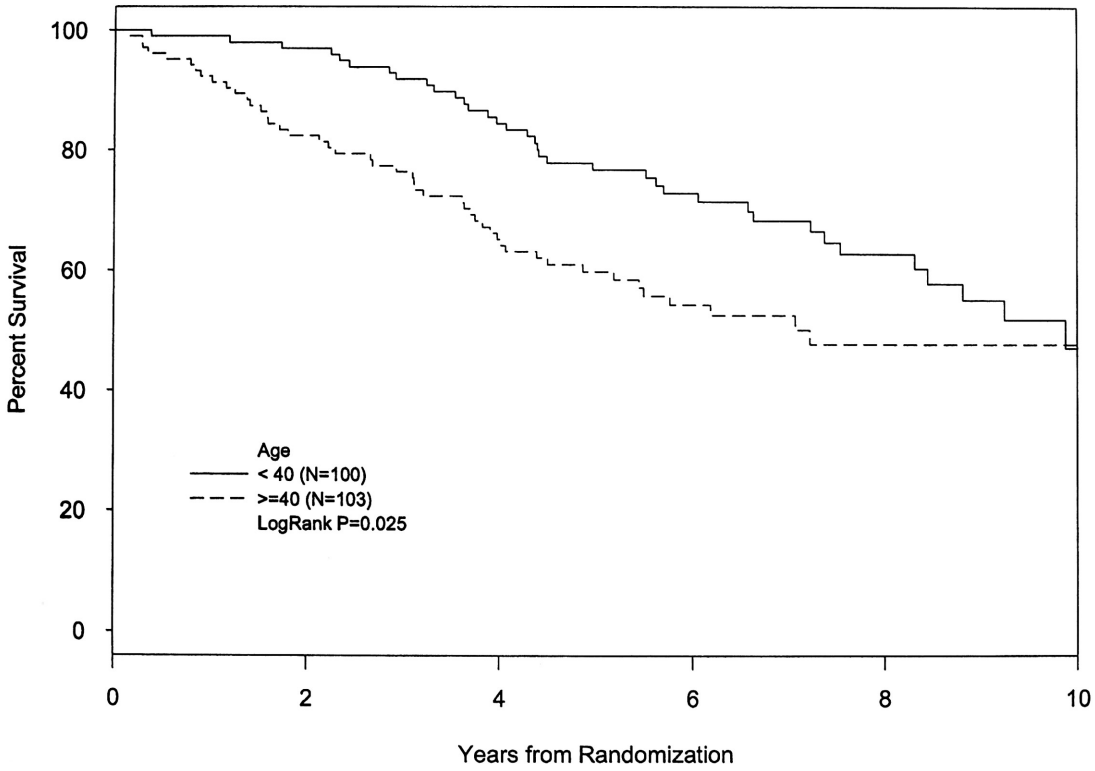

Fig. 7. Survival curves by age for the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group Intergroup Study (from Shaw et al., 2002)

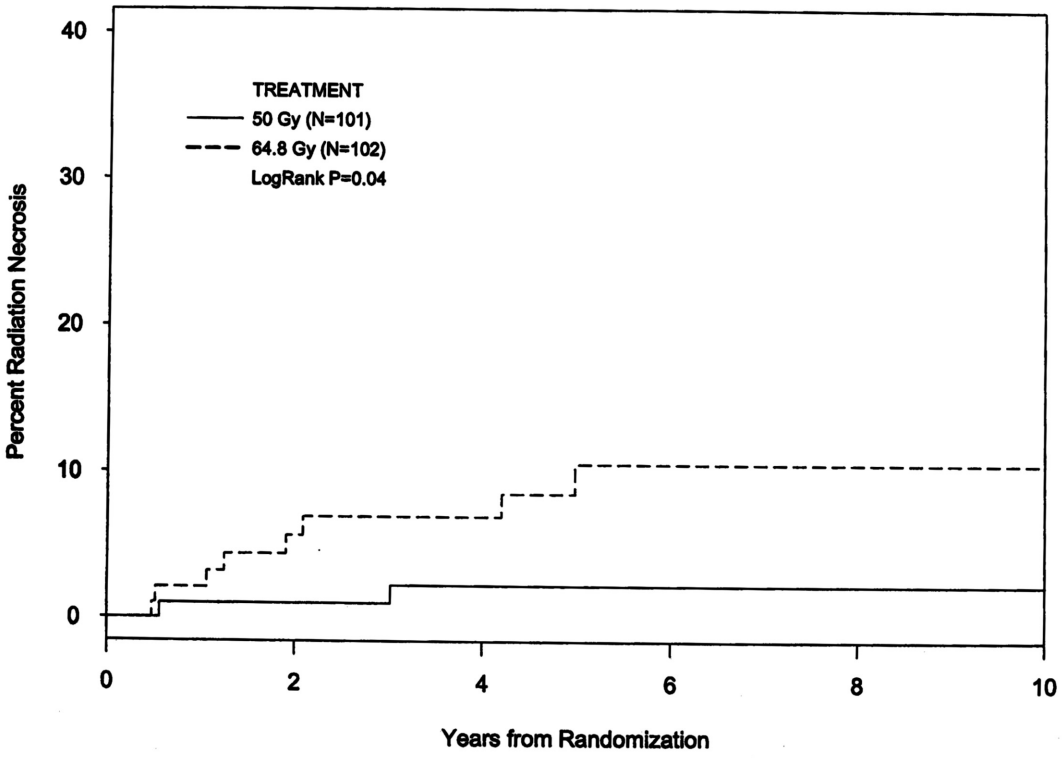

Fig. 8. Time to neurotoxicity (radionecrosis) for the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and Eastern Cooperative Group Intergroup Study (from Shaw et al., 2002)

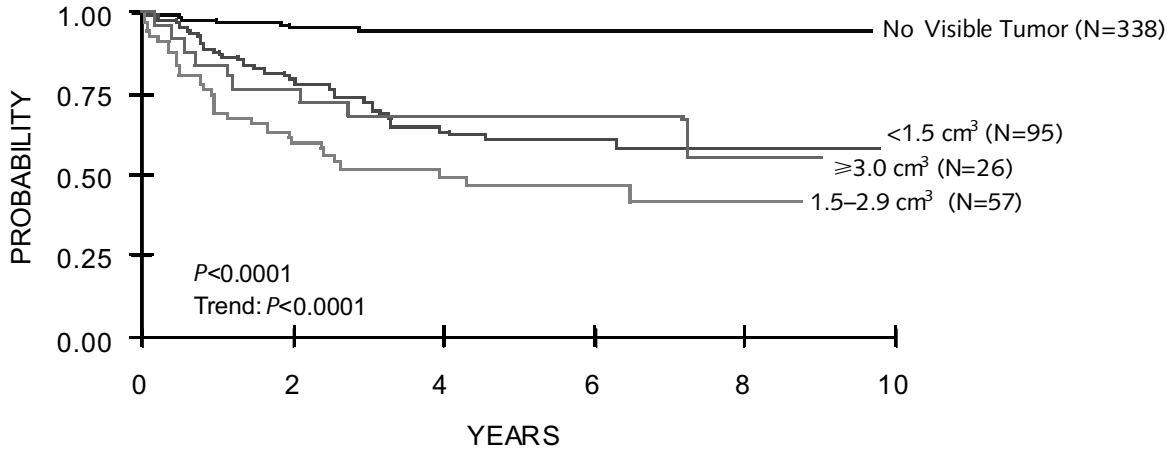

Fig. 9. Progression-free survival curves by extent of surgical resection for the Children's Cancer Group and Pediatric Oncology Group Study (from Sanford et al., 2002)

Summary of Recently Completed and Ongoing Clinical Trials

The Radiation Therapy Oncology Group (RTOG, 2002) recently completed study 9802, in which adults with LGG were placed into risk groups and treated accordingly. Low-risk patients, defined as those who were <40 years old *and* underwent gross total resection, were observed postoperatively. High-risk patients, defined as those who were ⩾40 years old *or* those who underwent subtotal resection or biopsy, were randomized to RT alone (54 Gy to tumor with a 2-cm margin) or RT followed by 6 cycles of PCV chemotherapy (procarbazine, CCNU, and vincristine). The Radiation Therapy Oncology Group will soon open a randomized phase 2 study of RT (54 Gy) followed by temozolomide chemotherapy, or temozolomide both during and following RT. The EORTC is soon going to open a phase 3 LGG clinical trial in adults, randomizing them to monotherapy with either RT (50 Gy) or temozolomide, stratifying patients

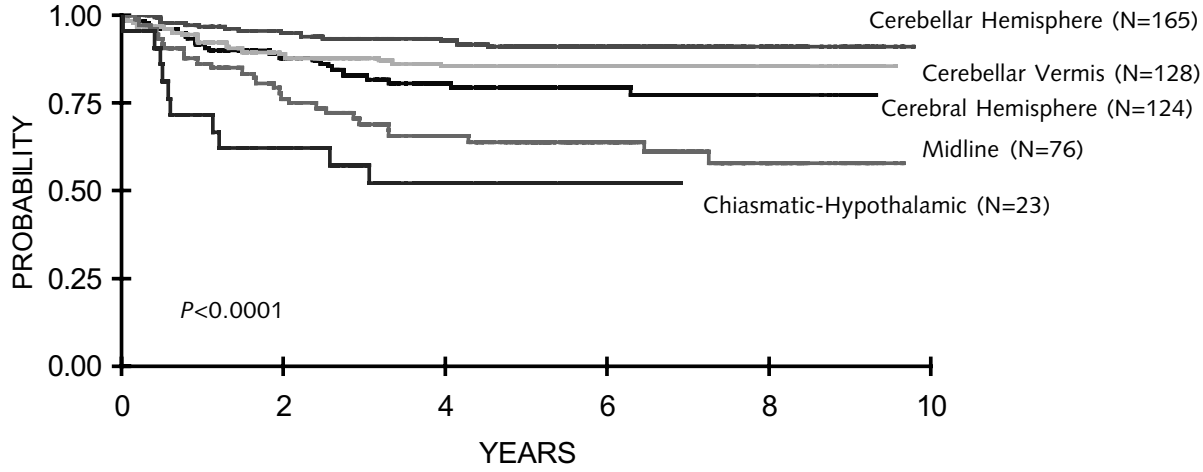

Fig. 10. Progression-free survival curves by location for the Children's Cancer Group and Pediatric Oncology Group Study, AANS, April 9, 2002 (from Sanford et al., 2002)

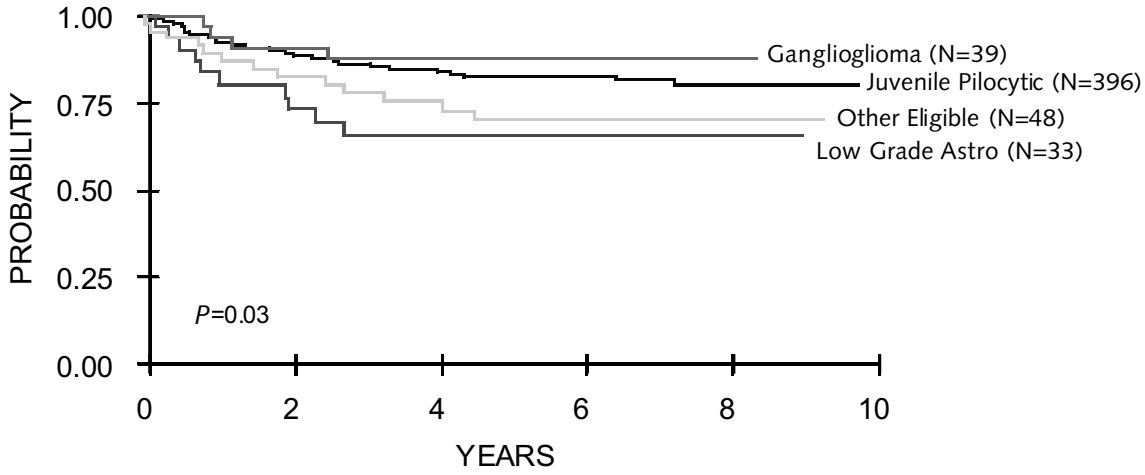

Fig. 11. Progression-free survival curves by histology for the Children's Cancer Group and Pediatric Oncology Group Study (from Sanford et al., 2002)

by chromosome 1p deletion (present vs. absent), age (<40 vs. ⩾40 years), and contrast enhancement (present vs. absent).[3] The Children's Oncology Group has 1 ongoing clinical trial in pediatric LGG. Children's Cancer Group study A9952 is a phase 3 study for children <10 years old with recurrent/progressive or newly diagnosed subtotally resected LGG in which the patients are randomized to "standard" carboplatin-vincristine chemotherapy or a combination of thioguanine and PCV (procarbazine-CCNU-vincristine). Patients are stratified by site (hypothalamic/optic vs. other), disease status (recurrent vs. newly diagnosed), and pathology (pilocytic vs. fibrillary vs. other). The Children's Oncology Group also has a phase 2 study in development for children ⩾10 years old who have LGG and are going to receive RT. Three-dimensional conformal techniques will be used to deliver 50.4 to 54 Gy to the tumor with a narrow margin, sparing as much surrounding normal brain as possible.

[3] van den Bent, M.J., personal communication, December 9, 2002.

Conclusions

Based on the data presented, the following evidence-based conclusions can be made. In adults with LGG, there is no difference in survival whether RT is given postoperatively or delayed to the time of recurrence. When RT is administered, lower doses produce a survival outcome similar to that produced by higher doses, but with less neurotoxicity. However, about half of adults with LGG will develop tumor progression by 5 years despite surgery with or without postoperative RT. Data on whether chemotherapy (PCV or temozolomide), either alone or with RT, improves outcome is forthcoming from recently completed or ongoing prospective clinical trials. In children, gross total resection results in ⩾90% long-term OS and PFS, independent of patient age or tumor histology or location. However, about one-third to one-half of children will suffer tumor progression following incomplete tumor resection. The role of chemotherapy and RT for incompletely resected and recurrent pediatric LGG continues to be explored in clinical trials.

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