Long-Term Analysis of Children with Low-Grade Glioma Continues to Show Increased Survival

BY ROBERT H. CARLSON

Children with low-grade gliomas are known to have superior five- and 10-year overall survival rates compared with adults with the disease. Now, a new study confirms that adult survivors of pediatric low-grade glioma also have a low incidence of glioma-related death, even 20 years after diagnosis.

In the study, now available online ahead of print in *Pediatric Blood & Cancer* (***DOI: 10.1002/pbc.24958***), the overall cancer-specific survival rate was 87 percent, in the analysis of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database of 4,040 children.

"This highlights that pediatric low-grade gliomas are very unlikely to undergo malignant transformation resulting in tumor-related death, which contrasts with the natural history of adult low-grade gliomas," said the researchers—senior author was Peter Manley, MD, a pediatric neuro-oncologist at Dana-Farber/Boston Children's Cancer and Blood Disorders Center.

But the analysis also showed that children treated with radiotherapy had a reduced overall survival and greater risk of disease death than those not receiving radiotherapy—approximately 70 percent at 20 years.

Cranial radiotherapy has largely fallen out of favor, but it was a common component of regimens for pediatric low-grade glioma in the 1970s and 1980s, and 18 percent of the patients in the cohort received radiation as part of their treatment.

Interestingly, tumor grade did not have an impact on survival. "Grade 1 did better [than grade 2], but even those with grade 2 had overall survival rates well over 70 percent [at 20 years]," Manley said. "That was very eye opening to us."

Children treated with radiation therapy had a reduced overall survival and greater risk of disease death compared with those not treated with radiation therapy, with a hazard ratio of 3.9. This held true whether surgical resection was total or partial.

Patients with subtotal or no resection had a small but statistically significant increase in the risk of disease-related death compared with those with total resection on multivariate analysis, with a hazard ratio of 1.5, but this was not statistically significant, he said.

But children who had subtotal resection and no radiation still had a significantly superior outcome compared with those who had total resection who underwent radiotherapy.

Although the SEER database did not show the incidence of radiation-induced secondary malignancies, the hazard ratio of death due to non-glioma-related causes was 2.4 in patients treated with radiation, suggesting that radiation-induced mortality may have accounted for some of the deaths that were not directly due to glioma, the authors reported.

Deaths were classified simply as "death due to glioma" or "death not due to glioma." Other causes of death such as secondary malignancies and radiation-induced tumors, or radiation

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No More Hyphen in Sloan Kettering!

Memorial Sloan Kettering Cancer Center (MSKCC) has dropped the hyphen that had been in its name ("Memorial Sloan-Kettering Cancer Center"). The overall look of the logo has also been updated.

Avice Meehan, MSKCC's Chief Communications Officer, explained in an interview that the simplified design is better suited for web and digital communications than the previous logo—"because it had so much detail, it didn't work very well on the web." The updated version keeps the same elements the institution has had as part of its visual identity since its founding in 1884 (the oval, arrow, and crossbars that form a shield), she noted. And retaining the founding date was important, she added. "We know from research we've done that it means a great deal to many people that we have had one mission and one focus for a very long time. And that's the conquest of cancer."

The hyphen though, she added has actually "come and gone over the years"—and it was not part of the name when the cancer center moved to its current location on York Avenue on the East Side of Manhattan in 1939.

The updates were made "very collaboratively," Meehan said. Senior leadership, physicians, the Board, and the communications team all had input—though the impetus to begin the update came from the Boards of Overseers and Managers (MSKCC's board of trustees), she said: "the very highest levels of the organization." The new logo took effect earlier this year, but will continue to be rolled out over the next two years to complete updates to all of the institution's signage, stationery, and print materials, Meehan said.

After *OT* tweeted the early online version of this item on March 20, MSKCC tweeted back: "Our surgeons performed the radical hyphenectomy last month."

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necrosis, were not classified as deaths due to glioma.

The analysis covered pediatric patients up to 19 years of age, who were diagnosed with a grade 1 or 2 glioma between 1973 and 2008; median age at diagnosis was nine.

Gross Total Resection Not Necessary

Manley, who is also Director of the Stop & Shop Family Pediatric Neuro-Oncology Outcomes Clinic, which focuses on survivorship issues, said that whether resection was total or partial did not affect overall survival.

"It appears that low-grade gliomas in children have a different biology than in adults—children's don't transform into more malignant tumors as adults' tumors do," he said in an interview. "The difference in the biology of adult and pediatric biology low-grade gliomas is one of the most important thing to understand."

> "This highlights that pediatric low-grade gliomas are very unlikely to undergo malignant transformation resulting in tumor-related death, which contrasts with the natural history of adult low-grade gliomas."

PRATITI BANDOPADHAYAY, MD, PHD: "Treatment strategies for pediatric tumors should aim for disease control during childhood and adolescence with an emphasis on minimizing long-term treatment-induced toxicities.

He noted that the study's first author, Pratiti Bandopadhayay, MD, PhD, a pediatric neuro-oncologist at Dana-Farber, is now investigating the molecular basis of gliomas to understand the differences between adult and pediatric disease.

Treatment for pediatric low-grade glioma varies, Manley said. Observation is appropriate for some patients after a gross total resection, while those with residual disease or progression might be retreated with chemotherapy. The most common regimens are vincristine-carboplatin, and the "UCSF" regimen of 6-thioguanine-procarbazine-CCNU-vincristine, he said.

Sicker Patients More Likely to Receive Radiotherapy?

Asked for her opinion for this article, Yasmin Khakoo, MD, Program Director in the Pediatric Neuro-Oncology Fellowship and Associate Attending Pediatric Neurologist at Memorial Sloan Kettering Cancer Center, said it is not surprising that patients who received radiation did not do as well in the long term—possibly due to sicker patients getting radiation, to different radiation techniques, and perhaps because second malignancies were not as amenable to treatment as they are today."

A limitation of the study, she said, is that it does not indicate what patients died of, which the authors do acknowledge in the paper. The researchers were also unable to determine progression-free survival from the data.

"The SEER data base is good, but is not the most robust because it does not include the data we collect now to assess patient outcome, and it does not include how many patients received other modalities such as chemotherapy," Khakoo said.

"And obviously if you are saying that patients who were radiated had a poor outcome you may be self-selecting for patients who had more aggressive disease. They may have had as many as six chemotherapy regimens before they were randomized to radiation or not radiation and might not have survived the tumor to begin with."

YASMIN KHAKOO, MD: "The SEER data base is good, but is not the most robust because it does not include the data we collect now to assess patient outcome, and it does not include how many patients received other modalities such as chemotherapy,"

The data may not be entirely relevant today considering the quality of radiation given in 1973, she noted. "Today's more focused modalities would have fewer side effects such as radiation vasculopathy and radiation necrosis which were more frequent in the past. We see patients today who were radiated back then and now have side effects."

One small group of patients was not discussed in the study, she pointed out: those with neurofibromatosis (NF).

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"In the 1970s, patients with NF who had optic pathway tumors or low-grade gliomas were receiving radiation, and we now know that patients with NF have a high second malignancy potential as well as vasculopathy potential with radiation, so we reserve radiation for refractory patients. We don't know what percentage of patients in this study had NF."

PETER MANLEY, MD: "The difference in the biology of adult and pediatric low-grade gliomas is one of the most important things to understand."

Another question concerned classifications: "We now have subclassifications of grade 1 and grade 2 based on molecular as well as other histopathological features that we didn't have in the '70s and '80s," she said. "For example, we have juvenile pilocytic astrocytoma [JPA], which is grade 1, but recently we've been noticing a new classification called a pyelomyxoid astrocytoma, which in the 1970s looked the same as a JPA, but we know now it's a subset of JPA that is more aggressive."

JPAs have molecular signatures such as BRAF mutation, and now there are drugs that target that lesion, Khakoo said. "We wouldn't irradiate a patient now with a BRAF mutation because there is better targeted therapy.

She said the study is interesting but probably will not change practice because clinicians generally try to avoid cerebral radiation in pediatric patients. "We learned a lot from those studies done earlier about the effects of radiation."