Authors:
Peter M.K. de Blank, MD, MSCE, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, peter.deblank@cchmc.org
Katharine R. Lange, MD, Children's Minnesota, Minneapolis, MN, katharine.lange@childrensmn.org
Mengqi Xing, MR, St. Jude Children's Research Hospital, Memphis, TN, Mengqi.Xing@STJUDE.ORG
Sedigheh Mirzaei Salehabadi, PhD, St. Jude Children's Research Hospital, Memphis, TN, Sedigheh.Mirzaei@STJUDE.ORG
Deokumar Srivatava, PhD, St. Jude Children's Research Hospital, Memphis, TN, Kumar.Srivastava@STJUDE.ORG
Tara M. Brinkman, PhD, St. Jude Children's Research Hospital, Memphis, TN, Tara.Brinkman@STJUDE.ORG
Kirsten K. Ness, PhD, St. Jude Children's Research Hospital, Memphis, TN, kiri.ness@stjude.org
Kevin C. Oeffinger, MD, Duke University Medical Center, Durham, NC, kevin.oeffinger@duke.edu
Joseph Neglia, MD, MPH, University of Minnesota Medical School, Minneapolis, MN, jneglia@umn.edu
Kevin R. Krull, PhD, St. Jude Children's Research Hospital, Memphis, TN, kevin.krull@stjude.org
Yutaka Yasui, PhD, St. Jude Children's Research Hospital, Memphis, TN, yutaka.yasui@stjude.org
Paul Nathan, MD, MSc, The Hospital for Sick Children, Toronto, Ontario, Canada, paul.nathan@sickkids.ca
Rebecca Howell, PhD, The University of Texas MD Anderson Cancer Center, Houston, TX, rhowell@mdanderson.org
Lucie M. Turcotte, MD, MPH, MS, University of Minnesota Medical School, Minneapolis, MN, turc0023@umn.edu
Wendy Leisenring, ScD, Fred Hutchinson Cancer Research Center, Seattle, WA, wleisenr@fredhutch.org
Gregory T. Armstrong, MD, MSCE, St. Jude Children's Research Hospital, Memphis, TN, Greg.Armstrong@stjude.org
Daniel C. Bowers, MD, University of Texas Southwestern Medical Center, Dallas, TX, daniel.bowers@utsouthwestern.edu
M. Fatih Okcu, MD, MPH, Baylor College of Medicine, Houston, TX, MFOKCU@texaschildrens.org

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Late Mortality and Morbidity of Adult Survivors of Childhood Glioma Treated Across Three Decades: A Report from the Childhood Cancer Survivor Study

PURPOSE: Pediatric low-grade glioma therapy has evolved to delay or eliminate radiation. The impact of therapy changes on long-term outcomes remains unknown.

METHODS: Cumulative incidence of late mortality (death >5 years from diagnosis), subsequent neoplasms (SNs), and chronic health conditions (CHCs, CTCAE grading criteria) were evaluated in the Childhood Cancer Survivor Study among 5-year survivors of glioma diagnosed 1970-1999. Outcomes were evaluated by diagnosis decade and by treatment exposures received ≤5 years following diagnosis (surgery-only, chemotherapy ± surgery, and cranial radiation ± surgery or chemotherapy). Relative risk (RRs) with 95%CIs estimated long-term outcomes using multivariable piecewise exponential models.

RESULTS: Among 2,684 eligible survivors (age at diagnosis (median [range]), 7 years [0-20 years]; time from diagnosis, 24 years [5-48 years]), exposure to cranial radiation decreased [51% (1970s), 45% (1980s), 25% (1990s)] along with late tumor recurrence (>5 & ≤15 years from diagnosis) [9.8% (1970s), 8.8% (1980s), 5.0% (1990s)]. The 15-year cumulative incidence of late mortality was 10.3% (1970s), 6.5% (1980s), and 6.0% (1990s) ($p<0.001$, comparison of cumulative incidence curves). The 15-year cumulative incidence of grade 3-5 CHCs was 19.7% (1970s), 17.8% (1980s), and 14.2% (1990s) ($p<0.0001$). A reduction in SN incidence was not

observed. In multivariable analyses excluding treatment exposure, later diagnosis (1990s vs. 1970s) was associated with lower risk of late mortality, grade 3-5 CHCs and SNs. Inclusion of treatment exposure in the model attenuated the effect of diagnosis decade. Radiation or chemotherapy exposure increased risk compared to surgery alone for late mortality (radiation RR 4.95, 95%CI 3.79-6.47; chemotherapy RR 2.88, 95%CI 1.85-4.48), CHCs (radiation RR 4.02, 95%CI 3.28-4.94; chemotherapy RR 1.66, 95%CI 1.13-2.45), and SNs (radiation RR 4.02, 95%CI 3.06-6.13, chemotherapy RR 2.08, 95%CI 1.03-4.23)).

CONCLUSION: Late mortality and CHCs decreased in childhood glioma survivors diagnosed from 1970-1999 largely due to therapy changes, particularly avoidance of cranial radiation, without increased late recurrence.