Second Tumors in Pediatric Patients Treated with Radiotherapy to the Central Nervous System

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Background

● Second malignant neoplasm (SMN) is a well-recognized risk of cancer treatments, including radiotherapy and chemotherapy, and this risk has been demonstrated to be increased in children receiving radiation as opposed to their adult counterparts.

● Rates of development of second malignancy are difficult to study, as second malignant neoplasms may develop twenty years or more after completion of cancer treatment.

● Clearly, development of second cancers may significantly impact quality of life and survival outcomes; however, efforts to reduce radiation dose with intent of reducing risk of SMN must be balanced with need for adequate dosing to control primary tumors.

● This study was undertaken in order to investigate the rates of second cancers in pediatric patients treated with radiotherapy to the central nervous system with long-term follow up, as well as patterns and relationships of development of SMN in this population.

Materials and Methods

● This study was designed as a retrospective cohort study considering sequential patients treated with curative-intent radiotherapy to the central nervous system at the University of Florida between 1963 and 2006.

  ● Patients receiving radiotherapy for primary central nervous system (CNS) tumors as well as CNS radiotherapy for leukemia were included.

  ● All patients were 19 years of age or less.

  ● Patients who received only total body irradiation were not included.
● 370 total patients were identified.
  ● Median treatment age was 8.1 years (range 0.2 – 19 years), with 317 patients being over the age of 3 years.
  ● 47% of patients (n = 172) received partial brain radiotherapy.
  ● 21% (n = 79) received whole brain radiotherapy.
  ● 32% (n = 119) received craniospinal radiotherapy.
  ● Primary diagnosis was most commonly glioma (n = 115), followed by acute leukemias (n = 96), medulloblastoma (n = 62), and ependymoma (n = 41).

● Any subsequent neoplasm that was of different histology that the primary tumor was classified as a second malignant neoplasm.

● Primary tumor histology, age at treatment, volume of irradiated tissue, dose to tumor bed, treatment with chemotherapy, and primary tumor location were analyzed for prognostic value.

Results

● Median follow-up was 4.7 years (range 0.1 – 44.9 years).

● Of the 370 patients considered, 173 survived for at least 5 years following completion of radiotherapy.

● In total, 16 second tumors were observed. These included:
  ● 10 cases of meningioma
  ● 4 cases of second glioma
    ● Of note 3/4 cases of glioma developed in patients receiving primary CNS radiotherapy for treatment of leukemia.
  ● 1 case of sarcoma
  ● 1 other tumor

● The actuarial incidence of second tumor was 3% at 10 years of follow up, 8% at 20 years of follow up, and 24% at 30 years of follow up.

● The first second tumor was observed at 6.2 years of follow-up. The risk of development of SMN appeared to increase steadily over increased follow-up with no sign of plateau at 30 years.

● Median time to developing meningioma was 23.5 years, and glioma 6.2 years.

● On multivariate analysis, no single risk factor was associated with development of a second tumor, including age at time of radiotherapy, radiation dose, and volume of tissue irradiated.

● When overall survival of five-year survivors only was considered, 10 year overall survival was 94%, 15 year 86%, and 20 year 82%.
  ● The most common cause of death in 5 year survivors was primary tumor recurrence.
  ● This was followed by death from second tumor (this included death resulting from all four secondary gliomas and two meningiomas).
  ● Death from unrelated causes was the third most common cause of death.

● Although salvage was possible for 90% of patients who developed secondary meningioma, secondary gliomas were uniformly fatal.

Author’s Conclusions
● The authors conclude that the risk of second tumor after CNS radiation is high and does not plateau with long-term follow-up.

● They describe that there appears to be a relationship between histology of primary and secondary tumor, and that the majority of second tumors are meningiomas, with high rates of successful salvage.

Clinical/Scientific Implications

● This study represents a comprehensive examination of a cohort of patients with prolonged follow-up after radiation to the central nervous system.

● Although risk of SMN after radiotherapy in childhood has been previously well-documented, this detailed analysis provides several interesting pieces of information:

   ● First, the fact that the most common cause of death in 5-year survivors remained primary tumor recurrence is a very important observation. Control of primary brain tumors remains the most important factor in long-term survival, and this should be kept in mind even as efforts to reduce long-term toxicity ensue.

   ● Having said this, the second-most common cause of death remains secondary tumor, despite the fact that most second tumors are meningiomas and appear to be salvageable. These two observations point to the important balance that must be achieved between treatment delivery and risk of late effects.

● The authors point out that the majority of gliomas developed in patients who had received CNS radiotherapy for leukemias. Although small sample size limits the validity of this conclusion, we may be somewhat encouraged by the fact that the vast majority of children with leukemia no longer receive CNS radiotherapy. Secondary gliomas were associated with dismal prognosis in this study, and consideration of only patients receiving radiation for primary CNS tumors might be interesting and potentially more applicable to contemporary practice than the combined data presented here.

● The authors’ observations that the vast majority of second tumors developing following CNS radiotherapy are meningiomas raises important questions regarding surveillance of cancer survivors. Patients developing meningiomas after CNS radiotherapy were salvageable in 90% of cases. Information regarding the 10% who were not salvageable would be of interest in consideration of need for screening of the survivor population. For example, if indication exists that the fatal meningiomas might have been salvageable if discovered earlier, screening could potentially be considered to be of benefit. While screening recommendations must always be produced with caution, and take into consideration patient well-being and well as resource allocation, screening of this high-risk group could potentially be beneficial.