Radiation therapy is associated with increased late mortality in long-term adult survivors of childhood low grade glioma: A population based study.

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Running title: Determinants of long-term survival in PLGG
Abstract:

PURPOSE: To uncover clinical risk factors and the impact of radiotherapy on children and adult survivors of childhood low grade glioma (PLGG).

PATIENTS AND METHODS: We collected long-term follow-up information for all PLGG patients diagnosed in all Ontario, Canada from 1985-2012 (n=1202) and determined factors affecting long-term survival. The impact of upfront (first line) radiation treatment on overall survival was determined in a discovery cohort of clinically relevant (incompletely resected) Ontario PLGG patients and an independent population based validation cohort from the Surveillance, Epidemiology and End Results (SEER) database (n=2402).

RESULTS: At a median follow-up of 12.73 (0.02-33) years; only 93 deaths (7.7%) were recorded with 20 years overall survival (OS) of 90.1% ± 1.1%. Children with NF1 had excellent survival and no tumor-related deaths during adulthood. Adverse risk factors included pleomorphic xanthoastrocytoma tumor type (p<0.001) and thalamic location (p<0.001). For patients surviving >5 years post-diagnosis, upfront radiotherapy was associated with three-fold increased risk of overall late deaths (p=0.001) and four-fold increased risk of tumor-related deaths (p=0.013). On multivariate analysis radiation therapy was the most significant factor associated with late all deaths and tumor-related deaths (HR 3 [1.3-7.0; p=0.012] and HR 4.4 [1.3-14.6; p=0.014] respectively). Similar association of radiotherapy and late deaths was observed in the validation cohort (p<0.001). In contrast to early deaths, late mortality was not associated with PLGG progression but rather tumor transformation (54%), secondary malignancy (11%) and other non-oncological causes (35%).

CONCLUSION: The chronic clinical course of PLGG is associated with excellent long-term survival and is hampered by increased delayed mortality in patients receiving upfront radiotherapy. These observations should be considered while deciding treatment options for these patients.
Introduction

Pediatric low grade gliomas (PLGG) are the most common brain tumor of childhood\(^1\) accounting for more than 35% of pediatric central nervous system malignancies. Children with PLGG may experience tumor progression multiple times and the resulting morbidity remains a concern.\(^1\) Short (<5 years) and intermediate term (5-10 years) overall survival is reported to be excellent and most children survive to adulthood.\(^3\)-\(^7\) Since follow-up is often erratic for adult survivors of PLGG, convincing data are lacking on very long-term outcome (>10 years post diagnosis).\(^5\) Specifically, information is difficult to gather on the exact timing, causes of death and associated risk factors in the survivors during adulthood.

Multiple risk factors have been identified to be associated with progression-free and overall survival of PLGG.\(^3\)-\(^7\) These include patient factors (age at presentation or diagnosis, gender and a preexisting diagnosis of neurofibromatosis type 1),\(^8\)\(^9\) and tumor-related factors (presence of disseminated disease and certain pathological subtypes).\(^6\)\(^10\)\(^11\) There are disparities between these studies partially due to differences in pathological classification of PLGG and the emergence of new entities such as pilomyxoid astrocytoma and pleomorphic xanthoastrocytoma which were not recognized in older studies.\(^10\)\(^13\) Furthermore, studies incorporating patients imaged prior to the widespread use of magnetic resonance imaging (MRI)\(^5\) or from non-population based referral centres lead to inherent selection bias.\(^14\)\(^15\)

The impact of surgical resection and the use of radiation therapy have been extensively studied.\(^16\)-\(^19\) While complete surgical resection is consistently associated with improved survival, the extent of resection highly depends on tumor location.\(^20\) Historically, the
majority of non-resectable symptomatic PLGG patients were irradiated as the first line treatment (upfront treatment) and existing reports suggest excellent tumor control in a significant proportion of these patients. However, in the context of a low-grade tumor, especially in young children, long-term sequelae associated with radiation treatment is a concern. Follow up studies are lacking to document survival data in PLGG patients during adulthood and the impact of risk factors and treatment on long term outcome.

In order to address these issues, we constructed a unique population-based database including all children diagnosed and treated for PLGG since widespread use of MRI in the province of Ontario, Canada; we validated our observations with a second large independent cohort of patients for whom clinical outcomes are available. Our findings present important insights which may affect future management and treatment approaches to PLGG in view of long-term outcome information.

**Patients and Methods**

**Patients**

For this population-based, retrospective study, we assembled clinical data from a cohort of pediatric patients (0–18 years of age) diagnosed with a grade I/II glioma at any of the five pediatric cancer centers in Ontario between January 1, 1985 and October 1, 2012 (n=1202). The detailed characteristics for the entire cohort are shown in table 1. These are the only institutions that treat children with brain tumors in Canada’s largest province (population >12 million) and virtually all patients are exclusively treated at their residential location, therefore no selection bias is expected.
**Data collection**

Data on the primary tumor, treatment and follow-up information (childhood and adult) were available through the Pediatric Oncology Group of Ontario Network Information System (POGONIS). POGONIS was launched in 1985 and collects detailed demographic, disease, treatment and outcome data on all patients with a malignancy treated at any of Ontario’s five pediatric cancer centers prospectively. Through its team of trained data managers, POGONIS captures 98% of cancer patients in Ontario\(^b\). The Cancer Care Ontario (CCO) health system data resource - Ontario Cancer Registry (OCR) tracks clinical data related to important life events, including date and causes of death on all residents; this information is updated every month by health workers, with accuracy of 95%\(^c\) and is also captured by POGONIS. These resources enabled us to collect accurate long-term follow-up data for >95% of patients in real time. Methods of data procurement and the study design were approved by Research Ethics Board of The Hospital for Sick Children.

Each individual patient data were recorded until the last update in October 2012. Survival was defined as years from initial diagnosis to last date of follow-up or death as on or before 31\(^{st}\) Oct 2012. Factors such as gender, age at diagnosis, histopathology, tumor location and upfront radiation treatment were used to stratify patients.

For histopathology stratification, only patients treated at The Hospital for Sick Children (SickKids) were considered where 683 out of 803 were diagnosed by biopsy. Neurofibromatosis type 1 (NF1) status was also available only for the Sickkids cohort. Detailed cause of death was collected for the Sickkids cohort (n=803). Further information is available in the supplementary methods.
To assess the impact of upfront radiation (defined as the primary medical treatment with or without surgery within one year of diagnosis) on long term survival, we used a discovery cohort of clinically relevant (not completely resected) Ontario PLGG patients. To focus on long term implications, only patients surviving the first 5 years post initial diagnosis and treatment were considered. An independent validation cohort of PLGG was available through the SEER cohort recently described by Bandopadhayay et al. Similarly, only patients surviving at least 5 years were included for this analysis. Tumor-related deaths were defined as glioma progression or transformation excluding secondary malignancies outside radiation field and other non cancer related mortality. Further information on methods used in this study is available in the supplemental materials and methods.

**Statistical analysis**

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) v20. Survival was calculated using the Kaplan-Meier method and log-rank test. The hazard ratio was calculated by Cox regression analysis. In all cases $p<0.05$ was considered significant.

**Results**

**Long-term survival of PLGG**

Complete clinical and survival data were available for 1202 patients with a median follow-up of 12.73 years (range, 0.02 – 33.33 years). Patient demographic distribution, tumor location, and follow-up duration were similar between participating centers (Supplemental Table S1).
Overall, there were 93 deaths (7.7%). Ten, 20 and 30-year overall survival (OS) were 93.1%±0.8%, 90.1%±1.1% and 88%±1.5% respectively (Figure 1A). Although excellent overall outcome was observed, late deaths occurred up to 23 years post initial diagnosis.

We did not observe significant difference in survival based on gender (Supplemental Figure S1) or age (Figure 1B), with the exception of children with optic pathway glioma (OPG). Young children with OPG diagnosed at age ≤ 3 years had an inferior outcome as compared to older children (20-year OS was 80.4±6.1% and 97.9±1% respectively; p=0.007, Supplemental Figure S2).

**Survival for NF1 children with PLGG**

We identified 125 children with NF1 and PLGG of which 116 (92.8%) had OPG. Children with NF1 and tumors affecting the optic pathway had excellent survival outcome (20-year OS was 95.1±2.4%; Supplemental Figure S3A). All deaths occurred within the first 12 years following diagnosis and none after the age of 18. A total of four deaths noted: two unrelated to tumor or treatment, and two due to malignant transformation with upfront radiation treatment at 10.8 & 11.2 years after treatment. A total of four NF1 patients received upfront radiation treatment, of these two died of tumor transformation (as above) and two patients are alive at 16 and 26 years. Overall survival for patients with optic pathway glioma without NF1 was lower (20-year OS of 88.7±3.6%) but this did not reach statistical significance (p=0.06, Supplemental. Figure S3B).

**Association of histopathology and survival**
Pilocytic astrocytoma was the most common subtype and exhibited excellent 20-year OS of 95.5%±1.7% (Figure 1C). No significant differences in survival were observed for most histological subgroups (ganglioglioma, mixed glioma and low grade glioma NOS). Although the number of patients was small and follow up was shorter for the more recently described subgroup of pilomyxoid astrocytoma, no deaths were observed at the median follow-up of 6.83 years (n=10, range 2.47-13.39 years). In contrast, children with pleomorphic xanthoastrocytoma (n=10) had significantly lower survival with a 10-year OS of 42.9 ± 20.8% (p<0.001; Figure 1c);

**Tumor location and survival pattern**

Posterior fossa tumors had an excellent 20-year OS of 96.8% ± 1.1%, similar to Cerebral hemispheric tumors (89.1±2.7%), OPG (90.6±2.2%) and spinal tumors (89.7±2.7%); while tumors of the brainstem (83.1±3.4%) and thalamus (74.2±6.3%) had significantly lower 20-year overall survival (p<0.001; Figure 1D). Initial (<5 years post diagnosis) high number of deaths in brainstem and thalamic tumors may be due to biopsy bias. However, long-term (10-20 years post diagnosis) follow-up revealed higher late mortality for thalamic tumors (Figure 1D). Examining other risk factors revealed that these thalamic tumors did not differ from tumors at other locations with respect to pathological subtype, age of presentation or gender. Furthermore, biopsy bias, cannot explain these late deaths.

**Association of upfront radiotherapy with long term survival**

In order to examine other causes of late deaths in patients with thalamic tumors we specifically analyzed survival for children who survived >5 years post-diagnosis. Patients who received upfront radiation treatment showed significantly lower survival
than those who did not (OS at 20 years of 76.9±11.7% and 96.9±3.1%; p=0.039, Supplemental Figure 4).

To further explore this observation we carefully constructed a discovery cohort of clinically relevant Ontario PLGG patients for which total resection was not performed and survived the first 5 years (discovery cohort, n=607). Long-term OS for patients who received upfront radiation was significantly lower than patients who did not (20-year OS 84±3.9% versus 95.6±1.2%; p<0.001, Figure 2A). Importantly, the use of upfront radiation treatment was associated with threefold increase in risk of all deaths (HR 3.3, 95% CI 1.6-6.6; p=0.001). Furthermore, for the Sickkids cohort (n=385) where comprehensive data on causes of death was available, tumor-related survival was significantly inferior for patients who received upfront radiation compared with those who did not (20-year OS 87.4±4.9% versus 97%±1.1%; p=0.007, Figure 2C) and upfront radiation treatment increased the risk of tumor-related death by four-fold (HR 3.9, CI 1.3-11.9; p=0.013). On multivariate analysis, upfront radiation treatment was the most significant factor associated with late overall deaths and tumor-related deaths (p=0.012 and p=0.014 respectively; Table 2).

To test whether the observed late deaths in patients treated with radiation is applicable to other population based cohorts we performed similar analysis on the SEER database, recently reported by Bandopadhyay et al5 (validation cohort). Survival patterns for the validation cohort mimicked the findings for our discovery cohort as shown in figure 2B for all deaths (20 year-OS of 84.4±1.9% and 95.3±0.8% for children treated with and without radiation respectively; p<0.001) and Figure 2D for tumor-related deaths (20 year-OS of 89±1.72% and 94.3±0.8% for children treated with and
without radiation respectively; p=0.001). The risk of late death for children undergoing radiation increased threefold for all deaths (HR 3.3, CI 2.3-4.7; p<0.001) and tumor-related deaths (HR 3.4, CI 2.1-5.5; p=0.001).

**Early and late causes of death in PLGG**

Overall, 55/803 patients from SickKids died during the study period. The most common causes of death were transformation to malignant glioma (n=26) and tumor progression (n=10). Three patients developed secondary malignancies and 16 died due to non-oncological causes. Complete information of cause of death is shown in supplementary Table S2. Half of all deaths occurred in the first five years from diagnosis (n=29/55; 52.7%) and 17 (30%) deaths occurred in adulthood (> 18 years age).

Causes of death differed significantly with time from diagnosis (Figure 3). While 81% of early deaths (<5 years after diagnosis) were due to tumor progression or transformation, none of the late deaths (>5 years after diagnosis) were due to tumor progression. Other non glioma related causes accounted for 46% of late deaths.

**Discussion**

In this large population based study of children with PLGG; we were able to demonstrate excellent survival for these patients into adulthood, provide valuable information on patient subpopulations such as children with NF1 and identify various factors affecting survival which may be important in the management of these individuals. This study has the longest reported median follow-up time (12.73, 0.02-33 years) and to our knowledge is the first to utilize large population based inclusion of all patients diagnosed and followed up in MRI era with accurate information regarding treatment timings and causes of death.
Most large PLGG studies report 5-year progression free survival of 30-40% following most treatment regimens. Since many of these patients experience multiple progressions during the course of their disease and hence various lines of treatments, it may be tempting to apply a more aggressive regimen at progression to avoid patient demise. Despite multiple progressions, we observed >90% survival at 20-25 years post diagnosis in absence of aggressive modalities such as radiotherapy and no late mortality due to tumor progression. This observation adds a new dimension to recent studies which demonstrate excellent long-term outcome for these children and supports the notion that PLGG may be different in its clinical and biological behavior as compared to adult counterpart.

We did not observe any significant impact of the most common pathological subtypes on long-term overall survival. Important findings are the lack of detrimental outcome for pilomyxoid astrocytomas and the poor survival associated with pleomorphic xanthroastrocytoma. Pilomyxoid astrocytoma has been described as an aggressive type of PLGG with young age of onset and poor prognosis. Since then several groups have shown that survival for older patients diagnosed with this pathological subtype is not necessarily poor. Our current study demonstrating excellent long-term survival of these patients further supports these encouraging findings. In contrast, less than half of patients with pleomorphic xanthoastrocytoma in our study are long-term survivors. This worrisome observation warrants further confirmation.

We and others have reported high frequency of the \textit{BRAF/KIAA1549} fusion and favorable outcome in PLGG. Recently, \textit{BRAF V600E} mutations and \textit{CDNK2A} deletions were reported in some of these patients to be associated with poorer
outcomes.\textsuperscript{36,37} These molecular signatures may help in accurate prediction of long term outcome and determine which patients may benefit from a less and more aggressive treatments accordingly.

Radiotherapy is still commonly used for the treatment of PLGG and has shown superior progression-free survival (PFS) as compared to chemotherapy.\textsuperscript{17-19} However, long-term survival post radiation is reported in very few studies and have shown associated increased risk for vascular events and secondary radiation induced malignancies.\textsuperscript{22,38,39} Studies comparing patients who were irradiated upfront to non-radiation approaches are subject to selection bias at several levels. Firstly upfront radiation treatment is currently reserved for more aggressive PLGG. This is highlighted by the early deaths (1-3 years post diagnosis) observed in these cohorts\textsuperscript{5}. Second, these are usually deep seated tumors for which only a small biopsy sample is available leading to biopsy bias where presumably a low grade glioma may actually represent a heterogeneous tumor with high & low grade components. This may also explain large number of tumor transformation related deaths in first few years of diagnosis (<5 years). Analysis of patients which survived 5 or more years bypasses many of these limitations and enables a more accurate analysis of late deaths possibly related to radiotherapy.

Our study raises major concerns regarding the association of radiotherapy with increased tumor-related late deaths. The unique pattern of late deaths in both the Ontario and SEER populations (US) support the validity of these findings. Since no plateau has been reached, the impact of vascular events and tumor related deaths may be even higher with longer follow-up. These observations further question the role of radiation in the management of this chronic childhood disease with excellent survival.
One of the most interesting findings in this study is the lack of late deaths associated with tumor progression (Figure 3). Indeed, none of the NF1 patients died in adulthood and none of the other PLGG adults survivors in this study died of tumor progression. These intriguing observations support the current biological hypothesis that in RAS/MAPK driven tumors, oncogene induced senescence causes spontaneous growth arrest and tumor burnout in adolescent and young adults with PLGG.\textsuperscript{40,41} This information supports the concept that tumor progressions in the first few years of PLGG course are not necessarily associated with worse overall patient outcome and one should try to avoid toxic treatments with long term sequelae.

This study has the classic limitations of a retrospective study spanning decades of treatment strategies, pathological diagnoses and the inherent limitations of the POGONIS and SEER data collection. Nevertheless, the consistency of results between centers and cohorts strongly supports the robust observations, unique features and natural history of PLGG.

In summary, this study reinforces the concept that PLGG is a chronic disease which extends into adulthood and the need to manage these children with view of long-term effects of various treatment options. Since most patients will survive at least into mid-adulthood, treatment options such as radiation therapy should be considered with caution. Specifically, although Radiation therapy may be associated with better tumor control in early years it may lead to significant devastating sequelae affecting not only quality of life but also long-term survival during adult life.
Future studies detailing biological characteristics may enable better risk stratification of patients and allow use of less toxic therapies in low risk patients to reduce long-term morbidity and mortality.
References


Figure Legends

Figure 1: Long term overall survival of children with pediatric low grade glioma (PLGG) (A) All study patients; (B) All PLGG stratified by age at diagnosis; (C) Sick Kids PLGG stratified by pathology subtype. (D) All PLGG stratified by tumor location. Pilocytic astrocytomas (PA), Pilomyxoid astrocytoma (PMA), Pleomorphic xanthoastrocytomas (PXA), Low Grade Gliomas Non specified (LGG), gangliogliomas and Mixed glioma including oligodendroglioma.

Figure 2: The effect of radiation therapy on long term survival of PLGG. (A) Ontario discovery cohort including all deaths; (B) SEER validation cohort including all deaths; (C) SickKids discovery cohort tumor-related deaths; (D) SEER validation cohort including tumor-related deaths.
Table 1: Study population and characteristics.

<table>
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<tr>
<th>Ontario cohort (n=1202)</th>
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<tbody>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
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<table>
<thead>
<tr>
<th>Age at Diagnosis(years)</th>
<th>Median (Range)</th>
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<tr>
<td>&lt; 3</td>
<td>222 (18.5%)</td>
</tr>
<tr>
<td>3 - &lt; 8</td>
<td>421 (35%)</td>
</tr>
<tr>
<td>8 - &lt; 14</td>
<td>407 (33.9%)</td>
</tr>
<tr>
<td>14 - 18</td>
<td>152 (12.6%)</td>
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<table>
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<tbody>
<tr>
<td>Posterior fossa</td>
</tr>
<tr>
<td>Optic pathway</td>
</tr>
<tr>
<td>Lateral/peripheral brain</td>
</tr>
<tr>
<td>Brainstem</td>
</tr>
<tr>
<td>Thalamic</td>
</tr>
<tr>
<td>Spinal cord</td>
</tr>
<tr>
<td>Midline other</td>
</tr>
<tr>
<td>Other</td>
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</tbody>
</table>

| *Pathology                           N=683 |
|--------------------------------------|------|
| Pilocytic astrocytoma                | 284 (41.5%) |
| Low grade astrocytoma NOS            | 277 (40.5%) |
| Ganglioglioma                        | 61 (8.9%)  |
| Pilomyxoid astrocytoma               | 10 (1.5%)  |
| Pleomorphic xanthoastrocytoma        | 10 (1.5%)  |
| Oligodendroglialoma (mixed glial) & others | 41 (6.1%)  |

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</thead>
<tbody>
<tr>
<td>Alive</td>
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<tr>
<td>Dead</td>
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</table>

* Sick Kids Hospital patients only
Table 2: Cox regression model for multivariate analysis in discovery cohort.

<table>
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<tr>
<th>All Deaths</th>
<th>Covariable</th>
<th>Hazard ratio</th>
<th>95% Confidence limit</th>
<th>p value</th>
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<td>1.1</td>
<td>0.4 to 2.7</td>
<td>0.920</td>
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<tr>
<td></td>
<td>Location (Thalamic v other)</td>
<td>2.3</td>
<td>0.9 to 6</td>
<td>0.092</td>
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<tr>
<td></td>
<td>Pathology</td>
<td>1.6</td>
<td>0.5 to 5.1</td>
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<td>Grade 1 astrocytoma v other</td>
<td>0.3</td>
<td>0.04 to 2.4</td>
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<td>NF1 not biopsied v other</td>
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<tr>
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<td>Upfront Radiation treatment (Yes v No)</td>
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<td>1.3 to 7</td>
<td>0.012</td>
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<table>
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<tr>
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<td>0.1 to 2.9</td>
<td>0.547</td>
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<td>Location (Thalamic v other)</td>
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<td>0.6 to 9.4</td>
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<td>Pathology</td>
<td>2.8</td>
<td>0.7 to 11.2</td>
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<td>Grade 1 astrocytoma v other</td>
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<td></td>
<td>Upfront Radiation treatment (Yes v No)</td>
<td>4.4</td>
<td>1.3 to 14.6</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Figure 2

A) Overall Survival (years)

B) Tumour Related OS probability

C) Overall Survival (years)

D) Tumour Related OS probability

No Radiation

Radiation

No. at risk

p = 0.000375

p < 0.0001

p = 0.00718

p < 0.0001

p = 0.000718

p < 0.0001

No Radiation

Radiation

No. at risk

p = 0.000375

p < 0.0001

p = 0.000718

p < 0.0001

No Radiation

Radiation

No. at risk

p = 0.000375

p < 0.0001

p = 0.000718

p < 0.0001

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p = 0.000375

p < 0.0001

p = 0.000718

p < 0.0001

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p < 0.0001

p = 0.000718

p < 0.0001

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p = 0.000375

p < 0.0001

p = 0.000718

p < 0.0001

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p = 0.000718

p < 0.0001

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Radiation

No. at risk

p = 0.000375

p < 0.0001

p = 0.000718

p < 0.0001

No Radiation

Radiation

No. at risk