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# The efficacy and long-term side effects of prophylactic cranial radiation therapy in childhood acute lymphocytic leukaemia (ALL) in Johannesburg, South Africa

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## ABSTRACT

### Background

Relapse disease is the main source of treatment failure in acute lymphoblastic leukaemia despite improvements in the efficacy of upfront treatment. Even with improved outcomes globally, low to middle income countries continue to experience inferior cure rates. There is paucity of local data to help inform and modify adopted international protocols.

### Objective

The aim of this study was to evaluate the efficacy of prophylactic cranial irradiation as part of multimodal treatment of acute lymphoblastic leukaemia in preventing relapse, identify factors associated with relapse, and long-term sequelae of prophylactic cranial radiation in a population of paediatric patients in Johannesburg, South Africa.

### Materials and Methods

This was a retrospective analysis of patients' medical records of acute lymphoblastic leukaemia treated in a public academic institution in Johannesburg, who received prophylactic cranial irradiation as part of the modified BFM-95 protocol. Records of fifty-one (51) patients treated from 2009 to 2016 were included in the study. Five-year overall survival and event-free survival as well as cumulative incidence of relapse were estimated using the Kaplan-Meier analytic method. Cox regression model was used for analysis of prognostic factors, estimating hazard ratios with 95% confidence intervals. For growth evaluation, z-scores were generated from height measurement and the generalized estimation model was used to analyse height differences between two radiation doses [12 Gy and 18Gy] and association between height and clinical variables.

### Results

The estimated 5-year overall survival (OS) and event-free survival (EFS) was 64% (95% CI: 49% - 75%) and 57% (95%CI: 42% - 70%) respectively.

In total, 18 out of 51 (35%) patients experienced relapse with an incident rate of 7.0%, (95% CI, 4.4% – 11.1%), translating to a cumulative probability of relapse at 3 and 5 years being 33% (95% CI: 19% – 56%) and 45% (95% CI, 27% – 73%) respectively. The bone marrow was a frequent site of relapse with an incidence rate of 4.6%, (95% CI, 2.6% – 8.2%) occurring

in 12 out of 18 patients whilst fewer cases occurred in the central nervous system, incidence rate of 2.3%, (95% CI, 1.0% – 5.2%). Of the six (6) patients that experienced relapse in the central nervous system, only one had isolated central nervous system recurrence.

Unfavourable cytogenetics (MLL rearrangement or BCR-ABL), and non-adherence to maintenance phase of the ALL treatment were predictors significantly associated with an increased risk of relapse [($p=0.04$) and ($p<0.001$].

There was a high rate of mortality in the subgroup of patients that experienced relapse, 88% (16/18).

There were differences in height z-scores observed between the 12 Gy and 18Gy radiation doses which were marginally statistically significant ($p=0.053$). Children treated with 12 Gy were able to maintain normal growth with an average height z-score>0. By contrast, children who were treated with 18Gy had negative average z scores in the first 3 years after completing treatment but thereafter experienced growth velocity. A small proportion of patients 4/51 (7.8%) had significant neurocognitive impairment requiring special remedial education.

**Conclusion**

The outcomes were poor in this study with low overall and event-free survival and high incidence of relapse. However, prophylactic cranial irradiation still appears to be effective in preventing CNS relapse for both the medium and high-risk groups with acceptable side effect profiles. Poor compliance with treatment and unfavourable cytogenetics were important prognostic factors for relapse.

These results are comparable to the experience of low to middle income countries that utilize international adopted acute lymphoblastic leukaemia treatment protocols. Strategies to better understand the unique biology and conditions that impact outcomes in low to middle income countries continue through international collaborative trials should be encouraged to improve on progress made in acute lymphoblastic leukaemia management and producing protocols suitable for diverse populations.

**Keywords**: ALL, CNS relapse, LMIC, prophylactic cranial irradiation