





Assessment of Cranial Radiotherapy Treatment in T-cell Lymphoblastic Lymphoma: Retrospective Study from Tertiary Care Center

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Abstract

Introduction Leukemia-like regimens given for acute lymphoblastic leukemia (ALL) are the cornerstone of treatment for T-cell lymphoblastic lymphoma (LBL) and can produce complete remission rates exceeding 90%. For central nervous system (CNS) prophylaxis, intrathecal chemotherapy and cranial irradiation are used to prevent future CNS recurrence.

Objective The purpose of this study was to assess CNS relapse rate after cranial prophylaxis treatment given at our institute.

Materials and Methods In this retrospective analysis, between July 2013 and June 2019, 149 files of lymphoblastic lymphoma were reviewed. Out of these, 53 patients received cranial irradiation. All patients were given CNS-directed therapy in the form of intrathecal methotrexate and patients with CNS-negative disease and primary tumor complete response or more than partial response after chemotherapy were given prophylactic cranial irradiation (18 Gy/10#), and in patients with upfront CNS involvement, therapeutic cranial irradiation (24 Gy/12#) was delivered. Radiotherapy was delivered as per the standard conventional protocol on a linear accelerator.

Results Out of 53 patients (age range: 2–50 years, mean=16.79 years, 26 [49.1%] pediatric [<14 years], 27 [50.9%] adults [>14 years]), 13/53 (24.5%), and 40/53 (75.5%) patients were on MCP 841 and BFM 90 protocols, respectively. Also, 48 (90.56%) patients received prophylactic cranial irradiation (25 [52.1%] pediatric, 23 [47.9%] adults). Moreover, 3/48 (6.25%) (2 [4.16%] pediatric, 1 [2.08%] adult) patients had CNS failure after receiving prophylactic cranial irradiation. For 48 target patients, with the median follow-up of 27.27 months (26.1 months–pediatric, 28.2 months–adults), EFS (event-free survival) in the brain was 93.8% (92%: pediatric, 95.7%: adults). Also, the difference between pediatric and adult groups was not statistically significant (p -value = 0.662). Five (9.43%) patients had CNS-positive disease upfront and received therapeutic cranial irradiation.

Conclusion In BFM 90/MCP 841 protocol in lymphoblastic lymphoma, prophylactic cranial irradiation and intrathecal methotrexate have been the standard of care as the

Keywords

- ▶ CNS relapse
- ▶ cranial radiotherapy
- ▶ lymphoblastic lymphoma

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CNS-directed therapy to prevent cranial infiltration. Though our results are not at par with the published world literature, further research and efforts are required to prevent CNS relapse in a selected sub-set of patients with lymphoblastic lymphoma.

Introduction

Lymphoblastic lymphoma (LBL) is a neoplasm of lymphoblasts, more commonly of T-cell origin than of B-cell origin that resembles acute lymphoblastic leukemia (ALL), as suggested by the 2008 World Health Organization classification.^{1,2} Usually, in most cases, bulky mediastinal disease in young men is the standard presentation of lymphoblastic lymphoma (the male-to-female ratio is 2:1). Leukemia-like regimens given for ALL are the cornerstone of treatment for T-cell lymphoblastic lymphoma and can produce complete remission rates exceeding 90%.^{3,4} The central nervous system (CNS) is involved at diagnosis in only 2 to 7% of cases.⁵ However, CNS relapse can be seen in up to one-third of LBL patients if CNS prophylaxis treatment is not delivered.⁶ For CNS prophylaxis, intrathecal chemotherapy and cranial irradiation are used to prevent future CNS recurrence. Long-term toxicities of central nervous irradiation are great and not well studied in LBL.⁷ The purpose of this study was to assess CNS relapse rate after cranial prophylaxis treatment given at our institute.

Materials and Methods

In this retrospective analysis, we assessed both pediatric and adult patients with lymphoblastic lymphoma registered in our institute between July 2013 and June 2019. We retrieved files from the medical record department with permission. A total of 149 patients were registered during this period. Out of 149, 53 patients had received cranial irradiation and were assessed for the stated objective.

For all patients (pediatric and adults) who had biopsy-proven T-cell lymphoblastic lymphoma and received cranial irradiation (prophylactic/therapeutic), we retrieved data including clinical presentation, investigations done, chemotherapy protocol used, cranial radiotherapy planning (basic details of planning mentioned in files as per the department protocol) and last follow-up with clinical status.

Treatment protocol choice was dependent on consultant decision, patients' general condition, age, government beneficiary scheme, and financial status of the patient.

- MCP 841 protocol,⁸ included induction, induction phase II with cranial irradiation, reinduction, consolidation, and maintenance for 2 years.
- BFM 90 (Berlin Frankfurt Munster) protocol^{9,10} included preinduction, induction, and consolidation, reinduction chemotherapy followed by cranial irradiation, and maintenance chemo for up to 2 years.
- Mostly, pediatric and adolescent patients received the BFM 90 protocol treatment and adult patients received the MCP 841 protocol treatment.

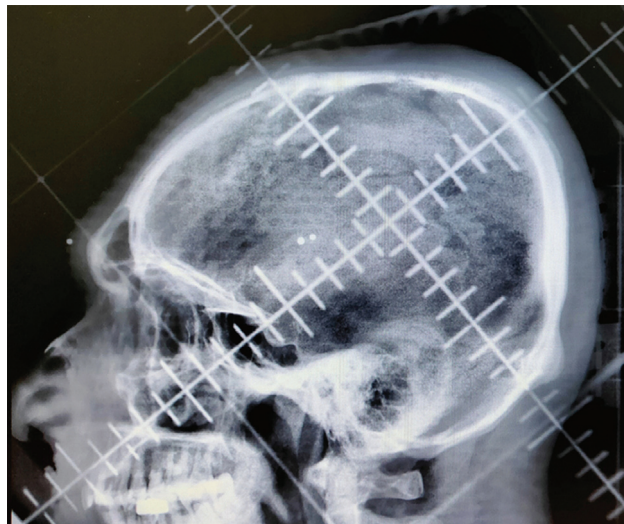


Fig. 1 Slanting filed radiotherapy planning skiagram showing field borders.

Response rates following chemotherapy (after induction in MCP 841 and after reinduction in BFM 90) were assessed by objective assessment (in most of the cases, CT scans). Patients with complete or partial response were referred for prophylactic cranial irradiation.

CNS-directed cranial prophylaxis treatment in the form of intrathecal methotrexate and prophylactic cranial irradiation was given in patients with CNS-negative disease, primary tumor complete response (CR), or partial response (PR) following chemotherapy.

Before starting prophylactic cranial irradiation, mandatory baseline investigations were CBC (Hb \geq to 10 g%, ANC count $>$ 1,000 cells/ μ L), bone marrow under remission (if involved), and CSF cytology-negative disease. We see for mediastinal mass to be under complete remission following chemotherapy, but, in a few subsets of patients, we looked for partial response (PR) following chemotherapy.

In patients with CSF cytology-positive disease or magnetic resonance imaging (MRI) suggestive of brain infiltration, we had given therapeutic cranial irradiation.

In all patients, whole-brain radiotherapy was given by slanting field technique (\rightarrow Fig. 1).

German helmet or slanting field technique is the most commonly used technique for whole-brain radiation therapy in developing countries. These techniques are simple, easy to perform, and are of low cost, making them widely popular in busy centers with limited facilities.

In all patients, marking was done on a conventional simulator.

For pediatric patients, a special immobilization device was developed in our radiotherapy department (\rightarrow Fig. 2).

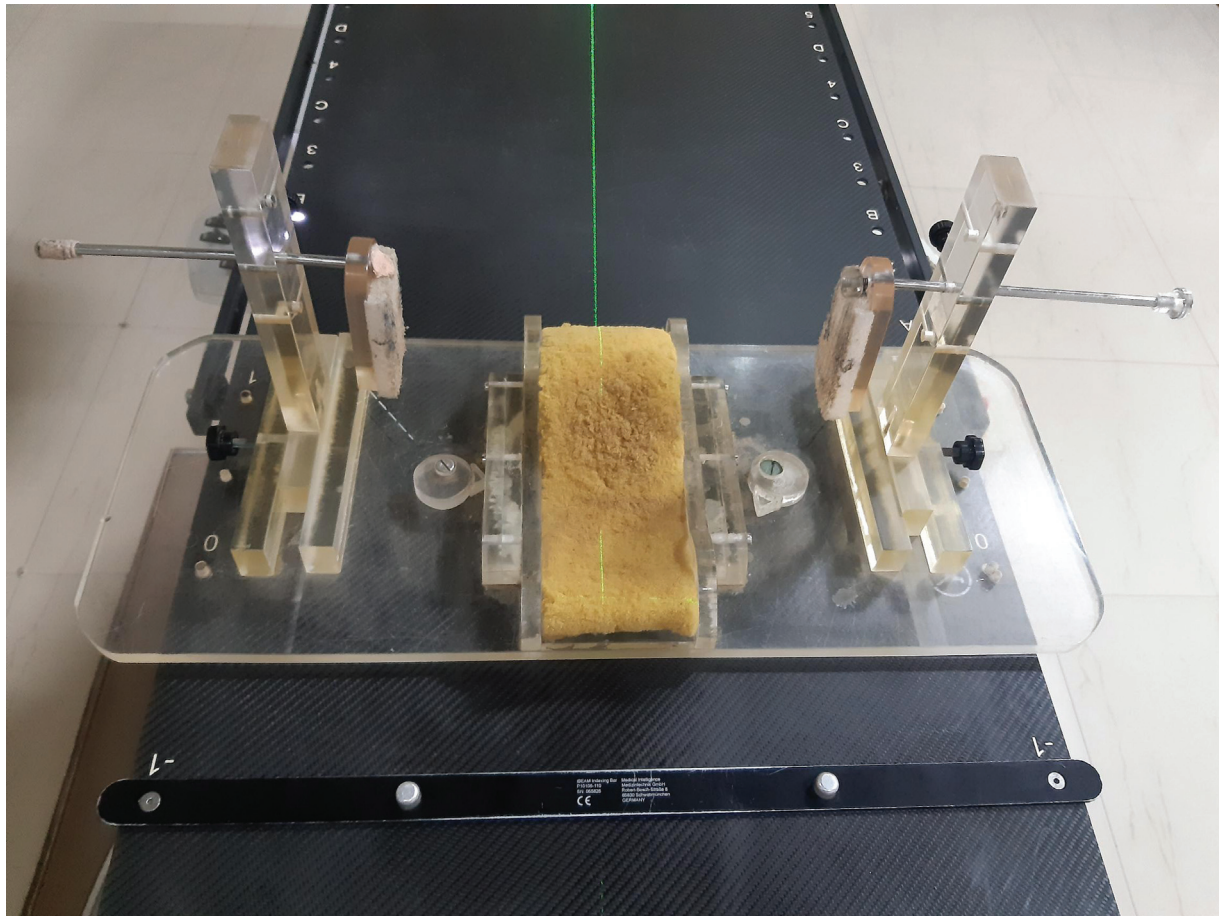


Fig. 2 Special immobilization device developed at our institute for pediatric patients. Mainly used to fix head position.

For adults, we asked patients to lie supine on the treatment couch with hands by the side and neck fully extended with the head resting in place during treatment.

For the radiotherapy treatment field, the superior border is just above the superior aspect of the skull with a minimum of 1 cm coverage, the inferior border is through the frontal sinus extending to cover the bones of the base of the skull. It also includes the spinous process of C1 and through the spinous process of C2 to ensure the posterior fossa is covered. The anterior border is anterior to the anterior aspect of the skull with a minimum of 1 cm coverage and the posterior border is posterior to the posterior aspect of the skull with a minimum of 1 cm coverage.

Technique: Bilateral conventional portals (slanting field technique)

Prophylactic cranial radiotherapy

Dose: 18 Gy/10#/5 days a week/2 weeks.

Therapeutic cranial irradiation

Dose: 24 Gy/12#/5 days a week/3 weeks.

We did not give craniospinal irradiation for CNS-positive disease.

For patients who had received prophylactic cranial irradiation, the respective medical department had advised for CSF cytology during follow-up assessment as per the symptoms.

The primary endpoint of the study was to assess CNS relapse rate after cranial prophylaxis treatment given at our institute in T-cell lymphoblastic lymphoma patients.

The primary aim of this study was to assess CNS relapse rate after cranial prophylaxis treatment given at our institute. So, only patients allocated to the target group—48 patients (CNS negative, and patients with CR or PR) were included and we calculated the event-free survival (EFS). EFS was calculated from the date of diagnosis to the event (CNS relapse). We excluded five patients who presented with upfront CNS involvement. Survival functions were calculated according to the Kaplan–Meier method,¹¹ with differences compared (between pediatric and adults) using the log-rank test.¹² Patients lost to follow-up were censored at the time of their last follow-up examination.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) software version 21 (IBM SPSS Statistics for Windows; Armonk, New York, United States; IBM Corp.). Continuous variables are reported as median with standard deviation (SD) and categorical variables as percentages. The association between categorical variables was evaluated for significance, period of treatment to relapse was calculated in each risk group, and Student's *t*-test was

Table 1 Characteristics of patients who received cranial irradiation in lymphoblastic lymphoma

Characteristics	Pediatric	Adult	Combined
Age group	<14 years	>14 years	
	26	27	53
Mean	9.65 years	23.67 years	16.79 years
Median	10 years	22 years	15 years
Range	2–13 years	15–50 years	2–50 years
Sex			
Male	23	24	47/53 (88.6%)
Female	3	3	6/53 (11.3%)
Stage	St Jude ^{22,23}	Ann Arbor ²⁴	
Stage II	3	13	16 (30.2%)
Stage III	14	–	14 (26.4%)
Stage IV	9	14	23 (43.4%)
CNS-negative disease upfront	25	23	48 (90.56%)
Bone marrow Involvement	9	9	18 (33.9%)
Mediastinal tumor	17	13	30 (56.6%)
CNS involvement upfront	1	4	5 (9.43%)
Treatment protocol			
BFM 90	20/26	20/27	40/53 (75.5%)
MCP 841	6/26	7/27	13/53 (24.5%)

Abbreviations: CNS, central nervous system; BFM, berlin frankfurt munster.

applied to study the relationship between relapse rates of the pediatric and adult populations. The test was considered significant if the *p*-value was < 0.05.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. The Gujarat Cancer & Research Institute (GCRI) Ethics Committee board approval was obtained (No: IRC/2021/P-58 on August 24, 2021). Because the study was retrospective, informed consent was not required and the study did not include any intervention. Waiver of informed consent was obtained from the Ethics Committee.

Results

In this retrospective analysis, from July 2013 to June 2019, 149 patients (pediatric and adults) with newly diagnosed T-cell lymphoblastic lymphoma were reviewed. Of these, 54

(age range: 2–50 years) patients received cranial irradiation. One patient received prophylactic cranial irradiation and did not return for a follow-up. So, 53 patients who received cranial irradiation were assessed.

► **Table 1** shows the characteristics of patients who received cranial irradiation in T-cell lymphoblastic lymphoma.

Forty-eight (90.56%) patients (25 pediatric, 23 adults) had CNS-negative disease and 5 (9.43%) patients (1 pediatric, 4 adults) had upfront CNS involvement.

In all 48 patients who were CNS-negative, CSF cytology was negative and brain imaging was not performed.

Five (9.43%) patients (1 pediatric, 4 adults) had upfront CNS involvement. In four patients (1 pediatric, 3 adults) CSF cytology was positive. In one adult patient, MRI brain was suggestive of infiltration. In three adult patients, in whom the CSF cytology was positive, two adult patients were offered MRI brain and it was suggestive of infiltration.

In 13/53 (24.5%) patients, the MCP-841 protocol was used; in 40/53 (75.5%) patients, the BFM 90 protocol was used.

Cranial Radiotherapy Treatment Analysis

► **Table 2** shows the characteristics of treatment and results for patients who received cranial irradiation. All 53 patients had received cranial irradiation. Forty-eight (90.56%) patients had received prophylactic cranial irradiation (18 Gy/10#) as per the treatment protocol. Five (9.43%) patients had upfront CNS involvement and they received therapeutic cranial irradiation (24 Gy/12#).

Combined (Pediatric and Adult) Group

Primary tumor (local) response (without CNS involved disease upfront) – 48 patients (Pediatric: 25, adult: 23 patients).

Thirty-seven patients (37/48) (77.08%) (17 [35.4%] pediatric, 20 [41.7%] adults) had primary tumor complete response (CR) before starting radiotherapy. Eleven patients (11/48) (22.9%) (8 [16.7%] pediatric, 3 [6.25%] adults) had partial response (>PR) before starting radiotherapy.

Prophylactic Cranial Irradiation

Forty-eight (25 [52.1%] pediatric, 23 [47.9%] adults) patients had received prophylactic cranial irradiation.

Three patients (3/48) (6.25%) (2 [4.16%] pediatric, 1 [2.08%] adult) had CNS failure after receiving prophylactic cranial irradiation.

CNS Failure after Prophylactic Cranial Irradiation

Three (2 pediatric and 1 adult) patients failed in CNS even after cranial prophylaxis treatment. Out of three patients, one patient had stage III disease and two patients had stage IV disease. On follow-up, all three patients had positive CSF cytology reports. All three patients had no relapse at any other site in the body.

Response Assessment after Therapeutic Cranial Irradiation

Out of five patients who had upfront CNS involvement, in follow up, two patients had negative CSF cytology report,

Table 2 Characteristics of treatment and results for patients who received cranial irradiation

Characteristics	Number of patients		
	Pediatric	Adult	Combined
1) CNS-negative disease	25	23	48 (90.56%)
Primary tumor			
Complete response (CR)	17/48 (35.4%)	20/48 (41.7%)	37/48 (77.08%)
Partial response (PR)	8/48 (16.7%)	3/48 (6.25%)	11/48 (22.9%)
Radiotherapy			
Prophylactic cranial irradiation received	25/48 (52.1%)	23/48 (47.9%)	48
CNS failure after prophylactic cranial irradiation	2/48 (4.16%)	1/48 (2.08%)	3/48 (6.25%)
CNS failure after prophylactic cranial irradiation (in correlation to primary tumor response)			
- Primary tumor CR	0/17	1/20	1/37
- Primary tumor PR	2/8	0/3	2/11
2) CNS-positive disease upfront			
Therapeutic cranial irradiation	1	4	5 (9.43%)
Site of tumor failure (after PCI)			
CNS (isolated)	2	1	3
Testis	1	-	1
Testis + medullary	1	2	2
Medullary	1	1	3
Kidney	-	1	1

Abbreviations: CNS, central nervous system; PCI, prophylactic cranial irradiation.

one patient had negative CSF cytology report and MRI was showing complete tumor regression, and in two patients follow up assessment was not available due to shorter follow up.

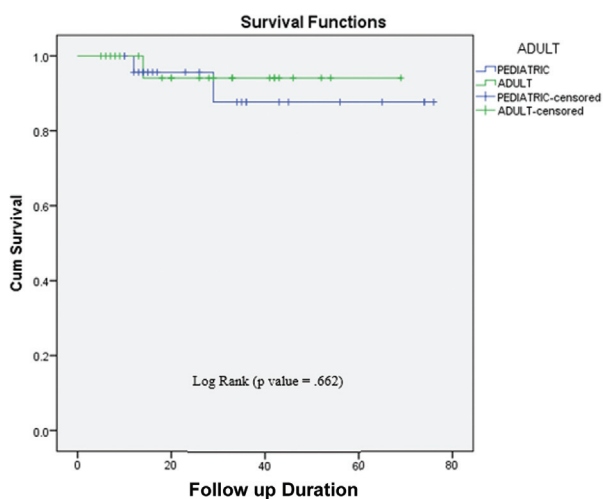


Fig. 3 Duration of Event Free Survival (EFS) in pediatric and adult patients.

Relapse (Event) Free-Survival in Brain after Prophylactic Cranial Irradiation (48 Patients)

With a median follow-up of 26.1, 28.2, and 27.27 months, EFS in the pediatric group, adult group, and the combined group was 92%, 95.7%, and 93.8%, respectively. Also, the difference between pediatric and adult groups was not statistically significant (p -value = 0.662).

► **Fig. 3** shows the probability of duration of EFS in pediatric and adult groups of patients.

Therapeutic Cranial Irradiation

Five patients (9.43%) (1 pediatric, 4 adults) had upfront CNS involvement and they received therapeutic cranial irradiation.

Discussion

Leukemia-like regimens given for ALL are the cornerstone of treatment for T-cell lymphoblastic lymphoma and can produce complete remission rates exceeding 90%.^{3,4} Central nervous system (CNS) is involved at diagnosis in only 2 to 7% of cases.⁵ However, CNS relapse can be seen in up to one-third of LBL patients if CNS prophylaxis treatment is not delivered.⁶

CNS relapse is mainly the dominant event once hematologic remission extends beyond 6 to 12 months.¹³ So, CNS preventive therapy evolved through subsequent studies at St. Jude Children's Research Hospital (SJCRH) and in Cancer and Leukemia Group B. Craniospinal irradiation or cranial irradiation (CrI) at 24 Gy (CrI with intrathecal methotrexate (ITMTX)), reduced the incidence of CNS relapse from >60% to <5 to 10%. Subsequent trials proved the advantage of CrI at 18 Gy combined with IT-MTX (intrathecal methotrexate) as the "standard" preventive regimen.¹⁴⁻¹⁶

The St. Jude study XI for childhood ALL has reported an isolated CNS relapse rate of 5%¹⁷ and Gelber et al¹⁸ in their analysis have reported a rate of 6%.

In a study by Raje et al (MCP 841 protocol), out of 623 patients, 568 patients received cranial radiotherapy and 12 doses of intrathecal methotrexate, 10 (1.75%) patients had developed isolated CNS relapse.⁸ In the MCP 841 protocol, the mainly pediatric patient population was included with age 3 to 6 years both inclusive and no mediastinal involvement. The cranial radiotherapy dose used was 20 Gy/10#. Out of the subjects who received cranial radiotherapy and 12 doses of intrathecal methotrexate, 10 patients had an isolated CNS relapse indicating a relapse rate of 1.76%. In addition, eight patients had CNS and bone marrow relapses. So, 18/568 (3.12%) patients had a CNS relapse rate.

In an initial study by Coleman et al¹⁹ using an ALL protocol for lymphoblastic lymphoma patients, intrathecal therapy was not given initially until 8 weeks into therapy, and 5 of 14 patients had a relapse in the CNS before receiving therapy. When IT chemotherapy was administered earlier during the treatment, CNS relapse was far less common (1/30 patients).

In the Berlin-Frankfurt-Munster (BFM) trials on childhood NHL, patients with T-LBL were treated according to the strategy for acute lymphoblastic leukemia (ALL)^{9,10} (NHL-BFM 90). The patient population selected was also the pediatric group with an age range between 1.1 and 16.4 years. Preventive CNS therapy consisted of cranial radiation therapy (CRT), intrathecal methotrexate (MTX), and intravenous MTX. The dose of prophylactic CRT was reduced from 18 Gy to 12 Gy, and high-dose MTX 5 g/m² was introduced. Preventive CNS therapy based on steroids, intrathecal MTX, intravenous high-dose MTX, and moderate-dose prophylactic CRT (12 Gy) proved highly efficient. Out of 105 patients, 1 patient had BM and CNS relapse combined with local tumor progression.

Our study was retrospective in nature. We have included both pediatric and adult age group patients. In addition, 88.6% of patients were male. In our study, 75.5% of patients were treated using the BFM 90 protocol and 24.5% of patients were treated using the MCP 841 protocol. So, not all patients were uniformly randomized or treated using the same protocol. Also, we can see that 11/48 (22.9%) patients had partial response following chemotherapy when they were referred for radiation.

We can also see that all patients had received two-dimensional (2D) conventional radiotherapy (slanting field technique). In MCP 841 (cranial RT dose: 20 Gy/10#) and BFM 90 (cranial RT dose: 12 Gy/6#) protocols, different radiotherapy regimens were used. However, trials have proved the advan-

tage of cranial irradiation at 18 Gy combined with IT-MTX as the standard preventive regimens in leukemia patients.¹⁴⁻¹⁶ And, in our department for prophylactic cranial irradiation, we used the same dose as 18 Gy to all patients.

In our study, 3/48 (6.25%) (2/48 [4.16%] pediatric, and 1/48 [2.08%] adult) patients had CNS failure after CNS prophylaxes treatment. As techniques have improved a lot and proper dose distribution can be achieved with 3DCRT/IMRT techniques, we can change the technique for prophylactic cranial irradiation to treat patients. Also, differences in chemotherapy of both studies would have also played a role in a higher rate of CNS recurrence. As in the BFM 90 original protocol, there was less CNS relapse after a moderate dose of RT in prophylactic cranial irradiation.

Also, our study had limitations such as uneven distribution of patients, combined group of pediatric and adults patients compliance to treatment, lost to follow-up, retrospective analysis.

Also, only cranial irradiation does not play a role to prevent CNS relapse after CNS prophylaxis treatment. It is mainly advantageous to prevent future CNS relapse. As mentioned, there would have been other factors also such as elevated LDH, high leukemic cell proliferation index, T-cell immunophenotype, white blood cell (WBC) count at baseline, baseline testicular involvement also plays a role; however, we have not assessed for the same. Our aim was mainly to study that even after prophylactic cranial irradiation, how many patients develop CNS relapse. So, we need to study in further detail the criteria mentioned above (high-end RT techniques with baseline laboratory and molecular level assessment and clinical presentation) to assess for CNS relapse.

With the recognition of adverse effects of radiotherapy, several patient characteristics such as high WBC count, T-ALL, very young age, and male sex have also been identified which are at an increased risk of CNS relapse.²⁰

For 48 target patients, with a median follow-up of 27.27 months (26.1 months: pediatric, 28.2 months: adults), EFS in the brain was 93.8% (92%: pediatric, 95.7%: adults). Also, the study was not a comparison between the pediatric and adult groups; however, based on statistical analysis, for both groups, the *p*-value (0.662) was generated and it was not statistically significant.

► **Table 3** shows a comparison of our study with various studies.

In recent studies, childhood NHL study of the BFM regimen without CRT-cranial radiotherapy (BFM95)²¹ was compared with historical BMF trials with radiation (BFM86 and BFM90) in stage III or IV patients without CNS disease at presentation. It showed that with the use of high-dose MTX and IT MTX, there were only 3 relapses out of 156 patients treated using the BFM 95 protocol when CNS irradiation was omitted.

Conclusion

In lymphoblastic lymphoma, prophylactic cranial irradiation and intrathecal methotrexate have been the standard of care as the CNS-directed therapy to prevent cranial infiltration. However, with recent BFM studies, the role of prophylactic

Table 3 Comparison of our study with various studies published

Study	Protocol	N	Cranial radiotherapy (CNS-negative)	Median follow-up	CNS relapse rates
Coleman et al ¹⁹	2 ALL protocols	44 (lymphoblastic lymphoma)	24 Gy	26 months	3% (after starting IT MTX earlier in second protocol) (combined)
BFM 90 ^{9,10}	ALL type protocols	105 (lymphoblastic lymphoma)	12 Gy	4.5 years	0.9%
MCP 841 ⁸	ALL protocol	568 (acute lymphoblastic leukemia)	20 Gy	21 months	1.76% (isolated)
Our study	ALL protocols	48 (lymphoblastic lymphoma: CNS-negative disease)	18 Gy	27.27 months	6.25% (isolated)

cranial irradiation also needs to be investigated in detail. We have seen more CNS relapses in comparison with published world literature; however, as discussed, it also depends on different variables and limitations in our setup. We further need to stratify our patients and offer the best available treatment to prevent CNS relapse.

Limitations of Study and Future Research Directions

In this study, we only analyzed our radiotherapy treatment approach. In our study, we found that only the slanting field whole-brain radiotherapy technique was used. None of the patients were treated with German helmet whole-brain radiotherapy treatment approach or higher radiotherapy techniques that provide considerable homogenous and improved dose distribution to the target, which may prevent future chances of relapse. Also, we did not look into the detail of factors such as high WBC count, very young age, male sex, elevated LDH, and high leukemic cell proliferation index, which may also play a role in CNS relapse. Also, the patient population was mixed (pediatric and adults), and the treatment protocol used was different (MCP 841 or BFM 90) for all patients according to the consultant's decision.

In the future, we would like to approach higher radiotherapy treatment techniques to be used for cranial radiotherapy to improve dose distribution. Also, we would like to assess all parameters listed above with the same patient population (pediatric or adults) to assess for CNS relapse rates in our institute.

Authors' Contributors

Dr. Maitrik Mehta proposed the stated study objective to be assessed and contributed to data collection, analysis of the data, conception and design, drafting the article, and final approval of the version to be published. Dr. Isha Shah helped in collecting and analyzing the data and helped in the preparation of the manuscript. Dr. Harsha Panchal helped in manuscript assessment and analysis of data.

Dr. Ankita Parikh, Dr. U. Suryanarayan, Dr. Jayesh Singh, Dr. Arun T. helped in manuscript editing. All authors approved the final version of the manuscript.

Finding

None.

Conflict of Interest

None declared.

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