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Response-Based Approach for Pediatric Hodgkin Lymphoma in Nations with Restricted Resources

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ABSTRACT

Background: Hodgkin lymphoma (HL) management varies throughout developing nations. This observational study aims to present the results of children having HL who received various combinations of chemotherapy treatment. The response-based method was used regardless of the risk classification.

Materials and Methods: We recruited patients≤ 18 years of age diagnosed with HL in an Iraqi cancer center between January 2014 and December 2021. By stratifying patients, three risk categories were identified. Every patient initially received two cycles of ABVD as induction chemotherapy. Following induction chemotherapy, patients showing a full radiological response continued on ABVD chemotherapy for 4-6 cycles without receiving radiotherapy. Patients showing a modest initial response received three additional courses of COPDac next to the third cycle of ABVD, followed by radiotherapy.

Results: This study included fifty-nine patients with a median age of 7 years. Stage III patients accounted for 33.9% (n=20), then stage II (32.2%). B symptoms were present in 25 patients. Eleven children had initial splenic involvement. Fifty-two individuals (n = 19; 32.2%) had bulky disease. Mixed cellularity was the most prevalent histology (n=44). The median duration of follow-up was 2.7 years. EFS was 78% ±10%, and survival was 92% at 5-year estimation. Bulky disease was the only factor with a substantial unfavorable impact on the result.

Conclusion: Response-based approach is a valuable strategy in nations with limited resources to prevent long-term sequelae from unnecessary radiotherapy.

Keywords: Pediatric Hodgkin lymphoma; Developing nations; Combination therapy

INTRODUCTION

Although pediatric Hodgkin lymphoma (HL) is treatable, the rate of cure varies, especially in underdeveloped nations [1,2,3,4,5].

Nations with low- and middle-income (LMIC) have sparse and scarce data regarding HL; prognostic variables differ from those in high-income countries (HIC) because of notable differences in healthcare access, radiological resources, and patient commitment to treatment [1,6,7,9,10].

Administration of only chemotherapy has been shown to be as effective as chemotherapy plus radiotherapy in treating patients who have fast early response (complete remission CR after two courses of chemotherapy). It's probably safe to omit radiation on those individuals[8,11,12]. The goal of

reducing treatment-related adverse effects has grown significantly. In HL, a combined chemotherapy treatment has been utilized with varying degrees of success [8,13,14,15].

This observational study aims to describe the clinical features and treatment outcomes of children aged 0 -18 years with HL, who received two combined distinct chemotherapy regimens: COPDac (cyclophosphamide, vincristine, prednisolone, and dacarbazine) and ABVD (dacarbazine, bleomycin, vinblastine, and doxorubicin). Response-based therapy was used in this study regardless of risk stratification. There was an evidence-based that both those regimens are effective in the management of HL.

Additionally, strategies used for patient monitoring, treatment compliance, treatment avoidance, and follow-up were also centered in this study.

MATERIALS AND METHODS

Patients $\leq$ 18 years of age with HL (all histologies) referring to the primary cancer center in Kerbala, Iraq, between January 2014 and December 2021 were enrolled in this study.

A baseline assessment was carried out within three weeks after the diagnosis. The pre-treatment evaluation comprised the following tests: started with computed tomography (CT) scans with contrast for the chest, neck, abdomen, and pelvis; erythrocyte sedimentation rate, as well as renal and hepatic function tests; and finally, a complete blood count (CBC) with differential. Bone marrow study was limited to high-risk patients. Due to the high expense, a positron emission tomography (PET) scan was performed optionally upon request by the guardian to evaluate treatment response.

Depending on Ann Arbor staging for lymphoma[16], Bulky disease is identified by a mediastinal mass occupying at least one-third of the intrathoracic cavity on an upright chest radiograph or a peripheral lymph node mass larger than 6 cm in its greatest dimension. The assessment also includes evaluating extranodal disease extension and B symptoms (documented unexplained fever exceeding 38°C, profuse night sweats, or apparent weight loss exceeding 10% over the previous 6 months). Based on these factors, patients are classified into three risk groups: low, intermediate, and high.

Low-risk: Stage IA or IIA without bulky disease or extranodal extension.

Intermediate-risk: Stage IA or IIA with a bulky disease or/and extranodal extension, IB or IIB without a bulky disease or/and extranodal extension, and stages IIIA and IIIB without bulky disease.

High-risk: Stage IIB or IIIB featuring bulky disease or extranodal extension alongside stage IV disease. After diagnosis confirmation, an interview was set up with the patient's parents and the pediatric oncologist to go over the status of this type of cancer, its stage, prognosis, available treatments, and any relevant family hurdles to prevent the patient from being abandoned. In addition, it was also necessary to inquire about the patient's residency, specifically whether they lived in an urban or rural region.

Treatment plan

For all patients, the initial course of treatment was ABVD, the conventional chemotherapy regimen. COPDac and radiation therapy were administered based on the overall response to induction treatment, which consisted of the first two cycles of ABVD chemotherapy. The ABVD regimen included intravenous (IV) doses of doxorubicin 25 mg/m², bleomycin 10 units/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² on the first and fifteen days. For COPDac chemotherapy, the treatment protocol included Prednisolone 40 mg/m²/day orally from the first to the fourteenth day; dacarbazine 250 mg/m²/day from the first to the third day; vincristine 1.4 mg/m² on the first and eighth days (maximum of 2 mg); cyclophosphamide 600 mg/m² IV on the first and eighth days.

The ABVD cycle was repeated every four weeks, contingent upon blood count recovery, while the COPDac cycle was administered every 3 weeks.

If, after the second course of chemotherapy, complete remission was not obtained, radiotherapy was administered after the completion of the entire course of chemotherapy. All initially involved sites at the presentation were subjected to radiotherapy. The radiation therapy regimen consisted of a total dose of 25.5 Gy delivered in fractions of 1.5 Gy each;

it was given irrespective of the age (as such dose has a minimal detrimental effect on the growth of children with age less than 14 years old).

Early response evaluation

Following the conclusion of the second ABVD cycle, a physical exam, CT scan, or PET-CT scan (if financially permitted) were used to assess each patient's response to chemotherapy. In the absence of a reasonable alternate explanation, Lymph node enlargement at the infraclavicular, supraclavicular, epitrochlear, preauricular, brachial, and greater than 1.5 cm transverse diameter in a popliteal area at the time of diagnosis indicated disease involvement. For cervical, axillary, inguinal, and mesenteric lymph nodes, diameters exceeding 2 cm indicated Hodgkin's lymphoma (HL). Any lesion of focal mass in visceral and other organs, such as the liver, kidney, or spleen, was deemed involved if no alternative explanation, such as a cyst, hemangioma, or abscess, was evident.

Indicators of a complete response included total resolution of all measurable disease, disappearance of any new lesions, resolution of any initial constitutional symptoms, reduction in the size of all nodal masses by 80% or more for the primary nodes or by 75% or more in the total diameter of previously confluent nodes, and a PET-negative scan, assessed by a nuclear medicine specialist using the Deauville score, aligning with physiological uptake of fluorodeoxyglucose (FDG) in the liver and mediastinum. A minimum of 50% reduction in the overall diameter of all identifiable lesions and the lack of constitutional symptoms (if present at the beginning of the disease) were indicators of a partial response.

The ABVD regimen was resumed in patients who achieved a complete response (CR) to induction chemotherapy, with a maximum of four cycles for the low-risk group and six cycles for the intermediate and high-risk groups. Radiotherapy was omitted in these cases.

Patients who did not achieve CR after two courses of ABVD (referred to as slow early responders) received three cycles of COPDac following the 3rd cycle of ABVD. Radiotherapy was subsequently administered after chemotherapy treatment.

After-therapy monitoring,

After the end of treatment, patients were seen every month for the first half of a year, every two months for the following half of a year, every three months for the second year, every four months for the third year, every six months for the fourth year, and once a year for the fifth year. Following the conclusion of treatment, routine laboratory tests (complete blood count, CBC with differential, erythrocyte sedimentation rate), ultrasonography, physical examinations, and chest x-rays were performed. After the course of treatment, CT scans of the neck, chest, abdomen, and pelvis were carried out three, six, and one year later. Further investigations were determined accordingly if the clinical condition indicated disease recurrence. Individuals were considered to be in complete remission if they showed no signs of disease progression or if any residual abnormalities at the original sites of the disease were either stationary or improved. To confirm disease progression or relapse, a biopsy was necessary.

Statistical analysis

The retrospectively collected data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS). Descriptive statistics, such as mean, range, frequencies, and percentages, were utilized to summarize the data. Survival analysis was conducted using the Kaplan-Meier method. The two-sided log-rank test was employed to assess potential predictive variables for overall survival (OS) and event- free survival (EFS), including splenic involvement, B symptoms of bulky disease, clinical stages, and risk stratification. Additionally, multivariate Cox regression analysis was utilized.

Overall survival (OS) was calculated from the date of diagnosis to the last follow-up date, or the date of death related to any cause. EFS was calculated as the difference between the date of diagnosis and the date of any disease progression, relapse, abandonment or death. A P-value of less than 0.05 was regarded as statistically significant.

RESULTS

Patient characteristics

Demographic characteristics of the patient cohort are shown in (Table 1) which included age, gender, origin (residency), histology type, and initial lymph node involvement. The median follow-up was 2.7 years and ranged from 0.1 to 7.5 years. Table 2 shows risk factors and treatment modalities for all enrolled patients. More than one-third of patients were staged III (33.9%), followed by stage II (32.2%), stage I (30.5%), and then stage IV (3.4%). Regarding risk stratification, the majority of patients were in the low-risk group (45.7%). B symptoms were present in 42.4% of patients (stage I = 1, stage II = 8, stage III = 14, stage IV = 2). Approximately one-third (32.2%) of patients had bulky disease.

Response to treatment

Twenty-one patients (35.6%) had a complete response following two cycles of ABVD chemotherapy; fifteen of these patients were classified as low risk, four as intermediate risk, and two as high risk. A total of 38 patients (64.4%) had a partial response; 12 had low-risk, 12 had intermediate risk, and 14 patients had high-risk disease; one patient did not respond to treatment and eventually passed away from a progressive disease even though he had more intensive therapy. Remarkably, despite a partial response to induction chemotherapy, ABVD chemotherapy was continued for two patients: one in the low-risk group and the other in the high-risk group. Upon the request of their families, both patients underwent radiotherapy following the completion of chemotherapy.

Due to partial response to induction chemotherapy, 36 patients received a combined chemotherapy regimen (i.e., ABVD plus COPDac) (Table 2); however, only 19 of those patients received radiation after chemotherapy. For the other 17 patients, radiotherapy was not administered due to either family decline (n = 6) or radiotherapy obstacles (prolonged duration of more than two months following chemotherapy completion, opposition from radiation oncologist due to the wide radiation field, or technological difficulties); 13 out of 17 patients were in the CR at the end of chemotherapy. Adverse reactions after ABVD were as follows: nausea and vomiting (n=39), fever and chills (n=4), mild anemia (n=11), mild neutropenia (n=4), and pain at the site of intravenous access (n=4).

Manifested side effects after COPDac included nausea and vomiting (n=18), increased appetite (n=18), generalized bone pain (n=8), epigastric pain (n=3), constipation (n=1), and pain at the site of intravenous cannulation (n=1).

Outcome

At five years, the estimates for OS and event-free survival EFS were 78% (Figure 2) and 92% (Figure 1), respectively. Considering predictive variables, only bulky disease demonstrated a significant statistical difference (Table 3); EFS was significantly higher in children without bulky disease (Figure 3). In multivariate analysis, the bulky disease continued as the only factor that significantly affected the survival. The 5-year EFS for children with bulky disease was 45%, while those without bulky disease had an EFS 96% (p = 0.001). OS for those with bulky disease was 77%, whereas those without bulky disease had OS 100% (p value=0.03).

Table 1: Characteristic features of enrolled children with Hodgkin's lymphoma.

Age	
Range (year)	2.5 to 16
Median (year)	7
Six	
Male	36
Female	23
Residence	
Urban	45
Rural	14
Histopathology	
Mixed cellularity	44
Nodular sclerosis	12
Lymphocyte rich	3
Lymph nodes groups	
Cervical LN	55
Supraclavicular LN	25
Axillary LN	7
Infraclavicular LN	1
Para aortic LN	19
Mediastinal LN	26
Inguinal LN	2

Table 2: Hodgkin's lymphoma care involves assessing risks and tailoring treatments.

Stage	
I	12
II	13
III	14
IV	2
Stratification	
Low.	27
Intermediate.	16
High.	16
B symptoms	
Yes	25
No	34
Splenic Involvement.	
No	48
Yes	11
Bulky disease [a]	
Yes	19
No	40
Type of chemotherapy	
ABVD, COPDac	36
ABVD	23
Radiotherapy	
No	40
Yes	19

[a] "Definition of bulky disease: A mediastinal mass-to-intrathoracic cavity ratio greater than 1/3 on an upright chest radiograph, or a peripheral lymph node mass measuring more than 6 cm in its longest diameter".

Table 3: Estimated 5-years EFS according to risk factors

Factor	Survival	P
Splenic involvement		
Yes	80%	0.4
No	96%	
B Symptoms		
Yes	90%	0.9
No	95%	
Bulky disease		
Yes	77%	0.03
No	100%	
Stage		
I	100%	0.5
II	90%	
III	80%	
IV	100%	
Risk		
High	85%	0.3
Intermediate	90%	
Low	100%	

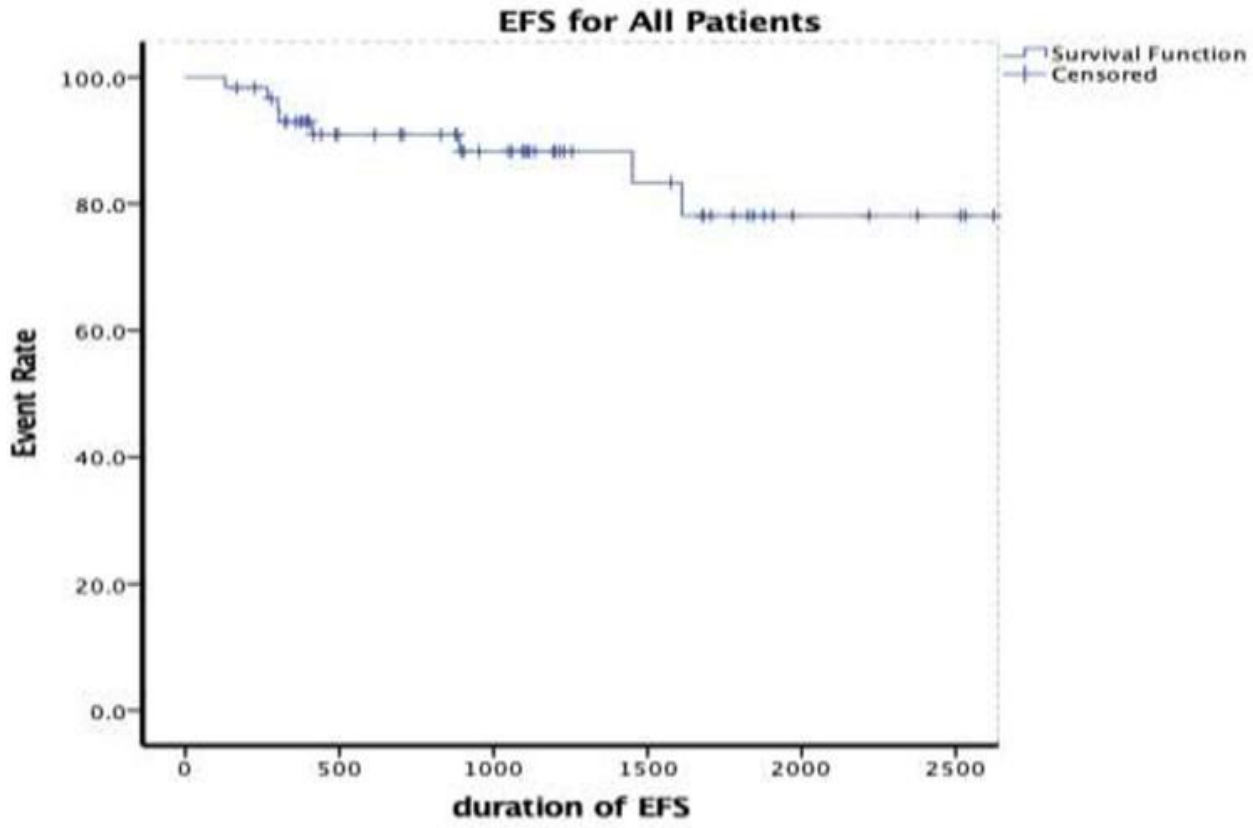

Figure 1. Estimated Event-free survival of enrolled children with HL (78%).

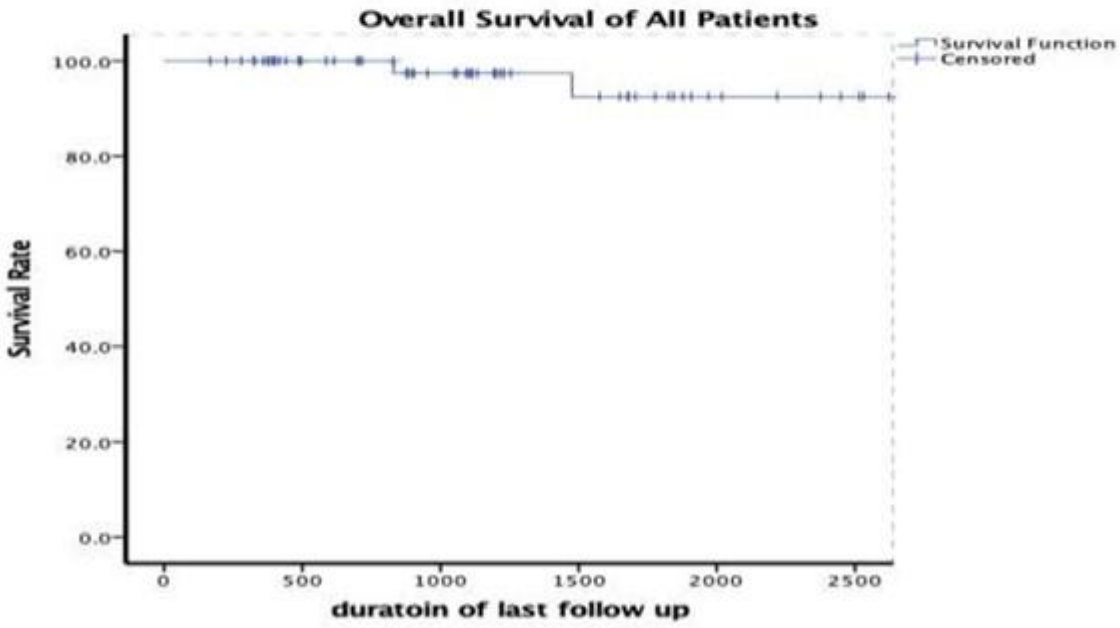

Figure 2. Projected overall survival of the enrolled children with Hodgkin's lymphoma (92%).

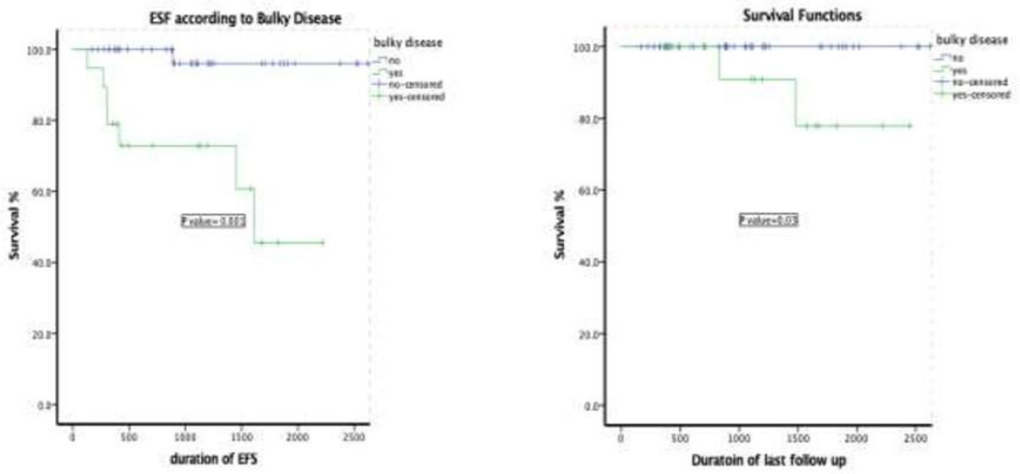

Figure 3. Survival according to bulky disease. (A) Five years EFS with and without bulky disease (45% vs 96%). (B) Five years OS with and without bulky disease (77% vs 100%). *Note*, EFS= event free survival; OS= overall survival

DISCUSSION

HIC has achieved superb outcomes for pediatric HL[11,14,17]. Nevertheless, LMIC results are inconsistent[5,14,18]. In pediatric HL, a combined modality therapy with non-cross-resistant components was utilized[8,13,15]. Response-based therapy, using a non-cross-resistant combination modality approach, was used in the current study to enhance the results of children with HL based on their initial response to induction treatment. This strategy aimed to reduce the use of radiotherapy, a significant challenge in low- and middle-income countries (LMIC) due to frequent delays caused by the high number of patients awaiting treatment. Furthermore, the combined modality strategy minimizes resistance to chemotherapy by exposing cancer cells to different chemotherapeutic agents; subsequently, superior outcomes are attained.

Although treatment abandonment (which refers to leaving off chemotherapy for four or more weeks) is more prevalent in LMICs because of social, cultural, and economic issues[6,7,9,10], attempts were undertaken to decrease this significant obstacle; This was achieved through a well-planned and organized first session meeting with the patient's caretakers, emphasizing on the reciprocal association between treatment compliance and positive outlook; moreover, all relevant challenges that might arise were discussed thoroughly.

There is a minor male gender predisposition in this study. Some other studies have demonstrated a male gender preference[3,7,19,20]. Most patients hailed from urban areas, possibly due to inadequate health awareness in rural regions, alongside potential environmental factors contributing to this trend. The incidence of malignancy may be affected by environmental factors, as illustrated by the study of urban-rural status in certain malignancies, such as lymphomas and leukemia[21,22,23]. Regarding histology, significant number of patients in this study exhibited mixed cellularity histology like some other studies conducted in LMIC[5,19,20,24]; however, nodular sclerosis histology predominated essentially in other studies on HIC[8]. Peripheral lymph node involvement was noted in all patients, a finding consistent with the majority of studies, highlighting cervical lymph nodes as the most frequently affected peripheral nodal sites [23,24,25].

B-symptoms were present in 42.4% of patients. The presence of B-symptoms has been shown to

adversely affect prognosis[26,27], other studies have not manifested this strong predictive influence[28]. Our findings suggest that children with B-symptoms do not significantly have worse outcomes; this may be due to the risk-stratified treatment approach, which could have mitigated the impact of this prognostic indicator. While splenic involvement has been proposed to be a risk factor that influences the outcome[29], results in this study did not indicate a substantial predictive significance.

Moreover, We found that bulky disease has a negative impact on the outcome; other published studies also demonstrated the same result[28,30]; The possible reason might be the relatively long duration between the onset of symptoms, diagnosis, and the start of therapy.

In this study, staging (p =0.5) or risk stratification (p =0.3) has no statistically significant impact on the outcome. Although similar results have been demonstrated in other studies[24,28], a response-based approach may contribute to this favourable outcome. Nevertheless, a limited population of patients might pose a contributory factor.

The estimated 5-year event-free survival (EFS) and overall survival (OS) rates for the entire patient group were 78% and 92%, respectively. Despite the substantial number of low-risk patients in this study, factors such as thorough clinical evaluation and clear communication between the paediatric oncologist and the patient's guardians, adherence to treatment, and the use of a combined chemotherapy strategy likely contributed to these positive outcomes.

Compared to other published studies from resource-limited nations, superior results were achieved from this study[1,2,3,4,8,19,24,26,28].

Even though the overall cumulative doses of alkylating drugs in this study are comparable to those in previous studies, the cumulative doses of bleomycin and anthracyclines were reduced; consequently, it is anticipated that the long-term cardiac and pulmonary toxicities associated with the use of those chemotherapy drugs will decrease. Furthermore, the justification for a chemotherapy response-directed RT strategy was explicit; In patients with chemotherapy-induced complete remission (CR), a response-adapted treatment strategy that omits radiation therapy (RT) may be feasible. Notably, technical difficulties with irradiation led to protocol violations in a significant number of patients (n=17) who did not receive RT following chemotherapy, contrary to medical advice. In this study, 38 patients (64.4%) did not undergo RT either due to a full response to chemotherapy induction (21 patients) or due to protocol violations (17 patients). This additionally confirms that it is safe to forego RT in children with CR following chemotherapy.

Finally, we employed this approach to maintain high cure rates and minimize long-term treatment-related morbidity and mortality in young patients with Hodgkin lymphoma.

It is noteworthy that this study has certain limitations. Firstly, the patient cohort is rather small. Secondly, a significant proportion of patients did not undergo RT due to protocol violations. It is anticipated that more collaborations will arise to build on this achievement.

CONCLUSION

Response-based approach can be utilized for pediatric HL in countries with limited resources; its value is to prevent undue radiotherapy and its detrimental consequences with concomitant good outcomes.

CONFLICT OF INTEREST

The authors assert that there are no known financial or personal relationships that could have impacted the findings of this study.

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