# Outcome of children with Hodgkin's disease

## *A 10-year experience from a single institution in Kuwait*

***Rakesh Mittal,*** *MD, DM,* ***Nisreen M. Khalifa,*** *MD, PhD,* ***Sahar O. Khalifa,*** *MBBCh, MD,*
***Ahmed M. Ragheb,*** *MS, MD,* ***Juzer Ali,*** *MBBS, MD.*

## ABSTRACT

**الأهداف:** تقييم نتائج علاج الأطفال المصابين بمرض هودجكنز خلال العشر سنوات الأخيرة بمركز الكويت لمكافحة وعلاج السرطان.

**الطريقة:** شملت الدراسة 63 طفل، تم تشخيصهم بمرض هودجكنز بواسطة الفحص الباثولوجي، كما تم تصنيفهم تبعا لنظام أن أربر للتدرج المرضى، خلال الفترة من يناير 1998 وحتى سبتمبر 2007 بوحدة أورام الأطفال – مركز مكافحة السرطان – الكويت.

**النتائج:** شملت الدراسة 37 ذكر (59%)، 26 أنثى (41%)، وكان متوسط الأعمار هو 10عام (المدى 15-3 عام). وكانت الأعراض المرضية (ب) تمثل 32% (20مريض)، والتضخم بالغدد يمثل 44% (28 مريض). كان 8 أطفال (13%) يعانون من الدرجة الثالثة من المرض، بينما 12 طفل (19%) كانوا يعانون من المرض في درجته الرابعة. تم استخدام العلاج الكيميائي كعلاج بدائي في 63 طفل، وقد تم علاج هؤلاء الأطفال بواسطة 6 جرعات كيمائية (8-2 جرعات)، وتم استخدام العلاج الإشعاعي في علاج 40 طفل (63%). وقد تم تسجيل الآثار الجانبية التالية: ضعف في فحوصات الدم من الدرجة الثالثة في 23 طفل (37%)، ومن الدرجة الرابعة في 14 طفل (22%)، وقصور في وظائف الغدة الدرقية في 20 طفل (32%). حقق 55 طفل (87%) استجابة كاملة للعلاج، بينما حقق 2 فقط (3%) استجابة جزئية، لذا كانت الاستجابة العامة 90%، وتطور المرض في 3 أطفال 5%، ولم نستطع تقييم الاستجابة عند 3 طفل آخرين (5%). كان متوسط زمن متابعة الأطفال 67 شهر (5.5 عام)، وكانت النسبة العامة للبقاء علي قيد الحياة لهؤلاء الأطفال هو 91%.

**خاتمة:** العلاج المشترك الكيميائي و الإشعاعي ذو آثار جانبية متوسطة الخطورة، كما أنه علاج فعال للأطفال المصابين بمرض هودجكنز.

**Objectives:** To evaluate the outcome of children with Hodgkin's disease over a period of 10-years from a single institution in Kuwait.

**Methods:** Sixty-three children with previously untreated Hodgkin's disease, who were diagnosed at the Pediatric Oncology Unit of Kuwait Cancer Control Centre, Shuwaikh, Kuwait from January 1998 to December 2007 were included in the study. All cases were proved by histopathology, and staging was carried out according to the Ann Arbor system.

**Results:** Our series included 37 (59%) males and 26 (41%) females with a median age of 10 years (range 3-15 years). B symptoms were present in 20 (32%) children. Bulky disease was noted in 28 (44%) children, with stages III in 8 (13%) and IV in 12 (19%) children. Chemotherapy was administered as a primary treatment in 63 children. The median number of chemotherapy cycles given was 6 (range 2-8). Radiotherapy was used in 40 (63%) children. Grade III hematological toxicity was observed in 23 (37%) and grade IV in 14 (22%) children. Hypothyroidism was observed in 20 (32%) children. Fifty-five children achieved a complete remission (87%) and 2 children achieved a partial remission (3%) with an overall response rate of 90%. Three children achieved a progressive disease (5%) and response could not be evaluated in 3 (5%) children. At a median follow-up of 67 months (5.5 years), the overall survival was 91%.

**Conclusions:** With moderate toxicity, combined modality therapy is effective in the treatment of childhood Hodgkin's disease.

***Saudi Med J 2010; Vol. 31 (1): 69-73***

*From the Unit of Pediatric Oncology (Mittal, Khalifa N, Khalifa S), Department of Medical Oncology, and the Department of Radiation Oncology (Ragheb, Ali), Kuwait Cancer Control Centre, Shuwaikh, Kuwait.*

*Received 27th October 2009. Accepted 12th December 2009.*

*Address correspondence and reprint request to: Dr. Rakesh Mittal, Unit of Pediatric Oncology, Department of Medical Oncology, PO Box 42262, Shuwaikh 70653, Kuwait. Tel. +965 24849100 Ext. 4532. Fax. +965 24810007. E-mail: rakeshmittal55@hotmail.com*

Hodgkin's disease (HD) or Hodgkin's lymphoma (HL) is a cancer of lymphatic system, which occurs, predominantly in young adults. It was named after the British physiologist Thomas Hodgkin, who first described the disease in 1832. In the United States, HD represents 6% of all childhood cancers with the highest incidence in the age group of 15-19 years.[1] In Kuwait, lymphoma is the second leading cancer for males and fifth leading cancer for females.[2] Kuwait Cancer Registry, which is a hospital based cancer registry, reported HD as the third most common cancer in children less than 15 years of age. In the last 3 decades, care of patients with HD has changed substantially making it one of the most curable malignancies in children and adolescents. Before the 1970's, children treated with high dose radiotherapy alone had a 10-year survival of 11%[3] only and similarly poor survival was obtained with single agent chemotherapy. The use of combined chemotherapy regimens with or without radiotherapy has significantly improved the prognosis of patients with HD. Combined chemo-radiotherapy has been the preferred treatment modality in most studies on childhood HD in the recent years, with 5-year overall survival (OS) rates of greater than 95% and 5-year event free survival of greater than 90% for all stages of disease.[4-12] In able to achieved this excellent survival, the focus is now shifting to prevention of late effects of treatment. Response-adapted therapy is now emerging as a means of reducing the long-term toxicity of the treatment while maintaining the efficacy.[13] Kuwait is a country with a population size of 3.39 million including approximately 1.05 million Kuwaiti citizens and 2.34 million non-Kuwaiti nationals comprising of different ethnic group such as South Asian, Iranian, Arab, and others. Kuwait Cancer Control Center is the only comprehensive cancer center of Kuwait. The pediatric oncology unit is part of the medical oncology department. It is responsible for the treatment of all children with pediatric solid tumors and lymphomas up to the age of 15 years. On an average, 50 new confirmed cases of malignancies are registered in our unit. The purpose of this report is to present the results of incorporation of these advances at a single institution in Kuwait and to analyze the outcome of their treatment.

**Methods.** All children with previously untreated HD who were treated at the Pediatric Oncology Unit of Kuwait Cancer Control Centre from 1998-2007 were included in the study. The study was retrospective and analyzed the case notes of 63 children with regards to age, gender, nationality, symptoms, staging, histopathology, lactate dehydrogenase level, therapeutic regimens, response to therapy, toxicity, follow-up and outcome. The imaging for staging purpose was carried out by x-ray of the chest, ultrasound of the neck and abdomen, CT scan of neck, chest, abdomen and pelvis, and gallium scan. Bone marrow aspiration biopsy was performed in patients who had "B" symptoms or had clinically advanced disease. In all the cases, the diagnosis was proved by histopathology and staging was carried out according to the Ann Arbor system.[14] The disease was described as "bulky", if peripheral lymphnodes were more than 6 cms or the mediastinal widening was more than one-third of the maximum chest diameter. Mostly, a combined modality approach has been used for the treatment of children. For low risk or early stage disease, only chemotherapy without radiotherapy was used. The most commonly used chemotherapy combination was doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD). Some of the children traveled abroad and were treated on alternative protocols but they all returned back and were followed-up in our hospital. The initial response assessment was carried out after completion of 2 cycles. Patients were assigned to low risk group if they had stage I-A, I-B, or II-A, intermediate risk were those with stage II-B or III-A, others were staged as high risk. For low risk patients, 4 cycles of ABVD cycles were used, while for intermediate or high risk patients, 6 cycles of ABVD with or without involved field radiation therapy (IFRT) was administered. Radiotherapy was delivered to involved field only and was given after completion of chemotherapy. Most of the children received a dose of 2100 cGy in 14 fractions over a 3 weeks period. After completion of the therapy, the disease assessment was carried out by x-ray of the chest, CT scan of neck, chest, abdomen and pelvis, and gallium scan. Response to treatment was defined on the basis of resolution of clinical, radiological, and radioisotopic resolution of disease at completion of therapy. Complete remission (CR) was defined as complete resolution of all the previously present clinical, radiological, and radioisotopic lesions, or reduction of initial tumor volume to more than 70%, but gallium positive lesions should become negative. Partial remission (PR) was defined reduction in the tumor mass between 50-70% with positive or negative gallium scan. Progressive disease (PD) was described as appearance of new lesions during course of treatment and children with <50% reduction in tumor size were described as non-responders. Patients were regularly followed-up following completion of treatment. Patients were called for follow-up every 2 months in their first year, every 3 months in their second year, 4 monthly in third and fourth year, and 6 monthly, subsequently. For children who received radiation to the neck and/or chest, thyroid function test (TFT) was performed at 6 months interval. A high thyroid stimulating hormone (TSH) value for consecutive 2 readings was taken as evidence of hypothyroidism and they were

started on replacement therapy. All the treatment was administered after taking due consent from the family. Since it is a retrospective analysis, ethical approval was not required. Overall survival and event free survival (EFS) were calculated using Kaplan-Meier method.[15] Overall survival was taken to be time from diagnosis until death or last follow-up. Event free survival was taken as time from diagnosis until last follow-up, death or progression of disease. The analysis was performed using SAS 8.02 statistical software (SAS Institute Inc. North Carolina, USA).

**Results.** Baseline characteristics of children are summarized in **Table 1**. There were more male patients (male to female ratios 1.4:1) with a median age of 10 years (range 3-15 years). Two-third of children were Kuwaitis. B symptoms were present in one-third of children. Nodular sclerosis subtype was the most common pathological type (46%), followed by mixed cellularity in 33%. Two patients were included due to incomplete data.

***Treatment summary.*** **Table 2** summarizes the details of treatment administered to children. Chemotherapy was administered as a primary treatment in 63 children, with ABVD being the most commonly used (62%) chemotherapy regimen. The median number of chemotherapy cycles given was 6 (range 2-8). Radiotherapy was used as the combined modality therapy in 40 (63%) children. Twelve children received only 4 cycles of chemotherapy, out of which 5 did not receive radiotherapy. Thirty-eight children received 6 cycles. Radiotherapy was given to 40 children. Out of 38 children who received 6 cycles, 10 children did not receive any radiotherapy. Chemotherapy protocols other than ABVD were combined cyclophosphamide, vincristine, procarbazine, and prednisone (COPP), chlorambucil, vinblastine, procarbazine, and prednisone (CHLVPP), COPP/ Adriamycin, bleomycin and vinblastine (ABV) hybrid regimen.

***Toxicity.*** All children had an acceptable toxicity profile. Grades III and IV hematological toxicity was

**Table 1 -** Baseline characteristics of patients.

| Characteristics of patients | N | (%) |
|---|---|---|
| *Gender* | | |
| Male | 37 | (59) |
| Female | 26 | (41) |
| *Nationality* | | |
| Kuwaitis | 44 | (70) |
| Non-Kuwaitis | 19 | (30) |
| *B symptoms* | | |
| No | 43 | (68) |
| Yes | 20 | (32) |
| *Histopathology* | | |
| Nodular sclerosis | 29 | (46) |
| Mixed cellularity | 21 | (33) |
| Lymphocyte predominant | 08 | (13) |
| Unclassified | 05 | (8) |
| *Disease status* | | |
| Bulky | 28 | (44) |
| Non-bulky | 35 | (56) |
| *Stage* | | |
| I | 03 | (5) |
| II | 38 | (60) |
| III | 08 | (13) |
| IV | 12 | (19) |
| DNK | 02 | (3) |
| *Lactate dehydrogenase* | | |
| Normal | 49 | (78) |
| High | 10 | (16) |
| Data not known | 04 | (6) |

Mean age: 10 years and range: 3-15 years.

**Table 2 -** Treatment details.

| Treatment details | n | (%) |
|---|---|---|
| *Chemotherapy* | | |
| ABVD | 39 | (62) |
| Others | 17 | (27) |
| ABVD + others | 5 | (8) |
| Data not known | 2 | (3) |
| *Disease status after chemotherapy* | | |
| Complete remission | 53 | (84) |
| Partial remission | 5 | (8) |
| Progressive disease | 2 | (3) |
| Not evaluated | 3 | (5) |
| *Type of radiotherapy* | | |
| Involved field radiotherapy | 34 | (85) |
| Mini mantle | 1 | (3) |
| Mantle | 2 | (5) |
| Inverted | 3 | (7) |
| *Outcome* | | |
| Complete remission | 55 | (87) |
| Partial remission | 2 | (3) |
| Progressive disease | 3 | (5) |
| Not evaluated | 3 | (5) |

Median number of cycles: 6 and range: 2-8.
ABVD - Doxorubicin (Adriyamycin), Bleomycin, Vinblastine, Dacarbazine

**Table 3 -** Toxicity.

| Toxicity | n | (%) |
|---|---|---|
| *Hematological toxicity* | | |
| Grade I | 3 | (5) |
| Grade II | 19 | (30) |
| Grade III | 23 | (37) |
| Grade IV | 14 | (22) |
| *Non-hematological toxicity* | | |
| Hypothyroidis | 20 | (32) |

Median number of months for occurrence of hypothyroidism (range) 24 months (5-57 months)

observed in 23 (37%) and 14 (22%) children. There was no toxicity related mortality or serious adverse events. Hypothyroidism was observed in 20 (32%) children with a median of 24 months (range 5-57 months) for occurrence (**Table 3**).

***Efficacy.*** In this series, at the end of therapy, 55 children achieved a CR (87%) and 2 children achieved a PR (3%) with an overall response rate of 90%. Three children achieved a PD (5%) and response could not be evaluated in 3 (5%) children. Out of the 55 children who achieved CR, only 2 relapsed at 43 and 9 months respectively. Both were salvaged with conventional chemotherapy and survived. Both the children with PR status died due to progressive disease after salvage, including high dose therapy in one child. There were 3 children with progressive disease. One child achieved CR status after salvage therapy and survived, while 2 underwent salvage with high dose therapy and stem cell transplant. One child died due to transplant related complications. Other child relapsed again after high dose therapy and left for native country and most probably died there. There were 4 documented deaths in our series. Two died due to progressive disease, one died due to transplant related complications and 4th one died due to septicemia during primary chemotherapy. At a median follow-up of 67 months (5.5 years), the OS was 91% and the median event free and OS was not reached (**Figure 1**).

**Discussion.** Our 10-year experience with HD reflects the progress reported in larger clinical trials designed for the treatment and evaluation of this disease. In the present study, 63 children with HD were treated with combination chemotherapy regimen with or without radiotherapy. Our analysis indicates a response rate of 90% and an OS of 91% at a median follow-up of 67 months. Available literature shows that in developed countries the peak of incidence for this disease occurs late compared with the developing countries, where it seems to peak between 5 and 9 years of age.[16-19] In this study, the median age at diagnosis was 10 years, a finding similar to what is reported in the previous studies. Hodgkin's disease is more common in male children.[20] This predominance was observed in our study as well. The nodular sclerosis and mixed cellularity subtypes were the most frequent in our study, similarly to the frequency found in underdeveloped countries.[17,18] In developed countries, the predominant histological type is nodular sclerosis.[21] More than half of the cases (60%) in our study were stage-II at the time of presentation. The combination of nitrogen mustard, vincristine, procarbazine, and prednisolone (MOPP) was introduced in the management of advanced HD more than 3 decades ago.[22] However, because of the high hematological toxicity of MOPP, as well as its induction of secondary acute myeloid leukemia, azoospermia and ovarian dysfunction[23,24] the identification of alternative drug combinations became a major priority. The ABVD regimen was developed in the mid-1970s consisting of adriamycin, bleomycin, vinbalstine, and decarbazine.[25] It did not cause infertility and have less hematological toxicity. However, the regimen is associated with a risk of cardiomyopathy and pulmonary dysfunction especially in children.[5] Most childhood treatment regimens combine various numbers of cycles of ABVD and MOPP derivatives. In our series, ABVD was the most commonly (62%) used chemotherapy regimen. Nearly 60% of patients suffered grades 3 and 4 hematological toxicity. We have not seen any instances of cardiomyopathy as yet. Combined modality therapy has been the preferred treatment modality in most studies on childhood HD in the recent years, with 5 year OS rates of greater than 95% and 5 year event free survival of greater than 90% for all stages of disease.[4-12] Adjuvant radiation therapy for advanced disease has been advocated due to relapse occurring at the site of bulky disease; however, no improvement in OS has been demonstrated.[26]

This is a retrospective analysis with a short follow-up. The median over all survival and event free survival cannot be commented.

## References


1. Horner MJ, Ries LAG, Harkins D, Krapcho M, Nayman N, Aminou R, et al. SEER Cancer Statistics Review, 1975-2003. Bethesda (MD): National Cancer Institute; 2006.
2. Parkin DM, Whelan SL, Ferlay J. Cancer incidence in five continents. International Agency for Research on Cancer, IARC Scientific Publications No 143. France: Lyon, IARC; 1997. p. 410-417.
3. Shah AB, Hudson MM, Poquette CA, Luo X, Wilimas JA, Kun LE. Long term follow-up of patients treated with primary radiotherapy for supradiaphragmatic Hodgkin's disease at St. Jude Children's Research Hospital. ***Int J Radiat Oncol Biol Phys*** 1999; 44: 867-877.
4. Raney RB. Hodgkin's disease in childhood: A review. ***J Pediatr Hematol Oncol*** 1997; 19: 502-509.
5. Hunger SP, Link MP, Donaldson SS. ABVD/MOPP and low-dose involved-field radiotherapy in pediatric Hodgkin's disease: The Stanford experience. ***J Clin Oncol*** 1994; 12: 2160-2166.
6. Sackmann-Muriel F, Zubizarreta P, Gallo G, Scopinaro M, Alderete D, Alfaro E, et al. Hodgkin's disease in children: results of a prospective randomized trial in a single institution in Argentina. ***Med Pediatr Oncol*** 1997; 29: 544-552.
7. Schellong G, Pötter R, Brämswig J, Wagner W, Prott FJ, Dörffel W, et al. High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: The German-Austrian multicenter trial DAL-HD-90. The German-Austrian Pediatric Hodgkin's Disease Study Group. ***J Clin Oncol*** 1999; 17: 3736-3744.

8. Landman-Parker J, Pacquement H, Leblanc T, Habrand JL, Terrier-Lacombe MJ, Bertrand Y, et al. Localized childhood Hodgkin's disease: response-adapted chemotherapy with etoposide, bleomycin, vinblastine, and prednisolone before low-dose radiation therapy-Results of the French Society of Pediatric Oncology study MDH90. ***J Clin Oncol*** 2000; 18: 1500-1507.
9. Donaldson SS, Hudson MM, Lamborn KR, Link MP, Kun L, Billett AL, et al. VAMP and low-dose, involved field radiation for children and adolescents with favorable, early -stage Hodgkin's disease: results of a prospective clinical trial. ***J Clin Oncol*** 2002; 20: 3081-3087.
10. Friedmann AM, Hudson MM, Weinstein HJ, Donaldson SS, Kun L, Tarbell NJ, et al. Treatment of unfavorable childhood Hodgkin's disease with VEPA and low-dose, involved field radiation. ***J Clin Oncol*** 2002; 20: 3088-3094.
11. Vecchi V, Pileri S, Burnelli R, Bontempi N, Comelli A, Testi AM, et al. Treatment of pediatric Hodgkin's disease tailored to stage, mediastinal mass, and age. ***Cancer*** 1993; 72: 2049-2057.
12. Hamilton VM, Norris C, Bunin N, Goldwein JW, Bunin GR, Lange B, et al. Cyclophosphamide-based, seven-drug hybrid and low-dose involved field radiation for the treatment of childhood and adolescent Hodgkin disease. ***J Pediatr Hematol Oncol*** 2001; 23: 84-88.
13. Hodgson DC, Hudson MM, Constine LS. Pediatric hodgkin lymphoma: maximizing efficacy and minimizing toxicity. ***Semin Radiat Oncol*** 2007; 17: 230-242.
14. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. ***Cancer Res*** 1971; 31: 1860-1861.
15. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. ***J Am Stat Assoc*** 1958; 53: 457-481.
16. Sackmann-Muriel F, Zubizarreta P, Gallo G, Scopinaro M, Alderete D, Alfaro E, et al. Hodgkin Disease in Children: Results of a prospective randomized trial in a single institution in Argentina. ***Med Pediatr Oncol*** 1997; 29: 544-552.
17. Büyükpamukçu M, Atahan L, Cağlar M, Kutluk T, Akyüz C, Hazar V. Hodgkin's disease in Turkish children: clinical characteristics and treatment results of 210 patients. ***Pediatr Hematol Oncol*** 1999; 16: 119-129.
18. Hesseling PB, Wessels G, Van Jaarsveld D, Van Riet FA. Hodgkin's disease in children in South Africa: epidemiological characteristics, morbidity and long term outcome. ***Ann Trop Paediatr*** 1997; 17: 367-373.
19. Lobo-Sanahuja F, García I, Barrantes JC, Barrantes M, Jiménez R, Argüello A. Pediatric Hodgkin's Disease in Costa Rica: Twelve year's experience of primary tretament by chemotherapy alone, without staging laparotomy. ***Med Pediatr Oncol*** 1994; 22: 398-400.
20. Stiller CA. What causes Hodgkin's disease in children? ***Eur J Cancer*** 1998; 34: 523-528.
21. Kennedy BJ, Fremgen AM, Menck RR. The National Cancer data base report on Hodgkin's disease for 1985-1989 and 1990-1994. ***Cancer*** 1998; 83: 1041-1047.
22. Devita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. ***Ann Int Med*** 1970; 73: 881-895.
23. Meadows AT, Obringer AC, Marrero O, Oberlin O, Robison L, Fossati-Bellani F, et al. Second malignant neoplasm following childhood Hodgkin's disease: treatment and splenectomy as risk factors. ***Med Pediatr Oncol*** 1989; 17: 477-484.
24. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et al. Breast cancer and other second neoplasm after childhood Hodgkin's disease. ***N Engl J Med*** 1996; 334: 745-751.
25. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with Adriamycin, Bleomycin, Vinblastine and Imidazole Carboxamide versus MOPP. ***Cancer*** 1975; 36: 252-259.
26. Bonadonna G, Valagussa P, Santoro A. Alternating non-cross resistant combination Chemotherapy or MOPP in Stage IV Hodgkin's disease. A Report of 8-year Results. ***Ann Intern Med*** 1986; 104: 739-746.


## Related topics

Al-Samawi AS, Aulaqi SM, Al-Thobhani AK. Childhood lymphomas in Yemen. Clinicopathological study. ***Saudi Med J*** 2009; 30: 1192-1196.

Al-Ashgar HI, Khan MQ, Ghamdi AM, Bamehriz FY, Maghfoor I. Gastrosplenic fistula in Hodgkin's lymphoma treated successfully by laparoscopic surgery and chemotherapy. ***Saudi Med J*** 2007; 28: 1898-900.

Tillawi IS. Primary pulmonary Hodgkin's lymphoma. A report of 2 cases and review of the literature. ***Saudi Med J*** 2007; 28: 943-948.

Yilmaz F, Uzunlar AK, Sogutcu N, Ozaydin M. Hodgkin's disease and association with Epstein-Barr virus in children in Southeast Turkey. ***Saudi Med J*** 2005; 26: 571-575.