Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJCBR

International Journal of Cancer and Biomedical Research

https://jcbr.journals.ekb.eg

The impact of omitting radiation in young adult females with Hodgkin's disease

Samah Semary, Emad Moussa, Asmaa Hamoda, Eman Nagib, Salma Abdel Aziz, Mahmoud Hamza, Madeha Elwakil and Mohamed Saad Zaghloul

EKB Egyptian Knowledge Bank بنك المعرفة المصري

PUBLISHED BY
EACR EGYPTIAN ASSOCIAN FOR CANCER RESEARCH
Since 2014

EGYPTIAN JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

The impact of omitting radiation in young adult females with Hodgkin's disease

Samah Semary[1,2], Emad Moussa[2,3], Asmaa Hamoda[2,4], Eman Nagib[5,6], Salma Abdel Aziz[7,8], Mahmoud Hamza[9], Madeha Elwakil[10,11] and Mohamed Saad Zaghloul[12,13]

[1]*Department of Oncology, Beni-Suef University, Beni-Suef, Egypt*
[2]*Department of Pediatric Oncology, Children Cancer Hospital Egypt*
[3]*Department of Clinical Oncology, Menufiya University, Cairo, Egypt*
[4 Department] *of Pediatric Oncology, National Cancer Institute, Cairo University, Cairo, Egypt*
[5]*Department of Pathology, National Cancer Institute, Cairo University, Cairo, Egypt*
[6]*Department of Pathology, Children Cancer Hospital Egypt, Cairo, Egypt*
[7]*Department of Nuclear Medicine, Children Cancer Hospital Egypt, Cairo, Egypt*
[8]*Department of Nuclear Medicine, National Cancer Institute, Cairo University, Cairo, Egypt*
[9]*Department of Clinical Research, Children Cancer Hospital Egypt, Cairo, Egypt*
[10]*Department of Radiodiagnosis, National Cancer Institute, Cairo University, Cairo, Egypt*
[11]*Department of Radiodiagnosis, Children Cancer Hospital Egypt, Cairo, Egypt*
[12]*Department of Radiotherapy, National Cancer Institute, Cairo University, Cairo, Egypt*
[13]*Department of Radiotherapy, Children Cancer Hospital Egypt, Cairo, Egypt*

ABSTRACT

Background: Ionizing radiation is a breast cancer risk factor. **Aim**: This retrospective study aims to compare the outcome of young adolescent females diagnosed with classic Hodgkin lymphoma who received chemotherapy with no radiotherapy to those who received chemotherapy followed by radiotherapy with the main goal to explore the impact of radiotherapy on the outcome and to record the late side effects of radiotherapy as well as the incidence of breast cancer. **Patients and Methods:** Young adolescent females (n=166) between 12 and 18 years old already diagnosed and treated with classic Hodgkin lymphoma were recruited from the Children's Cancer Hospital Egypt from July 2007 till the end of 2018. The no radiotherapy (RT) group (n=72 patients) received chemotherapy while omitting radiotherapy. The RT group (n=94 patients) received chemotherapy and radiotherapy. The 5-year OS in the two groups was 93% and 87%, respectively, and the 5-year EFS was 74% and 85%, respectively. **Results:** The initial stage and response to treatment using interim PET CT scans post-second cycle chemotherapy were documented. The outcomes were nearly identical in the no RT and RT groups. **Conclusion:** Omitting radiation therapy did not affect the 5-year EFS; nevertheless, the existence of positive B symptoms, an advanced stage initially, or a poor response to treatment all impacted the 5-year EFS.

Keywords: Breast cancer, Hodgkin lymphoma, Interim PET CT, Radiotherapy.

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/jcbr.2025.360082.1385

ARTICLE INFO

Article history
Received: February 12, 2025
Revised: March 03, 2025
Accepted: March 25, 2025

Correspondence to
Samah Semary, MD
Pediatric oncology, Clinical Oncology Department, Faculty of Medicine, Beni- Suef University, Children Cancer Hospital Egypt.
Email: samahsemary@yahoo.com

BACKGROUND

Classical Hodgkin lymphoma in children has a high curability exceeding 90%. However, long–term survivors are vulnerable to many late toxicities, including secondary cancers, infertility, and pulmonary and cardiovascular disease after chemo-radiotherapy (van Nimwegen FA et al., 2017). Radiotherapy is an effective treatment tool for classical Hodgkin lymphoma, as confirmed in many randomized and response adaptation trials (Wolden SL et al., 2012; Dörffel W et al., 2013). Childhood cancer survivors who are usually exposed to high-dose radiation to the chest at early ages experience an increased risk of breast cancer (Swerdlow AJ et al., 2000 and Bhatia S et al., 2003). Cumulative incidence increases with several factors, such as young age at initial treatment, radiation dose, radiation field size, and time elapsed from exposure to this modality of therapy. It is estimated that after 5–14 years of follow-up, those who were ≤ 20 years at diagnosis had a significantly higher risk of developing secondary breast cancer (De Bruin ML et al., 2009). Ten years of follow-up are needed to illustrate this increased risk of breast cancer, and it may persist up to 25 years of follow-up (Crump M, Hodgson D., 2009).

The average estimated radiation dose to the breast tissue varies considerably across these populations, ranging from 0.02 Sv to more than 20 Sv (Modan B et al., 1989; van Leeuwen FE et al., 2003). Childhood cancer survivors provide useful data on radiation-associated breast cancer, in particular, girls having Hodgkin lymphoma (HL) who received high-dose radiotherapy to the chest. For Hodgkin's lymphoma, particularly in children, the significant challenge is to tailor therapy to avoid not only overtreatment but

also undertreatment (Hasenclever D., 2002). Some studies showed no statistically significant difference in breast cancer risk between those diagnosed with HL in childhood, during puberty, or early adolescence (Modan B et al., 1989, Swerdlow AJ et al., 2000; Kenney LB et al., 2004). Several other reports on HL survivors showed the high risk of breast cancer among patients diagnosed before the age of 15 years (Wahner-Roedler DL et al., 2003). Konig et al. estimated the median absolute total risk for secondary breast cancer induction following mediastinal IMRT, using the Dasu model as 9.9% (range, 2.0–27.6%). Upon using proton beam therapy, this estimate percentage dropped to 4.5% (range, 0.0–15.5). Furthermore, the mortality risk from secondary breast cancer was estimated as 1.9% and 0.9% for IMRT and proton beam, respectively; this difference was statistically significant (König L et al.., 2020).

Our aim from this retrospective comparative study was to investigate whether, in patients with adequate response (Deauville ≤ 3) to iPET (interim PET) and morphological response after two cycles of ABVD, radiotherapy could be safely omitted and still maintain an excellent outcome while decreasing the potential for second breast cancer in female patients who are at the stage of formation and development of their breasts. The strategy of our practice is that the reduction of serious treatment-related complications can be displaced with minor reductions in treatment efficacy without affecting survival in such a salvageable disease as HL. Mauz-Körholz et al. have shown in a large prospective multinational study, including 1365 intermediate- and high-stage pediatric HL, that radiotherapy can safely be omitted in these patients who have an adequate response to a different chemotherapy induction regimen (OEPA) without jeopardizing the 5-year event-free survival or overall survival (Mauz-Körholz C et al., 2023). So, our study aim was to compare the outcome (overall survival, event-free survival) of females diagnosed and treated with classic Hodgkin lymphoma while omitting radiotherapy for fear of breast cancer with those who received radiotherapy to explore the impact of radiotherapy on the outcome of this group of patients and to assess the late side effects of this modality of therapy.

PATIENTS AND METHODS

This is a retrospective comparative study between 2 groups of patients; the no RT group includes young adolescent females aged 12-18 years old diagnosed and treated with classic Hodgkin lymphoma at the Children's Cancer Hospital-Egypt (57357 hospital) during the period from July 2007 till the end of December 2018, they all received chemotherapy (ABVD regimen), but no radiotherapy was administered due to concerns about subsequent breast cancer.

The RT group of female patients also aged 12-18 years old received chemotherapy and radiotherapy as treatment for classic Hodgkin lymphoma regardless of their response to chemotherapy after two cycles of ABVD (detected by interim PET). This was an earlier cohort of girls treated in the era of not adopting a response-based therapy.

All patients were clinically examined with full history taking and have undergone initial PET/CT scans for staging. Biopsies were taken for pathological confirmation of classic Hodgkin lymphoma, and interim PET/CT was done after two courses of chemotherapy (ABVD) to assess response to treatment.

The staging was done according to the Ann Arbor staging system. All patients received chemotherapy in the form of 4-6 cycles of ABVD (Adriamycin 25mg/m2 (day 1 and day 15), Bleomycin 10 units/m2 (day 1 and day 15), Vinblastine 6 mg/m2 (day 1 and day 15), and dacarbazine 375mg/m2 (day 1and day 15) according to their stage.

Our patients were divided into 3 stage groups: low risk (including stages IA and IIA without bulky disease); they were given four cycles of chemotherapy, followed by involved field radiation therapy, while intermediate risk (IIA bulky, IIB, IIIA) and High Risk (IIIB, IVA, IVB), were given six cycles of chemotherapy followed by involved field radiation therapy.

Although PET/CT assessment after two cycles of chemotherapy was done for all patients yet, we didn't adopt "response-based" therapy at that time, so all patients were assigned to radiation therapy except those with well-formed breasts or a large field to be exposed to radiation therapy, as determined by a radiation therapy specialist who refused to give those patients radiation after chemotherapy for fear of developing breast cancer.

Radiotherapy CT simulation was performed in all patients. Patients were immobilized with a thermoplastic mask with their arms by their sides. Each patient's clinical target volume (CTV) was delineated based on guidelines for involved field RT guided by initial PET/CT (Radford J et al., 2015). The clinical Target volume to planning target volume (CTV to PTV) Margins of 5–7 mm was added according to the departmental policy (Zaghloul MS et al., 2010). Patients were planned on the Monaco 6.1 treatment planning system (TPS) using either 3-dimensional conformal radiotherapy (3DCRT) or

volumetric modulated arc therapy (VMAT) ± voluntary deep inspiratory breath hold (DIBH) (Shaheen H et al., 2023). The treatment ranged between 1980 and 2520 cGy in 11- 14 fractions.

Statistical Analysis

We used the median and interquartile range (IQR) to report continuous variables, frequency, and percentage for categorical variables. We employed Fisher's exact test for categorical factors in descriptive tables. To account for small sample sizes within subgroups, we chose to group the subtypes "lymphocyte depleted classic Hodgkin lymphoma" and "Nodular Lymphocyte Rich classic Hodgkin lymphoma" from the pathology variable into the category "others." Furthermore, for the Hodgkin lymphoma stage, we combined stages 1 and 2 into the early-stage category and stages 3 and 4 into the advanced-stage category to facilitate statistical analysis. For survival analysis, overall survival was defined as death from any cause during the period from the date of diagnosis till the date of death or last follow-up. Event-free survival was defined as death, relapse, or secondary malignancy during the period from the date of diagnosis till the date of the event or lost follow-up. To compare survival curves, we used the log-rank test. We applied a multivariate Cox proportional hazards model to estimate hazard ratios (HR) for the variables included in our study. The "result of second PET CT" as a time-dependent covariate was included in our analysis. This variable allowed us to account for the time-varying effect of PET scan results on survival outcomes since PET CT is done a few weeks/months after the date of diagnosis, and the timing was variable between patients.

Ethics approval and consent to participate

All authors confirm that we obtained approval from the Council of Ethics for Scientific Research in The Children Cancer Hospital Egypt on 19/1/2023, with registration number 4/2023. The need for informed consent was waived by the ethics committee/IRB (The Council of Ethics for Scientific Research which is an organization accredited by Joint Commission International), it is a retrospective research article performed according to relevant guidelines and regulations to compare the outcome (overall survival, event-free survival) of females diagnosed and treated with classic Hodgkin lymphoma while omitting radiotherapy for fear of breast cancer with those who received radiotherapy to explore the impact of radiotherapy on the outcome of this group of patients and to assess the late side effects of this modality of therapy at Children Cancer Hospital Egypt (57357 hospital) during the period from July 2007 till the end of December 2018. We collected statistical data from the files of the patients who had written consent to follow the chemotherapy protocol for the treatment of pediatric classic Hodgkin lymphoma at Children Cancer Hospital Egypt.

RESULTS

A total of 166 female patients aged between 12 and 18 years old were diagnosed and treated with classic Hodgkin lymphoma at the Children's Cancer Hospital-Egypt (CCHE) during the period between July 2007 and the end of December 2018. Seventy-two patients (43.4%) received chemotherapy (risk-based) while omitting radiotherapy for fear of secondary breast cancer; 57 (79%) female patients were good responders, while 15 patients (21%) were poor responders at interim PET after two cycles of chemotherapy. In comparison, 94 patients (56.6%) received chemotherapy according to their risk status (risk-based), followed by radiotherapy regardless of the response to chemotherapy by interim PET. Sixty-five (69%) female patients were good responders, while 29 (31%) female patients were poor responders.

About 71% of all patients were diagnosed with nodular sclerosis classic Hodgkin lymphoma, while 22% were diagnosed with mixed cellularity classic Hodgkin lymphoma, Table 1. Sixty-six patients were considered low-risk patients (stage IA, IIA without bulky disease), 16 of them (22%) were in the no RT group 16/72, and 50 patients (53%) were in the RT group 50/94. Fifty-nine patients were considered high-risk patients (stage IIIB, IVA, or IVB); 39 of them (54%) were in the no RT group, while 20 patients (21%) were in the RT group, while the rest of the patients, 41 had the intermediate-risk disease (stages IIA bulky or stage IIB, IIIA), 17 patients (24%) were in the no RT group, and 24 patients (26%) were included in the RT group, Table1. PET CT scan was done for all patients at diagnosis and post-second cycle of chemotherapy; adequate responders were 122 (73%); 57 (46.7%) of them belong to the no RT group, while 65 patients belong to the RT group. Inadequate responders were 44 patients; 15 of them (21%) were in the no RT group, while 29 (31%) belonged to the RT group, Table 1.

We conducted a descriptive analysis of 166 patients, of whom 57% received radiotherapy. Most patients had either nodular sclerosis or mixed cellularity pathology, which accounts for 93% of all pathologies. Due to the small sample size within subgroups of the HL stage, we grouped patients into early and advanced stages; 26% of the "No radiotherapy" group were advanced stage compared to only 3.2%

Table 1. Patients' characteristics

Characteristic	N	Overall N = 166[1]	No radiotherapy, N = 72[1]	Radiotherapy, N = 94[1]	P-value
Age	166	15.00 (13.40, 16.17)	15.10 (13.80, 16.12)	14.80 (13.20, 16.17)	0.2
Pathology	166				0.7
Mixed Cellularity cHL		37 (22%)	17 (24%)	20 (21%)	
Nodular Sclerosis cHL		118 (71%)	49 (68%)	69 (73%)	
Others		11 (7%)	6 (8%)	5 (6%)	
Initial PET CT	166				>0.9
Negative		2 (1.2%)	1 (1.4%)	1 (1.1%)	
Not Done		11 (6.6%)	6 (8.3%)	5 (5.3%)	
Positive		153 (92%)	65 (90%)	88 (94%)	
Stage	166				
1A		7 (4.2%)	0 (0%)	7 (7.4%)	
1B		1 (0.6%)	0 (0%)	1 (1.1%)	
2A		58 (35%)	16 (22%)	42 (45%)	
2B		18 (11%)	7 (9.7%)	11 (12%)	0.001
3A		22 (13%)	10 (14%)	12 (13%)	
3B		23 (14%)	14 (19%)	9 (9.6%)	
4A		15 (9.0%)	6 (8.3%)	9 (9.6%)	
4B		22 (13%)	19 (26%)	3 (3.2%)	
Risk	166				
High risk		59 (36%)	39 (54%)	20 (21%)	
Intermediate risk		41 (25%)	17 (24%)	24 (26%)	0.006
Low risk		66 (40%)	16 (22%)	50 (53%)	
Chemotherapy cycles received	166				
4		52 (31%)	12 (17%)	40 (43%)	
5		1 (0.6%)	1 (1.4%)	0 (0%)	0.008
6		113 (68%)	59 (81.9%)	54 (57%)	
Result of interim PET CT	166				
Negative		122 (73%)	57 (79%)	65 (69%)	0.080
Positive		44 (27%)	15 (21%)	29 (31%)	
Vital status	166				
Alive		128 (77%)	57 (79%)	71 (76%)	
Dead		18 (11%)	9 (12%)	9 (9.6%)	0.7
Lost Follow Up		20 (12%)	6 (8.3%)	14 (15%)	
Performed BMT	166	9 (5.4%)	4 (5.6%)	5 (5.3%)	
[1]Median (IQR); n (%)					

in the radiotherapy group. At the same time, over 30% of the no-RT group were in the early stages compared to around 60% in the RT group. The advanced-stage patients were also more likely to be in the no RT group, with over 50% of the group being at high risk, while more than 50% of the RT group were at low risk. Furthermore, we found that the radiotherapy group had better results (better survival and lower mortality rates) but without statistical significance. Nine patients underwent bone marrow transplantation, and they were originally distributed between the "radiotherapy" and "No radiotherapy" groups. Twenty-three (13.8%) patients relapsed, 4 (17.4%) of whom were initially low-risk patients; one patient was not given radiation, and three patients were low-risk patients belonging to the radiotherapy group. Seven patients (35%) were in the intermediate risk group, 2 of them were in the no RT group, 5 of them were in the RT group, high-risk patients were 12 (52%), eight were in the no RT group, and four patients were in the RT group, Table 2.

The outcomes are nearly identical at the high-risk and the LR/IR risk groups separately. For the high-risk patients, 8/39 (20.5%) relapsed in the no RT group compared to 4/20 (20%) in the RT group. And for the LR/IR patients, 3/33 (9%) relapsed in the no RT group compared to 8/74 (11%) in the RT group, Table 1,2. This emphasizes that neither risk grouping nor radiation therapy had an impact on relapse.

Among the 23 patients who relapsed, 10 had positive interim PET CT (Inadequate responders), 70% of those who received radiotherapy but experienced relapse, and only 30% of those who didn't receive radiotherapy had relapse. On the other hand, for those who had a negative interim PET CT result (adequate responders), 38.5% and 61.5% experienced an event for those who had radiotherapy and those who did not, respectively, with a P-value of 0.07, Table 2. The multivariate Cox with time-dependent covariates for radiotherapy (event-free survival) were affected only by the presence of B-symptoms with significant P-value, Table 3.

Among the relapsed patients, nine patients relapsed early post first line of treatment, 6 (66.6%) patients were in the no RT group, 3 (33.3%) were in the RT group, the rest of the relapsed patients, 14 (61%) had late relapses, five were in the no RT group, and nine patients in the RT group, with no significant P-value, Table 2. Eight patients (35%) among the relapsed patients had autologous bone marrow transplantation; 5 of them were in the RT group, and only one patient experienced 2nd relapse post-auto bone marrow transplantation, Table 2.

Table 2. Analysis of the relapsed patients

Characteristic	N	Overall, N = 23[1]	No radiotherapy, N = 11[1]	Radiotherapy, N = 12[1]	P-value
Stage	23				
2A		4 (17%)	1 (9.1%)	3 (25%)	0.4
2B		4 (17%)	1 (9.1%)	3 (25%)	
3A		3 (13%)	1 (9.1%)	2 (17%)	
3B		5 (22%)	2 (18%)	3 (25%)	
4A		2 (8.7%)	1 (9.1%)	1 (8.3%)	
4B		5 (22%)	5 (45%)	0 (0%)	
Result of interim PET CT	23				0.070
Negative		13 (57%)	8 (73%)	5 (42%)	
Positive		10 (43%)	3 (27%)	7 (58%)	
Relapse type	23				0.4
Early Relapse		9 (39%)	6 (55%)	3 (25%)	
Late Relapse		14 (61%)	5 (45%)	9 (75%)	
Performed BMT	23	8 (35%)	3 (27%)	5 (42%)	0.3
Relapses after BMT	8	1 (12%)	0 (0%)	1 (20%)	>0.9
[1]n (%)					

Table 3. Multivariate Cox with time-dependent covariates for radiotherapy (event-free survival)

Characteristic	HR[1]	95% CI[1]	p-value
age_category			
10 – 15	—	—	
>15	1.78	0.86, 3.71	0.12
B.symptoms			
No	—	—	
Yes	3.03	1.40, 6.57	**0.005**
Early/Advanced_stage			
Early	—	—	
Advanced	1.91	0.83, 4.36	0.13
Interim PET CT			
	3.60	0.98, 13.3	0.054

[1]HR = Hazard Ratio, CI = Confidence Interval, [2]one-sided p-value for non-inferiority

For the overall survival (OS) outcome, at a follow-up of 56 months, 18 deaths occurred. Multivariate analysis showed that omitting radiotherapy reduces the hazard of all-cause mortality with a hazard ratio of 0.77. That is a 23% reduction in the mortality hazard when compared with patients having radiotherapy.

Multivariate Cox with time-dependent covariates for event-free survival, at a median follow-up of 52 months, showed that the total number of events was 32, and omitting radiotherapy appears to increase the hazard of events with a hazard ratio of 1.21. That is a 21% increase in the event hazard compared to non-omitting radiotherapy and holding all other variables constant. Both positive B symptoms and inadequate PET CT response increase the hazard of the event. However, only B symptoms are statistically significant at the 0.05 level, Table 3.

The 5 years overall survival among the group of patients who presented initially with early stage and those who presented with advanced stage were 96% and 85%, respectively, with a P-value of 0.016 (Supplementary Figure 1). In contrast, the 5 years overall survival for the patients who were presented with positive B symptoms and those without B symptoms were 81% and 96%, respectively, with a significant P-value of 0.011 (Supplementary Figure 2). The 5 years overall survival for patients who did not receive radiotherapy at the end of their protocol and patients who received radiotherapy after their chemotherapy protocol were 93% and 87%, respectively, but this was not statistically significant P-value, 0.37 (Supplementary Figure 3). Also, the 5 years overall survival for good responders versus poor responders detected by interim PET CT was 94% and 83%, respectively, with a P-value of 0.1 (Supplementary Figure 4). The 5-year event-free survival among the group of patients presented initially with an early and advanced stage was 89% and 71%, respectively (P-value =0.0061), figure 1. The 5-year event-free survival rates for patients with positive B symptoms and those without B symptoms were 64% and 90%, respectively (P-value=0.00017) (Supplementary Figure 5).

Figure 2 shows the 5-year event-free survival among good and poor responders to chemotherapy detected by interim PET CT: 88% and 61%, respectively (P-value = 0.0014). The 5-year event-free survival for patients who did not receive radiotherapy and those who received radiotherapy after their chemotherapy protocol were 74% and 85%, respectively (P-value =0.062).

DISCUSSION

A combined-modality approach in Hodgkin Lymphoma (HL) yields excellent response rates and event-free survival (EFS) (Mauz-Körholz C et al., 2015). Survivors of pediatric HL might suffer an increased risk of secondary malignancies,

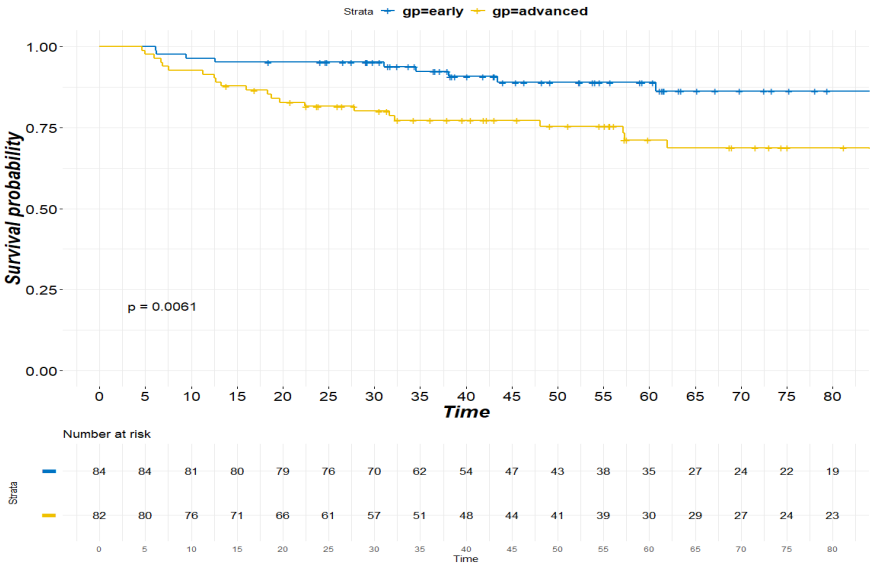

Figure 1. The three-year event-free survival among the group of patients presented initially with early or advanced stage is 92%, and 77%, respectively, and the 5 years event-free survival for them are 89%, and 71%, respectively, with significant P-values 0.0061.

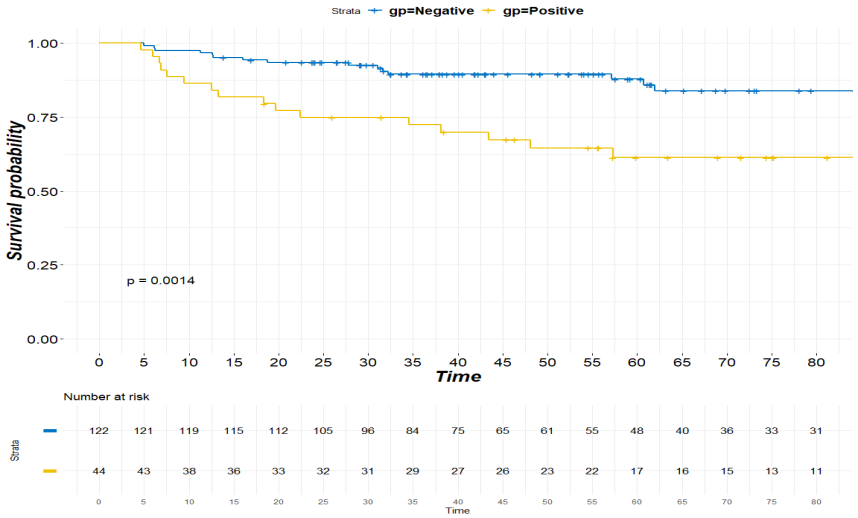

Figure 2. The three-year event-free survival among good and poor responders to chemotherapy detected by interim PET CT is 90% and 72%, respectively, and 5 years of event-free survival for them is 88% and 61%, respectively, with significant P-value 0.0014.

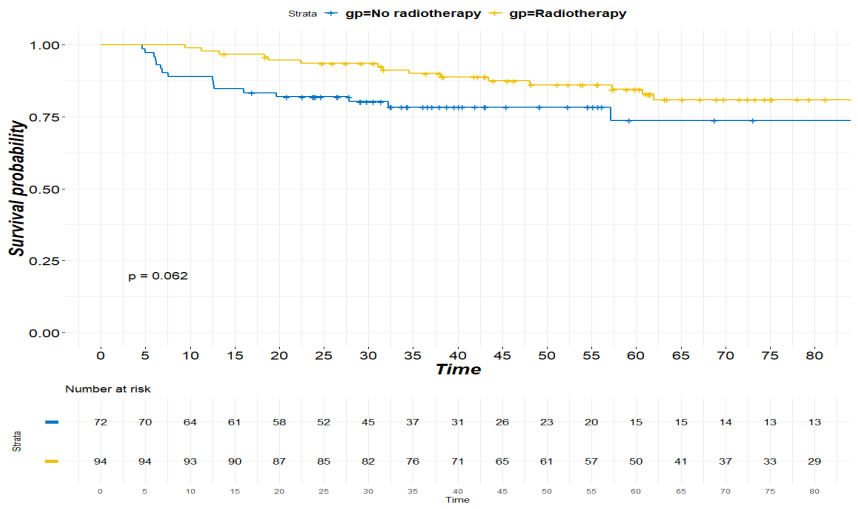

Figure 3. The five-year event-free survival among the patients who did not receive radiotherapy and who received radiotherapy post their chemotherapy protocol are 90%, and 78% respectively, and 5 years event event-free survival rates of 74%, and 85% respectively with P-value 0.062.

cardiovascular dysfunction, and endocrinopathies (Straus DJ., 2011, Mauz-Körholz C et al., 2015). The fine separation between achieving good survival rates and decreasing long-term toxicities necessitates the identification of patients who can be treated without radiotherapy (RT) and those who require intensified chemotherapy and/or RT. This is a question that has undergone long-term ongoing research literature.

In the current study, across several stages, our findings revealed that event-free survival did not improve for patients treated with radiation therapy when compared to those who did not get radiation therapy (Figure 3) (correlations were not statistically significant).

A Report from the Children's Oncology Group randomly assigned patients who achieved complete remission after chemotherapy to receive RT or no further therapy. The EFS was inferior without RT, although the OS did not differ significantly (Wolden SL et al., 2012). However, the whole cohort included those who may benefit from the omission of RT and others for whom RT may be essential management to get a higher therapeutic ratio.

The present study was planned to investigate if the omission of RT is safe when there is great fear of a higher incidence of secondary malignancy at the stage of physiological development of the female breast. It is well established that ionizing radiation is an important breast cancer risk factor (Bhatia S et al., 2003). Radiation therapy has been associated with an increased risk of secondary malignancies within the radiotherapy field, such as lung and breast cancers (Clarke CA et al., 2005, Mauz-Körholz C et al., 2015). Although the risk is low, chemotherapy alone also carries a risk of treatment-induced malignancies, usually hematologic (Mauz-Körholz C et al., 2015). Nevertheless, some reports indicate that chemotherapy may even be more carcinogenic as the rate of secondary malignancy remains the same despite the reduction in radiotherapy field and dosage (Aleman BM et al., 2003, Schaapveld M et al., 2015).

High incidence of breast cancer was reported as the highest absolute excess risk (AER) of 30.8 (per 10 000 person-years) even with a lower but still significant standardized incidence ratio of 4.4 (Hodgson DC et al., 2007; van Leeuwen FE et al., 2016). Efforts to reduce the risk of secondary cancer have led over time to reduce the radiation field to what is currently known as involved site irradiation or even omit radiotherapy in certain specific categories (Hoppe BS et al., 2015). Nevertheless, for early stages, reduced field or reduced-dose radiotherapy did not appear to markedly affect efficacy or secondary malignancy risk (Franklin J et al., 2017). However, the follow-up is relatively short to reach a confirmed conclusion. On the other hand, in more advanced stages of HL, there was insufficient evidence to determine the effect of chemotherapy intensification on secondary malignancy. These observations were consistent with long-term results of the HD2000 trial of advanced-stage HL comparing three different intensified regimes, where lower mortality rates resulting from secondary cancer were observed after treatment with a less aggressive regimen (ABVD) (Merli F et al.., 2016).

The risk of treatment-related secondary cancer increases with time from initial diagnosis and treatment as the DNA damage induced by chemotherapy and radiation takes more prolonged periods to manifest into a clinically significant entity. The implementation of 3D conformal RT (3D-CRT), intensity-modulated radiotherapy (IMRT), and proton therapy (PT), along with reduced field sizes and lower RT doses, might lead to a reduction in the risk of second malignancies, though not yet confirmed.

Our focus in this retrospective study was on those young adolescent females suffering from HL who received or didn't receive radiation therapy as a part of their treatment protocol. The decision to include RT near the breast (mediastinal and/or axillae) was left to our radiation oncologists. It is essential to state that the reluctance to include radiotherapy in HL regimens is based on outcomes from previous radiotherapy techniques and misguided data. Radiotherapy doses and field sizes have decreased over time, with most consolidative RT being prescribed 20-30 Gy with a field size only 1-2 centimeters beyond the original PET-positive disease. The new radiotherapy consensus guidelines for HL changed the radiation volume from the previous extended large-field radiotherapy (Mantle or total nodal irradiation) to a much smaller volume (involved nodal or involved site) (Franklin J et al., 2006). These smaller volumes were less likely to be associated with acute or chronic severe morbidity, including secondary breast malignancy. The most significant challenge for including radiotherapy in early-stage HL comes from the NCIC HD-6 trial, which reported decreased survival for patients who received radiotherapy; as an essential historical reference, this trial should not be used to guide current treatment recommendations as it reports on one of the oldest radiotherapy techniques for HL (extended field radiotherapy).[30] In addition, the observed decreased survival in the patient cohort that received radiotherapy can largely be attributed to causes of death unrelated to radiotherapy (Swerdlow AJ et al., 2011).

While 64.5% of our patients had low-stage/intermediate-stage disease with a relapse rate of 9% in the RT group compared to 11% in the no-RT group, 66% of the advanced-stage patients did not receive radiation therapy, 20.5% of them relapsed, and 33.8% of the advanced-stage patients received radiation therapy, but 20% of them relapsed also. Additionally, 31% of our patients in the RT group were poor responders and received radiotherapy, but about 24% of them relapsed, while 21% of our patients in the no RT group were poor responders, did not receive radiotherapy, and 20% of them relapsed, this finding may further confirm our belief in that the outcomes are nearly equal for those who had radiotherapy and those who did not.

The Children's Oncology Group trial AHOD0031 showed similar EFS with or without RT in patients whose PET showed rapid early response after chemotherapy (Friedman DL et al., 2014). Furthermore, the Euro-Net- PHL-C1 study treating 713 early-stage HL patients revealed that those who had an adequate response after 2 OEPA courses and did not receive radiotherapy (440 patients) had a 5-year EFS of 86·5% (95% CI 83·3–89·8). On the other hand, for the 273 patients achieving an inadequate response and receiving radiotherapy, the 5-year event-free Survival was 88·6% (95% CI 84·8–92·5) (Mauz-Körholz C et al., 2023). This higher 5-year EFS in the RT group, although they had an inadequate response to therapy at the beginning, may emphasize that radiotherapy is beneficial for the outcome, although it can be safely omitted.

Some of our drawbacks in this study are that we wished to have enough time and data to compare long-term side effects in both groups, but unfortunately, 12 years of follow-up period were not enough.

Although our study was somehow randomized, girls who were forbidden from radiation therapy were not based on their stage or response to therapy but purely on their breast maturation and the extensiveness of the field of radiation.

Our analysis tried to assess the value of radiotherapy in the patients diagnosed with Hodgkin lymphoma treated with combined modality therapy. The 5-year event-free survival rates for patients who did not receive radiotherapy and those who received radiotherapy post their chemotherapy protocol were 74%, and 85%, respectively (*P*-value=0.062). On the other hand, there was no statistical difference between the 5-year OS, which was 87% and 93% for those who received RT and those who did not, respectively, with a P-value of 0.37.

The 5-year event-free survival was affected by the presence of advanced-stage patients who presented with positive B symptoms, or who had poor responses to chemotherapy detected by interim PET CT, nullifying the effect of radiation in those patients as it was affected by the presentation initially (advanced stage, or positive B signs/ symptoms).

Our mean follow-up period of 56 months, though relatively short, observed none of our patients from those who received radiation to have breast cancer or second malignancy.

CONCLUSION

Omitting radiotherapy in young adolescent females (12-18 years old) diagnosed and treated with classic Hodgkin lymphoma received chemotherapy while radiation therapy did not affect the 5 years EFS or OS, but presence of positive B symptoms, advanced stage initially or had poor response to treatment affected the 5 years EFS regardless of receiving radiation or not.

STUDY LIMITATIONS

In this study, several limitations should be considered when interpreting the results. Firstly, non-inferiority studies require a larger sample size compared to conventional superiority trials. However, the number of events was 18 for overall survival and 32 for event-free survival. Furthermore, while there was a strong indication to include radiotherapy as a time-dependent covariate, the study focused on omitting radiotherapy, as opposed to radiotherapy, as a predictor for survival. This made it challenging to add radiotherapy as a time-dependent covariate without impacting the interpretation of coefficients and hypothesis testing. Thus, omitting radiotherapy was added as a time-independent covariate. Lastly, the arbitrary decision-making process for determining which patients should receive radiotherapy was a significant source of bias in the study. The decision was made on a case-by-case basis based on expert opinion. The expected patient's poor prognosis might have influenced radiotherapy allocation. Thus, it is essential to note these limitations when interpreting the findings of the study.

ACKNOWLEDGMENT

Great thanks and warmest gratitude to all department members in our hospital who helped and provided us with all we needed to work on the study cases effectively.

LIST OF ABBREVIATIONS

18F-FDG	Fluorine F 18-Fludeoxyglucose
ABVD	Doxorubicin-Bleomycin-Vinblastine-Dacarbazine
AER	Absolute excess risk
CCHE	Children's Cancer Hospital Egypt
CRT	Conformal radiotherapy
CTV	Clinical target volume
DCRT	Dimension conformal radiotherapy
DIBH	Deep inspirational breath holds
EFS	Event-Free Survival
HD	Hodgkin disease
HL	Hodgkin Lymphoma
HR	Hazard ratio
IFRT	Involved-Field Radiation Therapy
IMRT	Intensity-modulated radiotherapy
iPET	Interim Positron Emission Tomography
IQR	Interquartile range
NLPHL	Nodular lymphocytic predominant Hodgkin lymphoma
OEPA	Prednisolone, Etoposide, Vincristine, Doxorubicin
OS	Overall Survival
PT	Proton Therapy
PTV	Planning target volume
RT	Radiotherapy
TPS	Treatment planning system

REFERENCES

Aleman, B., van den Belt-Dusebout, A., Klokman, W., van 't Veer, M., Bartelink, H., & van Leeuwen, F. (2003). Long-term cause-specific mortality of patients treated for Hodgkin's disease. Journal of Clinical Oncology, 21(18), 3431–3439.

Bhatia S, Yasui Y, Robison LL, Birch JM, Bogue MK, Diller L, DeLaat C, Fossati-Bellani F, Morgan E, Oberlin O, Reaman G, Ruymann FB, Tersak J, and Meadows AT. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol. 2003;21:4386–4394.

Christine Mauz-Körholz, Judith Landman-Parker, Walentyna Balwierz, Roland A Ammann, Richard A Anderson, Andische Attarbaschi, Jörg M Bartelt, Auke Beishuizen, Sabah Boudjemaa, Michaela Cepelova, Alexander Claviez, Stephen Daw, Karin Dieckmann, Ana Fernández-Teijeiro, Alexander Fosså, Stefan Gattenlöhner, Thomas Georgi, Lisa L Hjalgrim, Andrea Hraskova, Jonas Karlén, Regine Kluge, Lars Kurch, Thiery Leblanc, Georg Mann, Francoise Montravers, Jean Pears, Tanja Pelz, Vladan Rajić, Alan D Ramsay, Dietrich Stoevesandt, Anne Uyttebroeck, Dirk Vordermark, Dieter Körholz, Dirk Hasenclever, William Hamish Wallace. Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and an adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study. Lancet Oncol 2023; [24: 252–61].

Christine Mauz-Körholz, Monika L Metzger, Kara M Kelly, Cindy L Schwartz, Mauricio E Castellanos, Karin Dieckmann, Regine Kluge, Dieter Körholz.: Pediatric Hodgkin lymphoma. J Clin Oncol 33:2975-2985, 2015

Clarke CA, Glaser SL, Keegan TH, and Stroup A (2005) *Neighborhood socioeconomic status and Hodgkin's lymphoma incidence in California. Cancer Epidemiol Biomarkers Prev 14(6): 1441-1447, 2005.*

Crump M, Hodgson D. Secondary breast cancer in Hodgkin's lymphoma survivors. J Clin Oncol. 2009 Sep 10;27(26):4229-31.

David C Hodgson, Ethel S Gilbert, Graça M Dores, Sara J Schonfeld, Charles F Lynch, Hans Storm, Per Hall, Froydis Langmark, Eero Pukkala, Michael Andersson, Magnus Kaijser, Heikki Joensuu, Sophie D Fosså, Lois B Travis. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol*. 2007; 25:1489-1497.

Debra L Friedman, Lu Chen, Suzanne Wolden, Allen Buxton, Kathleen McCarten, Thomas J FitzGerald, Sandra Kessel, Pedro A De Alarcon, Allen R Chen, Nathan Kobrinsky, Peter Ehrlich, Robert E Hutchison, Louis S Constine, Cindy L Schwartz: Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: A report from the Children's Oncology Group Study AHOD0031. J Clin Oncol 32:3651-3658, 2014.

Flora E van Leeuwen, Willem J Klokman, Marilyn Stovall, Ellen C Dahler, Mars B van't Veer, Evert M Noordijk, Mariad A Crommelin, Berthe M P Aleman, Annegien Broeks, Mary Gospodarowicz, Lois B Travis, Nicola S Russell. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's Disease. J Natl Cancer Inst. 2003;95:971–980.

Francesco Merli, Stefano Luminari, Paolo G Gobbi, Nicola Cascavilla, Caterina Mammi, Fiorella Ilariucci, Caterina Stelitano, Maurizio Musso, Luca Baldini, Sara Galimberti, Francesco Angrilli, Giuseppe Polimeno, Potito Rosario Scalzulli, Angela Ferrari, Luigi Marcheselli, Massimo Federico. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV- CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. *J Clin Oncol*. 2016;34:1175-1181.

Franklin J, Pluetschow A, Paus M, Specht L, Anselmo AP, Aviles A, Biti G, Bogatyreva T, Bonadonna G, Brillant C, Cavalieri E, Diehl V, Eghbali H, Ferme C, Henry-Amar M, Hoppe R, Howard S, Meyer R, Niedzwiecki D, Pavlovsky S, Radford J, Raemaekers J, Ryder D, Schiller P, Shakhtarina S, Valagussa P, Wilimas J, and Yahalom J*: Second malignancy risk associated with the treatment of Hodgkin's lymphoma: Meta-analysis of the randomized trials. Ann Oncol 17(12): 1749-1760, 2006*

Hasenclever D. The disappearance of prognostic factors in Hodgkin's disease. Ann Oncol 2002; 13 (suppl 1): 75–78

Hoppe BS, Hoppe RT. Expert radiation oncology interpolations of involved-site radiation therapy guidelines in the management of Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys*. 2015; 92:40-45.

Jeremy Franklin 1, Dennis A Eichenauer, Ingrid Becker, Ina Monsef, Andreas Engert. Optimization of chemotherapy and radiotherapy for untreated

Hodgkin lymphoma patients concerning second malignant neoplasms, overall and progression-free survival: individual participant data analysis. *Cochrane Database Syst Rev*. 2017;9:CD008814

John Radford, Tim Illidge, Nicholas Counsell, Barry Hancock, Ruth Pettengell, Peter Johnson, Jennie Wimperis, Dominic Culligan, Bilyana Popova, Paul Smith, Andrew McMillan, Alison Brownell, Anton Kruger, Andrew Lister, Peter Hoskin, Michael O'Doherty, Sally Barrington. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015;372(17):1598–607.

Kenney LB, Yasui Y, Inskip PD, Hammond S, Neglia JP, Mertens AC, Meadows AT, Friedman D, Robison LL, and Diller L. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med. 2004;141:590–597

König L, Haering P, Lang C, Splinter M, von Nettelbladt B, Weykamp F, Hoegen P, Lischalk JW, Herfarth K, Debus J, and Hörner-Rieber J. Secondary Malignancy Risk Following Proton vs. X-ray Treatment of Mediastinal Malignant Lymphoma: A Comparative Modeling Study of Thoracic Organ-Specific Cancer Risk. Front Oncol. 2020 Jul 7;10:989.

Marie L De Bruin, Judith Sparidans, Mars B van't Veer, Evert M Noordijk, Marieke W J Louwman, Josée M Zijlstra, Hendrik van den Berg, Nicola S Russell, Annegien Broeks, Margreet H A Baaijens, Berthe M P Aleman, Flora E van Leeuwen: Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol. 2009, 27 (26): 4239-4246. 10.1200/JCO.2008.19.9174.

Mauz-Körholz C, Landman-Parker J, Fernández-Teijeiro A, Attarbaschi A, Balwierz W, Bartelt JM, Beishuizen A, Boudjemaa S, Cepelova M, Ceppi F, Claviez A, Daw S, Dieckmann K, Fosså A, Gattenlöhner S, Georgi T, Hjalgrim LL, Hraskova A, Karlén J, Kurch L, Leblanc T, Mann G, Montravers F, Pears J, Pelz T, Rajić V, Ramsay AD, Stoevesandt D, Uyttebroeck A, Vordermark D, Körholz D, Hasenclever D, Wallace WH, and Kluge R. Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study. Lancet Oncol. 2023 Mar; 24(3):252-261.

Michael Schaapveld, Berthe M P Aleman, Anna M van Eggermond, Cécile P M Janus, Augustinus D G Krol, Richard W M van der Maazen, Judith Roesink, John M M Raemaekers, Jan Paul de Boer, Josée M Zijlstra, Gustaaf W van Imhoff, Eefke J Petersen, Philip M P Poortmans, Max Beijert, Marnix L Lybeert, Ina Mulder, Otto Visser, Marieke W J Louwman, Inge M Krul, Pieternella J Lugtenburg, Flora E van Leeuwen. Second cancer risk up to 40 years after treatment for Hodgkinś lymphoma. *N Engl J Med*. 2015; 373:2499-2511.

Modan B, Chetrit A, Aldandary E, and Katz L. Increased risk of breast cancer after low-dose irradiation. Lancet. 1989;8639:629–631. doi: 10.1016/S0140-6736(89)92140-5

Shaheen H, Zaghloul MS, Ammar H, Aly B, Hassanin E, Mohsen SA, and Ahmed S. Voluntary deep inspiration breath-hold with volumetric modulated arc therapy in pediatric patients with mediastinal Hodgkin lymphoma. Future Oncol. 2023 Mar 15.

Straus DJ: Long-term survivorship at a price: Late-term, therapy-associated toxicities in the adult Hodgkin lymphoma patient. Ther Adv Hematol 2:111-119, 2011

Suzanne L Wolden, Lu Chen, Kara M Kelly, Philip Herzog, Gerald S Gilchrist, John Thomson, Richard Sposto, Marshall E Kadin, Raymond J Hutchinson, James Nachman. Long-term results of CCG 5942: a randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma--a report from the Children's Oncology Group. J Clin Oncol 2012; 30: 3174–80.

Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, Horwich A, Lister TA, and Linch DC. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol. 2000;18:498–509.

Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, Hoskin PJ, Lister TA, Radford JA, Rohatiner AZ, and Linch DC*: Second cancer risk after chemotherapy for Hodgkin's lymphoma: A collaborative British cohort study. J Clin Oncol 29(31): 4096-4104, 2011*.

van Leeuwen FE, Ng AK. Long-term risk of second malignancy and cardiovascular disease after Hodgkin lymphoma treatment. *Hematology Am Soc Hematol Educ Program*. 2016;2016:323-330.

Van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood 2017; 129: 2257–65.

Wahner-Roedler DL, Nelson DF, Croghan IT, Achenbach SJ, Crowson CS, Hartmann LC, O'Fallon WM. Risk of breast cancer and breast cancer characteristics in women treated with supradiaphragmatic radiation for Hodgkin lymphoma: Mayo Clinic experience. Mayo Clin Proc. 2003;78:708–715.

Wolden SL, Chen L, Kelly KM, et al.: Long-term results of CCG 5942: A randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma—A report from the Children's Oncology Group. J Clin Oncol 30:3174-3180, 2012.

Wolfgang Dörffel, Ursula Rühl, Heike Lüders, Alexander Claviez, Marion Albrecht, Jos Bökkerink, Harald Holte, Jonas Karlen, Georg Mann, Heinz Marciniak, Felix Niggli, Kjeld Schmiegelow, Ernst-Wilhelm Schwarze, Richard Pötter, Lutz Wickmann, Günther Schellong: Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: final results of the multinational trial GPOH-HD95. J Clin Oncol 2013; 31: 1562–68.

Zaghloul MS, Mousa AG, Eldebawy E, Attalla E, Shafik H, Ezzat S. Comparison of electronic portal imaging and cone beam computed tomography for position verification in children. Clin Oncol (R Coll Radiol). 2010; 22(10):850-61.