



# Consolidative mediastinal radiotherapy for advanced-stage classical Hodgkin lymphoma with bulky disease in patients who achieve complete response after chemotherapy in PET-CT era

Marcelo Junqueira Atanazio , Fernanda Maria Santos, Amanda Duran, Ana Carolina Arrais Maia, Lucas Bassolli Alves, Rodrigo Dolphini Velasques, Vanderson Rocha, Valeria Buccheri

Instituto do Cancer do Estado de São Paulo, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

## ABSTRACT

**Background:** The role of consolidation mediastinal radiotherapy (RT) for mediastinal bulky disease in advanced-stage classical Hodgkin lymphoma (cHL) is controversial in the positron emission tomography/computed tomography (PET-CT) era.

**Materials and methods:** We reviewed the medical charts of patients with advanced-stage (clinical stage IIX-IVX) cHL and mediastinal bulky that achieved a complete response after first line chemotherapy treatment between August 2010 and December 2020 and compared the results of those who received with those who did not receive consolidation mediastinal RT. Inclusion criteria required PET-CT imaging for staging and response assessment.

**Results:** We included 115 patients; 91 received mediastinal RT and 24 did not. Patient's characteristics were balanced between the two groups. The median age in patients that received and did not receive mediastinal RT was 28 years and 24.5 years, respectively. Median International Prognostic Score among patients that received and did not receive mediastinal RT was 2 and 2.5, respectively. Disease free survival (DFS) was statistically better in patients that received mediastinal RT ( $p = 0.013$ ). Two-year DFS for patients that received and did not receive mediastinal RT was 95.2% [95% confidence interval (95% CI): 87.6-98.2%] and 76.4% (95% CI: 52.2-89.4%), respectively. Overall survival (OS) was not different between the two groups ( $p = 0.617$ ). In multivariate analysis, not receiving mediastinal radiotherapy and only achieving partial response (vs. complete response) after 2 cycles of chemotherapy were factors predictive of lower DFS.

**Conclusion:** DFS, but not OS, was superior in patients that received mediastinal RT.

**Key words:** radiotherapy; Hodgkin's lymphoma; positron emission tomography

*Rep Pract Oncol Radiother* 2022;27(5):856-862

## Introduction

The role of consolidation radiotherapy for mediastinal bulky disease in advanced-stage classical Hodgkin lymphoma (cHL) is controversial. Prior to the advent of positron emission tomogra-

phy/computed tomography (PET-CT), consolidation radiotherapy (RT) to advanced-stage cHL was recommended for patients with bulky disease [1] — including mediastinal Bulky [2] — and in those who did not achieve complete remission after chemotherapy [3].

**Address for correspondence:** Marcelo Junqueira Atanazio, MD, Division of Hematology, Transfusion Medicine and Cell Therapy, Hospital das Rua, Av. Dr. Enéas Carvalho de Aguiar, 255, Zip code: 05403-000, São Paulo, Brazil, tel: + 55 11 2661-9575; e-mail: marcelojatanazio@gmail.com

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially

Functional imaging with PET-CT has proven to be superior to computed tomography in staging and assessing the response to treatment in cHL [4], and has become standard of care in cHL. For post-therapy evaluations its sensitivity and specificity ranged from 0.50 to 1.00 and 0.67 to 1.00, respectively [5]. With a more sensitive method for detecting active disease, the role of consolidation radiotherapy in complete remission must be revisited.

Two recent prospective trials evaluated consolidation RT in advanced-stage cHL with large masses in the PET era. Both found no benefit to patients randomized to RT [6, 7]. However, these studies did not exclusively evaluate patients with mediastinal bulky disease.

Mediastinal bulky disease poses specific challenges in cHL. Some authors have reported that mediastinal bulky may be associated with a different biology [8]. Besides, long term side effects of radiotherapy may be more harmful to the mediastinum than it is to other sites due to a toxic effect on the heart, lungs and breast tissue [9].

Therefore, in order to better understand the impact of mediastinal RT on survival we analyzed the outcomes of patients with advanced-stage cHL and mediastinal bulky who achieved complete response after first-line chemotherapy and compared the results of those who received and those who did not receive consolidation mediastinal RT.

## Materials and methods

### Study design

This is a retrospective single-center study, conducted at the Institute of Cancer of São Paulo (ICESP), University of São Paulo, a public tertiary referral hospital specialized in cancer treatment in Brazil. With almost 500 beds, it is the largest cancer hospital in this country.

The study was approved by the local Research Ethics Committee and, as it was retrospective, informed consent was not sought.

### Study population and definitions

This study enrolled patients diagnosed with stage II, III or IV cHL and mediastinal bulky that achieved a complete response after first line chemotherapy treatment, confirmed by PET, between August 2010 and December 2020.

Inclusion criteria required histopathological confirmation of cHL according to the World Health Organization classification and PET imaging for lymphoma staging and response assessment.

We excluded patients who were not treated with BEACOPP or ABVD regimen, who were HIV positive, who did not achieve a complete response to chemotherapy and who received mediastinal RT for reason other than treatment consolidation (eg. radiotherapy for oncological emergencies). Those with nodular lymphocyte predominant Hodgkin lymphoma were not enrolled.

Patients were staged according to the Ann Arbor system [10]. Mediastinal bulky was defined as a mass of > 35% of the transthoracic diameter [11].

Response to treatment was evaluated with PET-CT after 2–4 cycles of treatment and complete remission (CR) was defined as complete metabolic response, according to the five-point Deauville score criteria (scores 1–3) [12].

Disease free survival (DFS) was defined as the time interval from chemotherapy completion to disease relapse or death, whichever came first. Overall survival (OS) was stipulated as the time interval from diagnosis to death from any cause.

### Data collection

Data was collected retrospectively from electronic and physical records. The information collected consisted of baseline, first-line treatment characteristics and follow-up data.

Clinical data were entered into *Research Electronic Data Capture* (REDCap) electronic data capture tools hosted at the University of São Paulo [13].

### Treatment of the study population

Patients were either diagnosed at our center or had their biopsy specimen reassessed by our pathologists. All patients received 2-deoxy-2-[(18)F]fluoro-d-glucose PET-CT for initial staging, bone marrow biopsy was not done routinely.

Patients were treated with either 6–8 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). After 2 treatment cycles, an interim PET-CT study was performed. Patients with partial remission (Deauville score 4 or 5) underwent another PET-CT after 4 treatment cycles.

Refractory disease was defined as one of the following: positive PET (Deauville score 4 or 5) after 4 treatment cycles, progressive disease (Deauville score 5) after 2 or 4 treatment cycles or relapsing within 3 months of treatment completion. Node or organ biopsy were required to confirm refractoriness. Patients with refractory disease were excluded from this study.

In our center standard care for patients with mediastinal bulky and complete remission (Deauville score 1–3 PET after 2 or 4 treatment cycles) is undergoing mediastinal RT. Reasons for not receiving mediastinal RT were: bleomycin pulmonary toxicity, ongoing infection or concerns about radiotherapy side effects.

After treatment completion patients were followed with medical evaluation, hemogram and erythrocyte sedimentation rate assays every 3 to 6 months for 5 years and annually after that. PET-CT and biopsy were done if relapse disease was suspected.

Second line chemotherapy was done with ifosfamide, gemcitabine and vinorelbine. Chemosensitive patients underwent autologous stem cell transplant. Maintenance was not used.

### Statistical analysis

Differences between patients that received and did not receive mediastinal RT were examined by the Mann-Whitney test for continuous variables and the Chi-square test for categorical ones.

DFS and OS was calculated using the Kaplan–Meier method and the log-rank test was used in the comparison. Associations between covariates with DFS were assessed using Cox's proportional hazards model. Univariate analyzes were initially performed. All variables significant at a  $p < 0.20$  in univariate analyses were considered as possible predictor variables for the multivariable analyses with application of the stepwise forward method. The criterion for entry into the model was significance at a  $p < 0.20$  and the criterion for remaining in the model was significance at a  $p < 0.05$ . In these analyzes, originally quantitative variables were dichotomized according to cutoff points based on the literature. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit statistic. Listwise exclusion was used for Cox regression models. All test assumptions were checked as required.

Statistical significance was defined as  $p < 0.05$  and all statistical analyses and graphs were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## Results

Between August 2010 and December 2020, 173 patients with cHL, clinical stage II–IV and mediastinal bulky were diagnosed and treated at our center. Data from the 129 (89.1%) patients that achieved a complete remission were collected with 115 remaining after exclusion. The reasons for exclusions were: one patient was HIV-positive, 12 were not staged with PET-CT, one patient was treated with other chemotherapy protocol and one patient underwent radiotherapy prior to chemotherapy due to superior vena cava syndrome.

### Baseline patient characteristics

Patient characteristics are summarized in Table 1. Baseline patient characteristics were balanced between the two treatment groups. The median age of patients that received and did not receive mediastinal RT were 28 years (range 16–76 years) and 24.5 years (range 16–58 years), respectively. The most common histopathologic subtypes were nodular sclerosing followed by mixed cellularity. Clinical stage was II, III and IV was found in 46 (40.0%), 30 (26.1%) and 39 (33.9%) patients, respectively. Median International Prognostic Score among patients that received and did not receive mediastinal RT was 2 and 2.5, respectively.

Regarding laboratory findings at cHL diagnosis, hemoglobin concentration was lower than 10.5 g/dL in 30 (33.0%) and 8 (33.3%) patients that received and did not receive mediastinal RT, respectively. Albumin concentration was lower than 4.0 g/dL in 69 (78.4%) and 17 (70.8%) patients that received and did not receive mediastinal RT, respectively.

### Treatment characteristics

Chemotherapy protocol was escalated BEACOPP in 11 (9.5%), baseline BEACOPP in 1 (0.9%) and ABVD in 103 (89.6%) patients. Ninety-one (79.1%) received mediastinal RT as consolidation therapy. Median time between last chemotherapy completion and radiotherapy initiation was 37.5 days. Mean and median radiotherapy doses were

**Table 1.** Patients characteristics (n = 115)

Characteristics	No mediastinal radiotherapy (n = 24)	Mediastinal radiotherapy (n = 91)	p-value
<b>Gender</b>			
Male	5 (20.8)	37 (40.7)	0.096
<b>Age at diagnosis [years]</b>			
< 45	22 (91.7)	81 (89.0)	1.000
≥ 45	2 (8.3)	10 (11.0)	
<b>B symptoms</b>			
No	7 (29.2)	22 (24.2)	0.606
Yes	17 (70.8)	69 (75.8)	
<b>Clinical stage</b>			
Stage II or III	13 (54.2)	63 (69.2)	0.225
Stage IV	11 (45.8)	28 (30.8)	
<b>International Prognostic Score</b>			
0–2	12 (50.0)	46 (50.6)	1.000
3–7	12 (50.0)	45 (49.4)	
<b>Chemotherapy protocol</b>			
ABVD	22 (91.7)	81 (89.0)	1.000
BEACOPP	2 (8.3)	10 (11.0)	
<b>Hemoglobin concentration [g/dL]</b>			
N	24	91	0.191
Mean/Median	10.9/10.8	11.4/11.40	
Range	7.6–13.3	5.5–15.4	
<b>Leukocytes [10<sup>3</sup>/mm<sup>3</sup>]</b>			
N	24	91	0.912
Mean/Median	13.3/11.2	12.0/11.5	
Range	5.5–41.2	4.1–34.6	
<b>Lymphocytes (10<sup>3</sup>/mm<sup>3</sup>)</b>			
N	24	91	0.888
Mean/Median	1.6/1.4	1.4/1.2	
Range	0.5–4.1	0.2–5.0	
<b>Platelets [10<sup>3</sup>/mm<sup>3</sup>]</b>			
N	24	91	0.853
Mean/Median	422/400	419/399	
Range	222–854	181–911	
<b>Erythrocyte sedimentation rate [mm/h]</b>			
N	17	82	0.016
Mean/Median	76.6/84	54.0/46.5	
Range	7–139	4–125	
<b>Albumin [g/dL]</b>			
N	24	88	0.493
Mean/Median	3.6/3.7	3.5/3.6	
Range	2.0–4.5	2.0–4.6	

ABVD — doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP — bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone

30.3 Gy and 30.6 Gys (range 20.0–36.6 Gy), respectively. All patients received involved-field Radiation therapy.

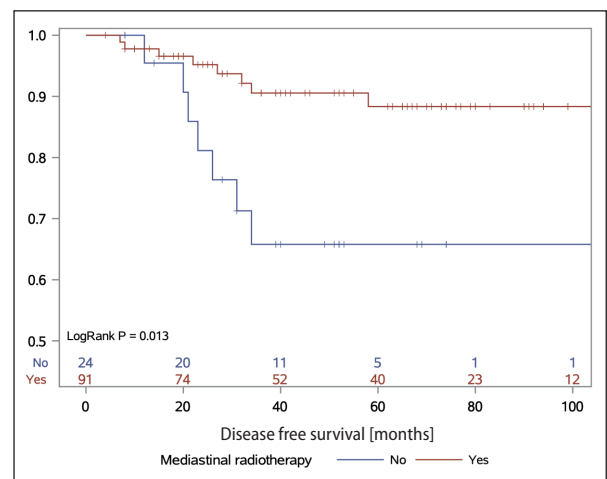
### Progression free and overall survival

The median follow-up was 52.0 months (range 4–120 months). Median DFS and OS were not reached.

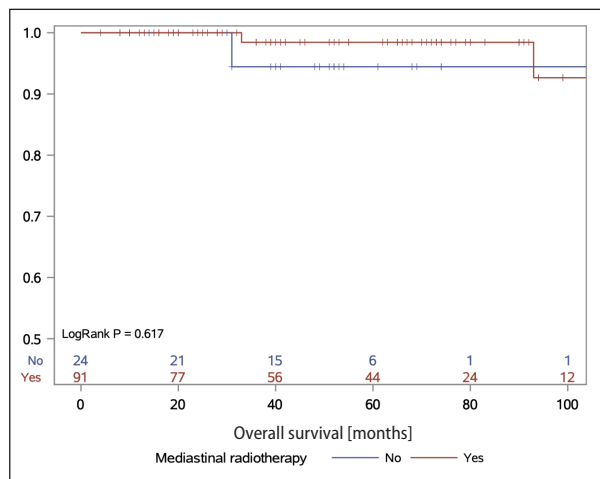
Two-year and 5-year DFS for the whole cohort were 92.1% [95% confidence interval (95% CI): 84.8–95.9%] and 83.1% (95% CI: 73.2–89.6%), respectively. DFS was statistically better in patients that received mediastinal RT (p = 0.013). Two-year DFS for patients that received and did not receive mediastinal RT was 95.2% (95% CI: 87.6–98.2%) and 76.4% (95% CI: 52.2–89.4%), respectively. Five-year DFS for patients that received and did not receive mediastinal RT was 88.3% (95% CI: 77.6–94.1%) and 65.8% (95% CI: 41.1–82.1%), respectively (Fig. 1).

During follow-up, 3 patients that received mediastinal RT died. The causes of death were respiratory insufficiency due to progressive disease, COVID-19 infection during rescue chemotherapy and metastatic breast cancer. One patient that did not receive mediastinal RT died, the cause of death could not be ascertained. He was in remission from cHL for 31 months. OS was not different between the two groups (p = 0.617) (Fig. 2).

Tables 2 shows univariate and multivariate cox regression analysis for DFS. In multivariate analysis, not receiving mediastinal RT [hazard ratio



**Figure 1.** Progression free survival rates stratified by receiving or not receiving mediastinal radiotherapy. Y axis has been modified so that tick marks start at 0.5



**Figure 2.** Overall survival rates stratified by receiving or not receiving mediastinal radiotherapy. Y axis has been modified so that tick marks start at 0.5

(HR): 6.07; 95% CI: 1.83–20.21] and achieving partial response after 2 cycles of chemotherapy (HR: 6.53; 95% CI: 1.90–22.48) were factors predictive of lower DFS.

### Discussion

This retrospective study aimed to investigate the impact of mediastinal RT on survival of advanced-stage cHL with mediastinal Bulky disease that achieved complete remission after chemotherapy in the PET era. We found that DFS, but not OS, was superior in patients that received mediastinal RT. To analyze the impact of RT in advanced-stage cHL with large nodal masses is not an easy task. Differences in definitions of advanced-stage lymphoma and bulky size make it difficult to compare results between studies. Thereby, the role of RT in advanced-stage cHL is yet to be determined.

Studies, prior to the PET era, comparing RT to no further treatment showed mixed results. Aleman et al. randomized 421 patients that achieved complete remission to chemotherapy (MOPP-ABV) to RT or no further treatment. No overall benefit from RT was observed; in patients with bulky, nodular sclerosing cHL, however, the relapse-free survival rate was significantly higher after RT [13]. An Indian study evaluated patients diagnosed with early-stage and advanced-stage cHL that achieved complete response after 6 cycles of ABVD. Those randomized to RT had an eight-year event-free survival of 88% vs. 76% (p = 0.01) in the no-further-treatment arm. Eight-year OS was 100% in the RT group vs. 89% (p = 0.002) in the no-further-treatment arm. Subset analysis showed that addition of RT improved outcomes in patients with age < 15 years, B symptoms, advanced stage, and bulky disease [2].

Two recent studies in the PET era that evaluated RT in advanced-stage cHL with large masses are worth mentioning. The phase 3 GITIL HD0607 study randomized 296 patients who had nodal masses larger than 5 cm at baseline and achieved PET negativity with ABVD, to RT or no further treatment. The authors found no differences between RT and no further treatment [6]. The FIL HD0801 trial published recently also investigated that role of RT in patients who achieved complete response to ABVD and a nodal mass larger than 5 cm. This study also found no benefit to patients randomized to RT. At 2 years, Intention-to-treat analysis showed DFS was 91.3% vs. 85.8% (p = 0.7) in patients randomized to RT and no further treatment, respectively [7].

The two aforementioned studies have an important difference from our study; they are not restricted to patients with mediastinal bulky. In our opin-

**Table 2.** Univariate and multivariate analysis of factors associated with progression free survival

Variables	Category	Reference	Univariate analysis		Multivariate analysis	
			HR (95% CI)	p-value	HR (95% CI)	p-value
International Prognostic Score	0 – 2	3 – 7	1.38 (0.51–3.76)	0.524	–	–
Mediastinal radiotherapy	No	Yes	3.21 (1.19–8.65)	0.015	6.07 (1.83–20.21)	0.018
Interim response after 2 cycles	Partial response	Complete response	3.19 (1.15–8.81)	0.018	6.53 (1.90–22.48)	< 0.001
B symptoms	Yes	No	2.71 (0.62–11.93)	0.170	–	–
Chemotherapy protocol	ABVD	BEACOPP	4.20 (0.43–40.72)	0.201	–	–

HR — hazard ratio; CI — confidence interval; ABVD — doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP — bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone



ion, mediastinal bulky disease cannot be analyzed in conjunction with bulky disease at other sites for three main reasons.

The first reason is that mediastinal bulky disease may be associated with a different biology than non-mediastinal bulky cHL. In diffuse large B-cell lymphoma disease site reflects its biology and prognosis [15]. Primary mediastinal B-cell lymphoma, which shows a better prognosis if compared to other aggressive B-cell lymphomas, has unique clinical and biological features [16]. Large mediastinal disease in cHL may suggest a link between Primary Mediastinal B-cell Lymphoma and mediastinal bulky cHL. Many molecular similarities between these two lymphomas have been described [17].

The second reason is that mediastinal bulky disease may be associated with a different prognosis and, therefore, RT may have a different impact in the mediastinum that it has at other sites. Qi et al. retrospectively studied 814 advanced-stage cHL patients to evaluate the significance of Bulky disease. Patients with mediastinal bulky had more favorable characteristics than non-bulky or non-mediastinal Bulky in terms of age, histology, and bone marrow involvement. Besides, mediastinal bulky was associated with better OS than non-bulky or non-mediastinal Bulky on univariable analysis (5-year OS, 92% vs. 86%; HR: 0.53; 95% CI: 0.34–0.84;  $p = 0.007$ ). The authors concluded that mediastinal bulky was associated with more favorable disease characteristics and improved survival, and suggested that maybe is associated with a more favorable biology [8]. Phan et al. evaluated the role of RT in 118 patients with stage III cHL. Those who received RT had better survival than those who did not. On multivariate analysis, mediastinal RT was associated with improved DFS ( $p = 0.003$ ) and OS ( $p = 0.029$ ). The pattern of failure analysis showed that most failures (23 of 28) occurred above the diaphragm. The authors concluded that consolidative RT after CR may benefit patients with initial disease above the diaphragm, whereas below-the-diaphragm disease seems to be well managed by chemotherapy alone [18].

The third reason is that mediastinal RT may have important long term side effects. In an extensive retrospective cohort of 1,474 Hodgkin lymphoma patients, mediastinal RT significantly increased the risks of myocardial infarction, congestive heart disease and valvular disease (2- to 7-fold) [19]. Su-

pra-diaphragmatic radiation was also associated with breast cancer in a cohort of 653 female patients treated at the Mayo Clinic [20].

Our study is subject to important limitations. As in our center standard of care is to perform mediastinal RT, it is possible that patients who did not receive mediastinal RT were more fragile or somehow different from patients that received RT. We tried to mitigate this possible bias by excluding HIV-positive patients, patients who did not achieve a complete response and patients who were not treated with ABVD or BEACOPP regimen. Retrospective studies are subject to selection bias and this may have affected our results. Despite that, to the best of our knowledge, this is the first study that focuses on the role of mediastinal RT on outcomes of advanced-stage cHL in the PET era.

Despite the small sample size, based on our findings, our study suggests that mediastinal RT can improve DFS in patients with advanced-stage cHL with mediastinal bulky. These data need to be confirmed with a prospective trial. However, as OS was not improved, until more data are available, the decision to perform mediastinal RT must be individualized. An old frail patient that cannot tolerate a second line treatment and stem cell transplantation may benefit from RT. A young female patient who is at high risk of breast cancer probably would not. Clinicians should be aware that understanding risk factors for relapse and RT long term effects are of utmost importance for decision making in this setting.

## Conclusion

In conclusion, we found that patients with advanced stage cHL that receive consolidative mediastinal radiotherapy have better DFS. But, as OS was not improved, clinicians and radiation oncologists must approach the issue on a case-by-case basis. Prospective data with larger samples are needed to understand the real role of RT in advanced-stage cHL with mediastinal bulky.

## Conflict of interest

The authors state that they have no conflict of interests

## Funding

None declared.

## References

- Johnson PWM, Sydes MR, Hancock BW, et al. Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLGLY09 randomized controlled trial (ISRCTN97144519). *J Clin Oncol.* 2010; 28(20): 3352–3359, doi: [10.1200/JCO.2009.26.0323](https://doi.org/10.1200/JCO.2009.26.0323), indexed in Pubmed: [20498402](https://pubmed.ncbi.nlm.nih.gov/20498402/).
- Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? *J Clin Oncol.* 2004; 22(1): 62–68, doi: [10.1200/JCO.2004.01.021](https://doi.org/10.1200/JCO.2004.01.021), indexed in Pubmed: [14657226](https://pubmed.ncbi.nlm.nih.gov/14657226/).
- Aleman BMP, Raemaekers JMM, Tomišić R, et al. European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys.* 2007; 67(1): 19–30, doi: [10.1016/j.ijrobp.2006.08.041](https://doi.org/10.1016/j.ijrobp.2006.08.041), indexed in Pubmed: [17097834](https://pubmed.ncbi.nlm.nih.gov/17097834/).
- Zinzani PL, Fanti S, Battista G, et al. Predictive role of positron emission tomography (PET) in the outcome of lymphoma patients. *Br J Cancer.* 2004; 91(5): 850–854, doi: [10.1038/sj.bjc.6602040](https://doi.org/10.1038/sj.bjc.6602040), indexed in Pubmed: [15266320](https://pubmed.ncbi.nlm.nih.gov/15266320/).
- Terasawa T, Nishihashi T, Hotta T, et al. 18F-FDG PET for post-therapy assessment of Hodgkin's disease and aggressive Non-Hodgkin's lymphoma: a systematic review. *J Nucl Med.* 2008; 49(1): 13–21, doi: [10.2967/jnumed.107.039867](https://doi.org/10.2967/jnumed.107.039867), indexed in Pubmed: [18077527](https://pubmed.ncbi.nlm.nih.gov/18077527/).
- Gallamini A, Rossi A, Patti C, et al. Consolidation Radiotherapy Could Be Safely Omitted in Advanced Hodgkin Lymphoma With Large Nodal Mass in Complete Metabolic Response After ABVD: Final Analysis of the Randomized GITIL/FIL HD0607 Trial. *J Clin Oncol.* 2020; 38(33): 3905–3913, doi: [10.1200/JCO.20.00935](https://doi.org/10.1200/JCO.20.00935), indexed in Pubmed: [32946355](https://pubmed.ncbi.nlm.nih.gov/32946355/).
- Ricardi U, Levis M, Evangelista A, et al. Role of radiotherapy to bulky sites of advanced Hodgkin lymphoma treated with ABVD: final results of FIL HD0801 trial. *Blood Adv.* 2021; 5(21): 4504–4514, doi: [10.1182/bloodadvances.2021005150](https://doi.org/10.1182/bloodadvances.2021005150), indexed in Pubmed: [34597375](https://pubmed.ncbi.nlm.nih.gov/34597375/).
- Qi S, Milgrom S, Dabaja B, et al. Two distinct prognostic groups in advanced-stage Hodgkin lymphoma revealed by the presence and site of bulky disease. *Blood Adv.* 2020; 4(9): 2064–2072, doi: [10.1182/bloodadvances.2019001265](https://doi.org/10.1182/bloodadvances.2019001265), indexed in Pubmed: [32396621](https://pubmed.ncbi.nlm.nih.gov/32396621/).
- Benveniste MF, Gomez D, Carter BW, et al. Radiation Effects in the Mediastinum and Surroundings: Imaging Findings and Complications. *Semin Ultrasound CT MR.* 2016; 37(3): 268–280, doi: [10.1053/j.sult.2015.11.002](https://doi.org/10.1053/j.sult.2015.11.002), indexed in Pubmed: [27261350](https://pubmed.ncbi.nlm.nih.gov/27261350/).
- Cheson BD, Fisher RI, Barrington SF, et al. Alliance, Australasian Leukaemia and Lymphoma Group, Eastern Cooperative Oncology Group, European Mantle Cell Lymphoma Consortium, Italian Lymphoma Foundation, European Organisation for Research, Treatment of Cancer/Dutch Hemato-Oncology Group, Grupo Español de Médula Ósea, German High-Grade Lymphoma Study Group, German Hodgkin's Study Group, Japanese Lymphoma Study Group, Lymphoma Study Association, NCIC Clinical Trials Group, Nordic Lymphoma Study Group, Southwest Oncology Group, United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014; 32(27): 3059–3068, doi: [10.1200/JCO.2013.54.8800](https://doi.org/10.1200/JCO.2013.54.8800), indexed in Pubmed: [25113753](https://pubmed.ncbi.nlm.nih.gov/25113753/).
- Lee C, Bloomfield C, Goldman A, et al. Prognostic significance of mediastinal involvement in Hodgkin's disease treated with curative radiotherapy. *Cancer.* 1980; 46(11): 2403–2409, doi: [10.1002/1097-0142\(19801201\)46:11<2403::aid-cn-cr2820461116>3.0.co;2-9](https://doi.org/10.1002/1097-0142(19801201)46:11<2403::aid-cn-cr2820461116>3.0.co;2-9), indexed in Pubmed: [7438015](https://pubmed.ncbi.nlm.nih.gov/7438015/).
- Biggi A, Gallamini A, Chauvie S, et al. International validation study for interim PET in ABVD-treated, advanced-stage Hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. *J Nucl Med.* 2013; 54(5): 683–690, doi: [10.2967/jnumed.112.110890](https://doi.org/10.2967/jnumed.112.110890), indexed in Pubmed: [23516309](https://pubmed.ncbi.nlm.nih.gov/23516309/).
- Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; 42(2): 377–381, doi: [10.1016/j.jbi.2008.08.010](https://doi.org/10.1016/j.jbi.2008.08.010), indexed in Pubmed: [18929686](https://pubmed.ncbi.nlm.nih.gov/18929686/).
- Aleman BMP, Raemaekers JMM, Tirelli U, et al. European Organization for Research and Treatment of Cancer Lymphoma Group. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med.* 2003; 348(24): 2396–2406, doi: [10.1056/NEJMoa022628](https://doi.org/10.1056/NEJMoa022628), indexed in Pubmed: [12802025](https://pubmed.ncbi.nlm.nih.gov/12802025/).
- Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016; 127(20): 2375–2390, doi: [10.1182/blood-2016-01-643569](https://doi.org/10.1182/blood-2016-01-643569), indexed in Pubmed: [26980727](https://pubmed.ncbi.nlm.nih.gov/26980727/).
- Dunleavy K. Primary mediastinal B-cell lymphoma: biology and evolving therapeutic strategies. *Hematology Am Soc Hematol Educ Program.* 2017; 2017(1): 298–303, doi: [10.1182/asheducation-2017.1.298](https://doi.org/10.1182/asheducation-2017.1.298), indexed in Pubmed: [29222270](https://pubmed.ncbi.nlm.nih.gov/29222270/).
- Roschewski M, Phelan JD, Wilson WH. Molecular Classification and Treatment of Diffuse Large B-Cell Lymphoma and Primary Mediastinal B-Cell Lymphoma. *Cancer J.* 2020; 26(3): 195–205, doi: [10.1097/PPO.0000000000000450](https://doi.org/10.1097/PPO.0000000000000450), indexed in Pubmed: [32496453](https://pubmed.ncbi.nlm.nih.gov/32496453/).
- Phan J, Mazloom A, Abboud M, et al. Consolidative radiation therapy for stage III Hodgkin lymphoma in patients who achieve complete response after ABVD chemotherapy. *Am J Clin Oncol.* 2011; 34(5): 499–505, doi: [10.1097/COC.0b013e3181f477a8](https://doi.org/10.1097/COC.0b013e3181f477a8), indexed in Pubmed: [21537149](https://pubmed.ncbi.nlm.nih.gov/21537149/).
- Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood.* 2007; 109(5): 1878–1886, doi: [10.1182/blood-2006-07-034405](https://doi.org/10.1182/blood-2006-07-034405), indexed in Pubmed: [17119114](https://pubmed.ncbi.nlm.nih.gov/17119114/).
- Wahner-Roedler DL, Nelson DF, Croghan IT, et al. 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(6): 708–715, doi: [10.4065/78.6.708](https://doi.org/10.4065/78.6.708), indexed in Pubmed: [12934780](https://pubmed.ncbi.nlm.nih.gov/12934780/).