Benefit of radiation therapy in stage III-IV Hodgkin lymphoma after chemotherapy

ประโยชน์ของการฉายรังสีในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดฮอดจ์กินระยะลุกลามหลังรักษาด้วยเคมีบำบัด

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Abstract

Background: The benefit of radiation therapy as a consolidation therapy after chemotherapy in advanced-stage Hodgkin lymphoma remains controversial, especially after the widespread use of positron emission tomography (PET)/computed tomography (CT) or Ga-67 scintigraphy.

Objective: We conducted a retrospective review in our institute to evaluate the benefit of consolidative radiotherapy in patients who received a modern chemotherapy regimen.

Materials and methods: Between January 2010 and December 2019, 33 patients with newly diagnosed stage III or IV Hodgkin lymphoma were identified from the Chulabhorn Hospital database. After excluding 15 patients who did not meet our inclusion criteria (1 HIV infection, 5 early-stage after reviewed, 5 did not used PET-CT or Ga-67 scintigraphy and 4 with incomplete medical history), the remaining 18 patients were enrolled.

Results: After a median follow-up of 48 months, the 3-year disease-free survival rate was 66.7% in patients who received radiation therapy, versus 55.6% in patients who did not receive radiation therapy ($p = 0.391$). The 3-year overall survival rate was 100% in both groups. In total, 11 patients (61%) had complete metabolic response (CMR) after first-line chemotherapy, whereas three (16.7%), one (5.6%), and three (16.7%) had a partial response, stable disease, and disease progression, respectively. Seven patients (38.9%) experienced relapse after treatment, and 71.4% of relapses occurred at the original disease site. Of 7 patients who had residual after first-line chemotherapy, three received further radiotherapy whereas four did not. Relapse occurred in all four patients who did not received radiotherapy after residual disease. No patients who achieved CMR in both the interim and post-treatment evaluations experienced relapse. Four of nine patients with bulky masses more than 7 cm in size had CMR after first-line chemotherapy. Interestingly, in this group, no relapse occurred in patients who did not receive radiation therapy, whereas one of three patients (33.3%) who received radiation therapy exhibited relapse. No grade 3–4 acute radiation toxicities occurred in this study, but two of nine patients (22.2%) had grade 3 late pneumonitis that required hospitalization. No secondary malignancy was observed.

Conclusion: Using functional imaging as an evaluation method, consolidation radiation therapy may not be necessary in advanced Hodgkin lymphoma.

Keywords: Bulky disease, Consolidation radiation therapy, Hodgkin lymphoma, Modern chemotherapy

บทคัดย่อ

หลักการและเหตุผล: ประโยชน์ของการฉายรังสีในมะเร็งต่อมน้ำเหลืองฮอดจ์กินระยะลุกลามหลังเคมีบำบัดยังไม่เป็นที่สรุปแน่ชัดโดยเฉพาะในยุคที่มีการใช้ PET/CT หรือ Ga-67อย่างแพร่หลาย

วัตถุประสงค์: เพื่อศึกษาประโยชน์ของการฉายรังสีในผู้ป่วยมะเร็งต่อมน้ำเหลืองฮอดจ์กินระยะลุกลามหลังได้รับเคมีบำบัดยุคปัจจุบัน

วัสดุและวิธีการ: ศึกษาผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งต่อมน้ำเหลืองฮอดจ์กินระยะสามและสี่ในโรงพยาบาลจุฬาภรณ์ย้อนหลังระหว่างปี พ.ศ.2553 ถึง 2562 จำนวน 33 ราย ผู้ป่วย 15 รายถูกคัดออก (1 มีเชื้อHIV, 5 เป็นระยะเริ่มต้น, 5 ไม่ได้ทำ PET/CT หรือ Ga-67 และ4ประวัติไม่ครบถ้วน) คงเหลือผู้ป่วย 18 ราย

ผลการศึกษา: ที่ค่ามัธยฐานระยะเวลาติดตาม 48 เดือน อัตราการควบคุมโรคที่ 3 ปีเท่ากับร้อยละ 66.7 ในกลุ่มที่ได้รับการฉายรังสี และร้อยละ 55.6 ในผู้ป่วยที่ไม่ได้รับ (p = 0.391) อัตราการรอดชีวิตที่ 3 ปีเป็นร้อยละ 100 ทั้งสองกลุ่ม ผู้ป่วย 11 ราย (ร้อยละ 61) ตอบสนองต่อเคมีบำบัดอย่างสมบูรณ์ 3 ราย (16.7%) ตอบสนองบางส่วน 1 ราย (5.6%) ไม่เปลี่ยนแปลง และ 3 ราย (16.7%)มีโรคลุกลาม มีผู้ป่วย 7 ราย (38.9%) ที่พบการกลับเป็นซ้ำของโรค โดยร้อยละ 71.4% ของการกลับเป็นซ้ำเกิดที่ตำแหน่งเดิมของโรคก่อนรักษา ในผู้ป่วย 7 รายที่มีรอยโรคเหลือหลังรับยาเคมีบำบัด 4 ใน 7 รายที่ไม่ได้รับการฉายรังสีมีการกลับเป็นซ้ำทั้งหมด ไม่พบการกลับเป็นซ้ำในผู้ป่วยที่ตอบสนองอย่างสมบูรณ์ทั้งในระหว่างและหลังรับยาเคมีบำบัด ผู้ป่วย 4ใน9 รายที่มีก้อนขนาดใหญ่มากกว่า 7 ซม.มีการตอบสนองอย่างสมบูรณ์ ผู้ป่วย 1 รายที่ไม่ได้รับการฉายรังสีในกลุ่มนี้ไม่พบการกลับเป็นซ้ำ ในขณะที่ผู้ป่วย 1 ใน 3 รายที่ได้รับการฉายรังสีมีการกลับเป็นซ้ำ (33.3%) ไม่พบพิษจากรังสีระยะเฉียบพลันระดับ3-4 แต่มีผู้ป่วย 2 รายเกิดพิษของรังสีเรื้อรังระดับ 3 ในปอดและจำเป็นต้องรักษาในโรงพยาบาล ไม่พบมะเร็งทุติยภูมิในการศึกษานี้

ข้อสรุป: การฉายรังสีในผู้ป่วยมะเร็งต่อมน้ำเหลืองฮอดจ์ระยะลุกลามอาจไม่มีความจำเป็น หากผู้ป่วยได้รับการประเมินการตอบสนองด้วย PET/CT หรือ Ga-67

คำสำคัญ: การฉายรังสี, เคมีบำบัดยุคปัจจุบัน, มะเร็งต่อมน้ำเหลืองชนิดฮอดจ์กิน, รอยโรคขนาดใหญ่

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1. Introduction

Hodgkin lymphoma is a relatively rare disease, comprising only 0.4% of newly diagnosed cancers globally in 2020[1]. However, its incidence is increasing in adolescents and young adults, and it is one of the most common malignancies in this patient group. Hodgkin lymphoma has a bimodal age distribution with two peaks at 25–34 and 60–70 years. Moreover, the incidence also differs by geographic location and ethnicity[2].

The treatment paradigm for Hodgkin lymphoma depends on the stage of the disease. In early-stage disease (stage I–II), the standard treatment is combined chemotherapy and radiation therapy. In comparison, the mainstay of advanced-stage treatment is systemic chemotherapy with or without radiation therapy and autologous stem cell transplantation. The development of intense systemic chemotherapy has substantially improved survival in patients with stage III–IV Hodgkin lymphoma, including an estimated 5-year survival rate of up to 80%–90% and a complete metabolic response (CMR) rate of 60-70% in recent decades[3,4,5,6].

Although chemotherapy is considered the primary treatment for advanced-stage Hodgkin lymphoma, the role of radiation therapy as a consolidation therapy for bulky disease and after partial remission after chemotherapy remains controversial. Many randomized studies and meta-analyses recorded conflicting results[4,7].

In the UK Lymphoma Group study[5], patients with advanced-stage (stage III–IV or early-stage disease with systemic symptoms or bulky disease) were randomly assigned to receive the ABVD regimen or two multidrug regimens (ChIVPP/PABIOE or hybrid ChIVPP/EVA). Radiation therapy was recommended for patients with initial bulky disease or incomplete responses to chemotherapy. The analysis revealed that consolidation radiation therapy significantly improved progression-free and overall survival[6]. In another prospectively randomized multicenter trial[3], despite an improvement of the freedom from treatment failure rate in patients who received radiation therapy, the benefit was limited to only patients who had residual disease after chemotherapy, whereas patients with bulky disease after a complete response to chemotherapy experienced no benefit.

Moreover, previous clinical trials did not use 18F-fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) as the standard imaging modality for staging and treatment response monitoring. The German Hodgkin Study Group HD 15 study was one of the earliest clinical trials that used 18F-fluorodeoxyglucose PET/CT to guide the use of radiation therapy[8]. In this study, consolidation radiation therapy (30 Gy) was delivered only in patients with a positive 18F-fluorodeoxyglucose PET/CT scan and a residual mass greater than 2.5 cm in size on CT. Only 4.5% of patients with negative 18F-fluorodeoxyglucose PET/CT scans who did not receive consolidation radiation therapy experienced disease progression or relapse.

With conflicting results concerning the benefits of consolidation radiation therapy, especially after the widespread use of 18F-fluorodeoxyglucose PET/CT in the modern era, and concerns about increasing the risk of late radiation-induced toxicity and secondary malignancy, we conducted a retrospective review in our institute to analyze whether consolidation radiation therapy is beneficial in patients with advanced-stage Hodgkin lymphoma, particularly after a complete response to modern chemotherapy regimens, among patients who underwent 18F-fluorodeoxyglucose PET/CT.

2. Materials and Methods

2.1. Patient selection

The medical records of patients newly diagnosed with stage III or IV Hodgkin lymphoma between January 2010 and December 2019 were identified from our hospital database. This trial was approved by the ethics committee of Chulabhorn Hospital, Bangkok, Thailand (Ethical number was EC086/2563)

The eligibility criteria were as follows: age of 15–70 years, diagnosed with previously untreated stage III or IV Hodgkin lymphoma according to the Lugano classification, a follow-up time of at least 2 years and at least one evaluation by 18F-fluorodeoxyglucose PET/CT or Ga-67 scintigraphy during treatment with chemotherapy. Patients with other cancers excluding nonmelanoma skin cancer or cervical carcinoma in situ were excluded. Patients with nodular lymphocyte predominant histology and HIV infection were also excluded.

According to our protocol, the first-line chemotherapy regimen consists of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD regimen) for 6 cycles. Because there was no clear protocol of adapted treatment guide using interim response before 2017, not all of patients who had residual disease after 2-4 cycles of ABVD received more intense chemotherapy regimen at that time.

Radiotherapy was considered in patients who had bulky mass more than 7 cm or residual disease after first-line chemotherapy treatment. In patients who received radiotherapy, we used either IMRT/VMAT or 3DCRT technique. A dose ranges between 30-46 Gy was given in daily fraction of 1.8-2.0 Gy. We assessed the response of treatment using the International Working Group consensus response evaluation criteria in lymphoma. All PET/CT scan or Ga-67 scintigraphs were centrally reviewed by the tumor board conference. The Deauville score of 4 and 5 was considered positive.

2.2. Statistical analysis

The primary endpoint was disease-free survival, which was defined as the time from diagnosis to disease progression. The secondary endpoints were overall survival, the pattern of relapse, and the complete response rate. Overall survival was defined as the time from diagnosis to death or last follow-up. The pattern of relapse

was categorized as in-field relapse or out-field relapse in patients who received radiation therapy. Complete response was defined as the disappearance of all detectable evidence of disease as evaluated by CT or negativity on PET/CT or Ga-67 scintigraphy even if post-treatment residual disease was detected by CT.

Survival outcomes were analyzed using the Kaplan–Meier method. The pattern of relapse and the complete response rate were determined using descriptive statistics and presented as percentages. Patients were divided into two groups based on the receipt of consolidation radiation therapy. Differences between the groups were compared using the Fisher's exact test, and an independent-samples t-test. Disease-free survival and overall survival were compared between groups using the log-rank test. Univariate analysis was analyzed using Cox regression model to retrieve the hazard ratio (HR), 95% confidence interval, and p-value. $p < 0.05$ denoted significance. Analyses was conducted with the use of Stata/SE 16.1 software (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Patient characteristics

In total, 33 patients with newly diagnosed stage III or IV Hodgkin lymphoma were identified from the Chulabhorn Hospital database. After excluding 15 patients who did not meet our inclusion criteria (1 was diagnosed with HIV infection, 5 were early-stage after reviewed, 5 did not used PET-CT or Ga-67 scintigraphy and 4 with incomplete medical history), the remaining 18 patients were enrolled (**Figure 1**). The mean age at diagnosis was 38.28 ± 20.63 years (range, 17–77), and five patients (27.8%) were older than 45 years. One-third of patients had an International Prognostic Score of 0–1. The majority of patients had mixed cellularity and a nodular sclerosis subtype (55.6% and 22.2%, respectively). Epstein–Barr virus infection was only tested in six patients, three of whom were positive, including two patients in the radiation therapy arm and one patient who did not receive radiation therapy (**Table 1**). All patients received complete radiation therapy and chemotherapy treatment as planned.

3.2. Outcomes

After a median follow-up of 48 months (range, 6–94 months), the 3-year disease-free survival rate was 66.7% among patients who received radiation therapy, versus 55.6% among patients who did not receive radiation therapy ($p = 0.391$). The 3-year overall survival rate was 100% in both groups (**Figure 2**). In univariate analysis, no factor significantly affected disease-free survival in this study (**Table 2**).

After complete treatment with first-line chemotherapy, all patients were evaluated response by functional imaging. Of all the 18 patients 11 (61%) had a CMR after first-line chemotherapy regimen, whereas 3 (16.7%), 1 (5.6%), and 3 (16.7%) had a partial response,

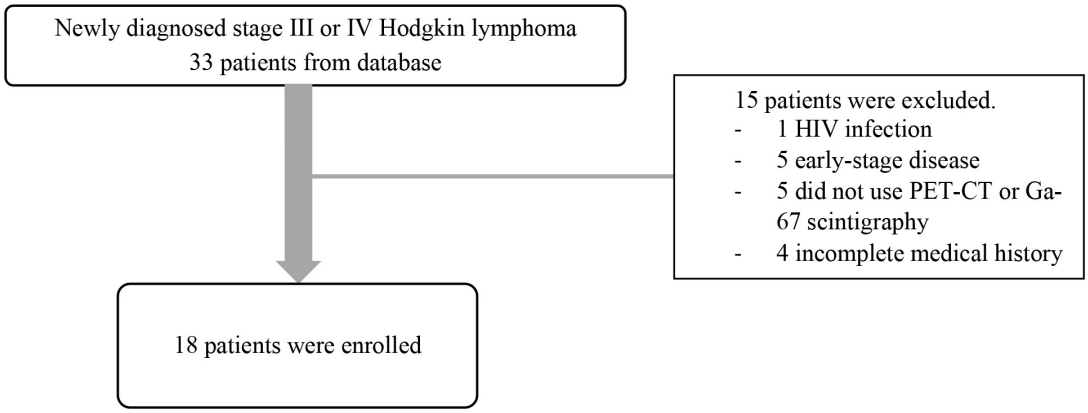


Figure 1. Consort diagram

Table 1. Patients' characteristics

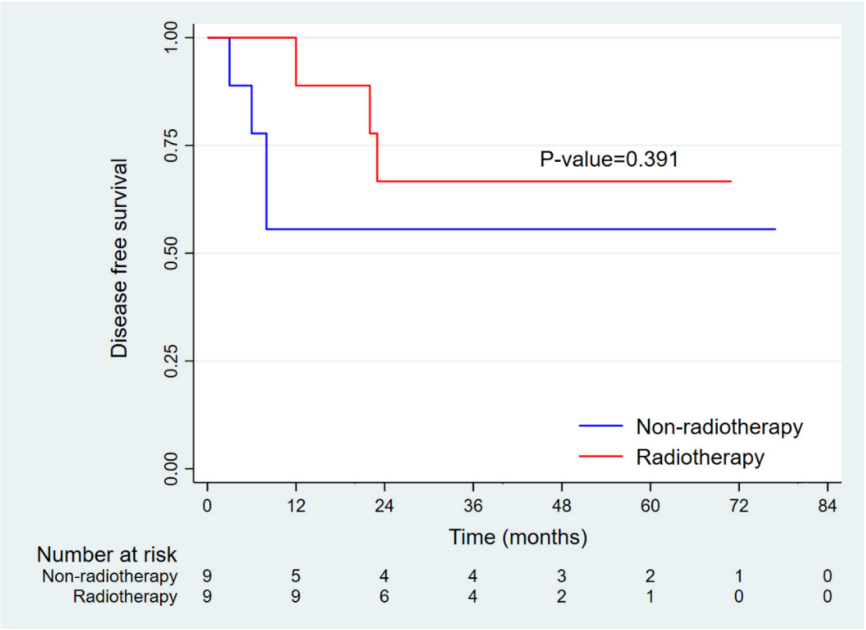
Characteristics	Radiation therapy, n (%) n=9	No radiation therapy, n (%) n=9	P-value
Age, years (Mean ± SD)	43.4 ± 24.3	33.1 ± 15.9	0.302[2]
Age, years			>0.999[1]
<45	7 (77.8)	6 (66.7)	
>45	2 (22.2)	3 (33.3)	
Sex			>0.999[1]
Male	3 (33.3)	4 (44.4)	
Female	6 (66.7)	5 (55.6)	
Staging			>0.999[1]
III	2 (22.2)	3 (33.3)	
IV	7 (77.8)	6 (66.7)	
ECOG			0.576[1]
0	7 (77.8)	6 (66.7)	
1	1 (11.1)	3 (33.3)	
2	0 (0.0)	0 (0.0)	
>2	1 (11.1)	0 (0.0)	

Characteristics	Radiation therapy, n (%) n=9	No radiation therapy, n (%) n=9	P-value
IPS			0.259[1]
0–1	3 (33.3)	3 (33.3)	
2–3	4 (44.5)	1 (11.1)	
>3	2 (22.2)	5 (55.6)	
Subtype			0.689[1]
MC	4 (44.5)	6 (66.7)	
NS	3 (33.3)	1 (11.1)	
LR	1 (11.1)	1 (11.1)	
LD	1 (11.1)	0 (0.0)	
Unknown	0 (0.0)	1 (11.1)	
EBV			0.169[1]
Positive	2 (22.2)	1 (11.1)	
Negative	3 (33.3)	0 (0.0)	
Bulky lesion size			0.030[1]
<5 cm	2 (22.2)	5 (62.5)	
5–7 cm	1 (11.1)	0 (0.0)	
7–10 cm	5 (55.6)	0 (0.0)	
>10 cm	1 (11.1)	3 (37.5)	
Bone marrow evaluation			0.352[1]
PET/Ga-67	1 (11.1)	0 (0.0)	
Biopsy	6 (66.7)	3 (33.3)	
Concordance	1 (11.1)	4 (44.5)	
Discordance	1 (11.1)	2 (22.2)	

Abbreviations: ECOG: Eastern Cooperative Oncology Group, IPS: International Prognostic Score, EBV: Epstein–Barr virus, PET: positron emission tomography, Ga-67: Ga-67 scintigraphy, MC: Mixed cellularity, NS: Nodular sclerosis, LR: Lymphocyte-rich, LD: Lymphocyte-depleted

[1]Fisher's exact, [2]Independent t test

(A)



(B)

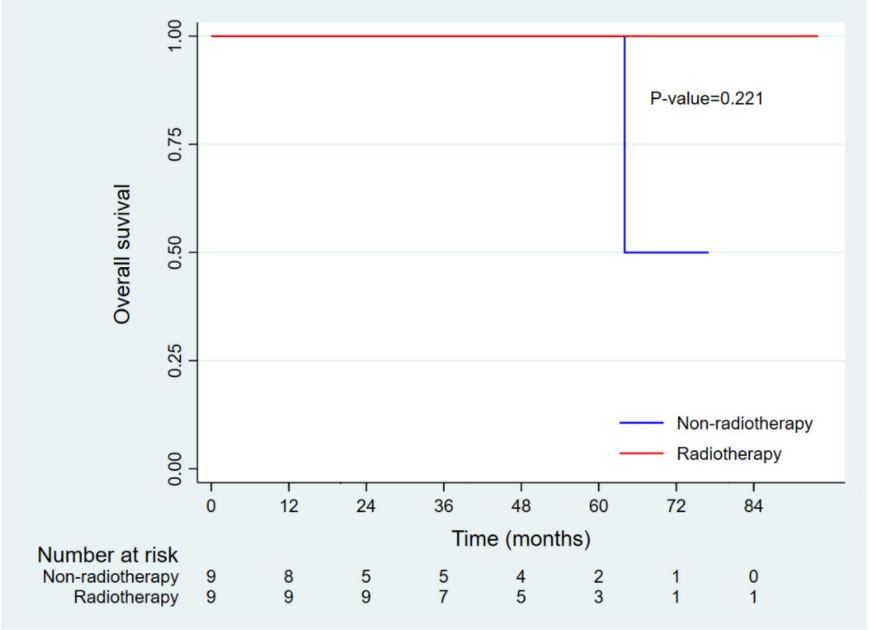


Figure 2. Disease-free survival (A) and overall survival (B) according to the receipt of radiation therapy

Table 2. An unadjusted hazard ratio using cox regression analysis for disease-free survival

Variables	HR (95% CI)	p-Value
Age, years	0.94 (0.88, 1.01)	0.092
Sex		
Male	1	
Female	2.34 (0.52, 10.44)	0.267
Staging		
III	1	
IV	1.37 (0.26, 7.18)	0.703
ECOG		
0	1	
1	-	-
2	-	-
>2	2.03 (0.24, 17.49)	0.520
IPS		
0–1	1	
2–3	1.19 (0.17, 8.50)	0.861
>3	1.54 (0.25, 9.38)	0.638
Subtype		
MC	1	
NS	2.22 (0.49, 10.07)	0.302
LR	-	-
LD	-	-
Unknown	-	-
EBV		
Negative	1	
Positive	1.00 (0.06, 15.99)	>0.999
Unknown	1.45 (0.17, 12.40)	0.737

Variables	HR (95% CI)	p-Value
Bulky lesion size		
<5 cm	1	
5–7 cm	-	-
7–10 cm	1.77 (0.29, 10.60)	0.533
>10 cm	1.92 (0.27, 13.73)	0.512
Radiation therapy		
No	1	
Yes	0.53 (0.12, 2.37)	0.403
Radiation therapy field		
IFRT	1	
ISRT	1.96 (0.17, 22.08)	0.586

Abbreviations: HR: hazard ratio, CI:confidence interval, ECOG: Eastern Cooperative Oncology Group, IPS:International Prognostic Score, EBV: Epstein–Barr virus, MC: Mixed cellularity, NS: Nodular sclerosis, LR: Lymphocyte-rich, LD: Lymphocyte-depleted, IFRT: Involved-field radiotherapy, ISRT: Involved-site radiotherapy

stable disease, and disease progression, respectively. Seven patients (38.9%) experienced relapse after treatment. Most relapses occurred at the original site of the disease (5/7 patients, 71.4%). No relapse was observed within the radiated field in any patient who received radiation therapy (**Table 3**).

Two of three patients who achieved CMR by functional imaging in both the interim and post-treatment evaluations received radiation therapy. None of these three patients experienced relapse. Four of eight patients who had a partial response but achieved CMR after treatment received radiation therapy. The only relapse in this group (1/8 patients, 12.5%) occurred in a patient who received radiation therapy (**Table 4**).

Seven patients had residual disease after first-line chemotherapy. In this group, 2 received salvage chemotherapy and radiotherapy, 4 received salvage chemotherapy alone and 1 received only salvage radiotherapy. Median size of residual mass before salvage radiotherapy was 3.8 cm (range 1.1 cm – 4.5 cm). Relapses occurred in two of three patients who received radiation therapy (66.7%) and all four patients who did not receive radiation therapy (100%). The description of treatment response in each patient was shown in **Table 5**.

Table 3. Treatment outcomes

	Radiation therapy, n (%)	No radiation therapy, n (%)	p-Value
Recurrence/Relapse in all patients			>0.999[1]
Recurrence	3 (33.3)	4 (44.4)	
No recurrence	6 (66.7)	5 (55.6)	
Pattern of recurrence/relapse in all patients			>0.999[1]
Original site	2 (66.7)	3 (75.0)	
New site	1 (33.3)	0 (0.0)	
Both original site and new site	0 (0.0)	1 (25.0)	
Pattern of recurrence/relapse in radiation therapy group			-
In-field recurrence	0 (0.0)	N/A	
Out of field recurrence	2 (66.7)	N/A	
Both in-field and out of field recurrence	1 (33.3)	N/A	
Interim response			>0.999[1]
CMR	2 (25.0)	2 (22.2)	
PR	5 (62.5)	6 (66.7)	
SD	1 (12.5)	0 (0.0)	
PD	0 (0.0)	1 (11.1)	
Response to first-line treatment			>0.999[1]
CMR	6 (66.7)	5 (55.6)	
PR	2 (22.2)	1 (11.1)	
SD	0 (0.0)	1 (11.1)	
PD	1 (11.1)	2 (22.2)	
Secondary malignancy	None	None	

Abbreviations: CMR: complete metabolic response by functional imaging, PR: partial response, SD: stable disease, PD: progressive disease, N/A: not applicable

[1]Fisher's exact test

Table 4. Treatment responses

	Total number (n=18)	Radiation therapy, n (%)	No radiation therapy, n (%)	Recurrence/Relapse (%)		
				Total number	Radiation therapy	No radiation therapy
CMR both interim and after first-line treatment	3	2/3 (66.7%)	1/3 (33.3%)	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
CMR only after first-line treatment	8	4/8 (50.0%)	4/8 (50.0%)	1/8 (12.5%)	1/4 (25.0%)	0/4 (0.0%)
Residual disease after first-line treatment	7	3/7 (42.9%)	4/7 (57.1%)	6/7 (85.7%)	2/3 (66.7%)	4/4 (100.0%)

Abbreviations: CMR: complete metabolic response by functional imaging

Table 5. Description of treatment and response in each patient

Patient No.	Age	IPS	Subtype	Stage	Bulky size (cm)	1st Regimen	Interim Response	1st line Response	Radiotherapy	Dose RT	Field	Technique	Pattern of Relapse
1	60	>3	MC	IV	7.1	ABVD	CMR*	CMR*	yes	36 Gy	IFRT	VMAT	-
2	41	>3	NS	IV	9.4	ABVD>escBEACOPP	SD*	PD*	yes	34Gy	IFRT	IMRT	Primary (Not in field)
3	73	0-1	LR	III	2.7	ABVD	PR*	CMR*	no				-
4	20	2-3	NS	IV	7.2	ABVD	PR**	PR*	yes	36	ISRT	IMRT	Primary (Not in field)
5†	36	0-1	MC	III	2.5	ABVD>escBEACOPP	PR*	SD*	no				Primary
6†	22	>3	NS	IV	15	ABVD>escBEACOPP	PR*	PR*	no				Primary Distant
7†	17	>3	MC	IV	14.7	ABVD	PD*	PD*	no				Primary
8	21	0-1	MC	III	7.4	ABVD	PR*	CMR*	yes	36 Gy	IFRT	IMRT	Distant
9	33	0-1	LR	IV	2.2	ABVD	No evaluation	CMR*	yes	36 Gy	ISRT	3D	-
10	78	>3	MC	IV	3.5	CVPa	PR**	CMR*	no				-
11††	41	>3	Unknown	IV	13.6	ABVD	PR**	CMR*	no				-
12	56	2-3	NS	III	4.9	ABVD	PR**	CMR*	yes	36Gy	IFRT	IMRT/3DCRT	-
13†	25	2-3	MC	IV	2.5	ABVD	CMR*	PD*	no				Primary
14	73	0-1	MC	III	2.7	ABVD	PR**	CMR*	no				-
15	25	2-3	MC	IV	8.6	ABVD	PR**	PR*	yes	36 Gy	IFRT	VMAT	-
16	18	2-3	LD	IV	6.3	ABVD>escBEACOPP	PR*	CMR*	yes	46 Gy	IFRT	IMRT	-
17	29	0-1	MC	IV	10.7	ABVD	CMR*	CMR*	yes	30 Gy	IFRT	unknown	-
18	29	>3	MC	IV	4.9	ABVD	CMR*	CMR*	no				-

Abbreviations: MC: Mixed cellularity, NS: Nodular sclerosis, LR: Lymphocyte-rich, LD: Lymphocyte-depleted, CMR: complete metabolic response by functional imaging, PR: partial response, SD: stable disease, PD: progressive disease, IFRT: Involved-field radiotherapy, ISRT: Involved-site radiotherapy, VMAT: Volumetric Modulated Arc Therapy, IMRT: Intensity Modulated Radiation Therapy

*Evaluated by functional imaging **Evaluated by CT scan

ΦChanged to CVP regimen due to severe pneumonitis after 1st cycle of bleomycin

†According to our protocol, patients with residual disease after first-line chemotherapy could receive either salvage radiotherapy or a second-line chemotherapy regimen

††Patient No. 11 did not undergo radiotherapy consultation based on the hematologist's personal decision.

Based on our institutional criteria of a mass greater than 7 cm in size, nine patients in our cohort had bulky masses. Among these patients, three did not receive radiotherapy (two were switched to second-line chemotherapy, and one did not undergo radiotherapy consultation due to the individual decision of the hematologist). Of the six patients who received radiation therapy, three experienced relapses, while two of the three who did not receive radiation therapy experienced relapses (50% vs. 66.7%). Four of five patients with bulky disease who experienced relapse had residual disease after first-line chemotherapy. Interestingly, in four patients who achieved CMR, the one who did not receive radiation therapy had no relapse. Meanwhile, one of three patients who received radiation therapy experienced a relapse (**Figure 3**).

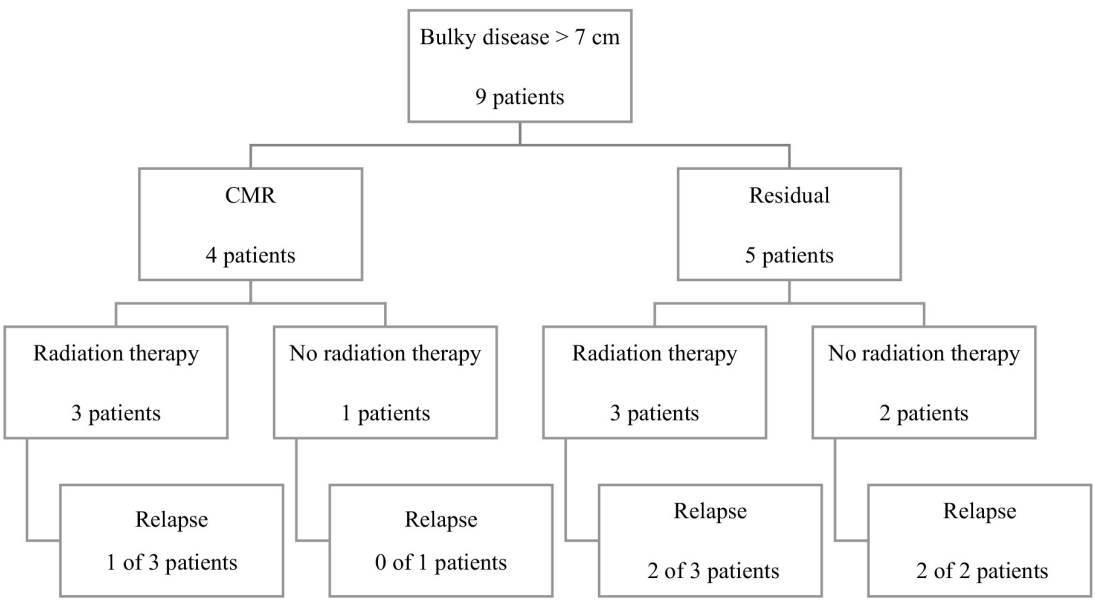


Figure 3. Treatment outcomes in patients with bulky disease

3.3. Radiation toxicity

Grade 1–2 acute radiation toxicity occurred in five of nine patients (55.6%), including three, one, and one case of mucositis, xerostomia, and gastrointestinal toxicity, respectively. No grade 3–4 acute radiation toxicity was noted in this study. However, two patients experienced grade 3 late pneumonitis that required hospitalization. The first patient with late grade 3 pneumonitis was Patient No. 1 in **Table 5**. This patient received consolidation radiotherapy to the bulky site at SPC and mediastinum after CMR. The dose administered was 36 Gy in 18 fractions, with V20 of the total lung at 30% and V5 of the total lung at 64%, which did not exceed the constraints of our protocol. The second patient was Patient No. 17 in **Table 5**. This patient also received consolidative radiotherapy after CMR to the neck and mediastinal area with 30 Gy in 15 fractions. However, since the latter patient had been radiated at another hospital, we cannot assess the lung dose in this case. No secondary malignancy was observed (**Tables 6**).

Table 6. Acute and late radiation toxicity in irradiated patients based on the criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer

Acute radiation toxicity		
Organ	Grade 1–2	Grade 3–4
Mucous membrane	3/9 (33.3%)	0/9 (0.0%)
Salivary gland	1/9 (11.1%)	0/9 (0.0%)
Gastrointestinal	1/9 (11.1%)	0/9 (0.0%)
Late radiation toxicity		
Organ	Grade 1–2	Grade 3–4
Lung	0/9 (0.0%)	2/9 (22.2%)

4. Discussion

Despite the detection of residual disease by CT after treatment, which occurs in up to 80% of patients with Hodgkin lymphoma, only some patients have evidence of disease relapse or progression[16]. This challenge has been overcome by the use of functional imaging such as Ga-67 scintigraphy and 18F-fluorodeoxyglucose PET/CT. 18F-fluorodeoxyglucose PET/CT proved superior to CT for assessing the response to treatment in Hodgkin lymphoma[17,18]. Regarding Ga-67 scintigraphy, one study described its superiority to CT in terms of restaging[19]. Based on the published literature, these functional imaging modalities have been used as standard imaging modalities for initial staging and response evaluation in both Hodgkin and non-Hodgkin lymphoma for a decade. In this study, we only included patients who underwent at least one evaluation by functional imaging, which is difficult to perform in most intuitions in Thailand because of financial problems and a lack of resources.

Our study revealed that consolidation radiation therapy might not be necessary for advanced Hodgkin lymphoma due to no difference in 3-year disease-free survival and overall survival rate. Regarding patients of bulky masses at the initial staging, the phase 3 GITIL HD0607 study enrolled 783 patients with advanced Hodgkin lymphoma, and 296 patients with a bulky mass greater than 5 cm in size at baseline who had negative PET in both the interim and end-of-treatment evaluations were randomly assigned to consolidation radiation therapy or no further treatment. The results revealed no differences in 6-year progression-free survival (91% vs. 95%, p = 0.62) and 6-year overall survival (99% vs. 98%, p = 0.61) between the groups[20]. In the phase 3 FIL HD0801 study, 116 patients with advanced Hodgkin lymphoma with bulky masses at least 5 cm in size at baseline who had CMR after two and six cycles of ABVD were randomly assigned to consolidation radiation therapy or observation. The intention-to-treat analysis also revealed no differences in 2-year event-free survival (87.8% vs. 85.8%, p = 0.34) and 2-year progression-free survival (91.3% vs. 85.8%, p = 0.7)[21]. In subgroup analysis, bulky masses greater than 7 cm in size had no influence on the efficacy of consolidation radiation therapy in both studies[20,21]. Our findings support the results of both phase 3 trials. This is evidenced by the absence of relapse in one patient with bulky disease who achieved CMR after first-line chemotherapy and did not receive radiotherapy (Figure 3). Additionally, among the three patients who achieved complete metabolic response (CMR) on both interim and end-of-treatment PET scans, no relapse was observed in one patient who did not receive radiotherapy (**Table 4**).

The current study had several limitations. First, as a retrospective study, several confounding factors could have affected the outcomes. Second, the number of patients enrolled was much smaller than expected according to the

required sample size. This affected the power of statistical analysis. Third, subgroup analysis with only univariate analysis might not be reliable because of the small sample size. Fourth, there may be selection bias in this study because some patients did not receive radiotherapy despite the presence of bulky disease or residual disease after first-line chemotherapy treatment. This was because, according to our protocol, patients with residual disease after first-line chemotherapy could receive either salvage radiotherapy or a second-line chemotherapy regimen, depending on the decisions of radiation oncologists and hematologists in the tumor board. For example, if the residual site was beyond the radiotherapy field, the second-line chemotherapy was more favorable.

5. Conclusions

In summary, our study revealed that by using functional imaging as an evaluation method, consolidation radiation therapy may not be necessary in advanced Hodgkin lymphoma.

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Conflicts of interest

None

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71: 209-49.
2. Tepper JE, Foote RL, Michalski JM. Gunderson & Tepper's Clinical Radiation Oncology (5th edition). Philadelphia, PA: Elsevier; 2021.
3. Borchmann P, Haverkamp H, Diehl V, Cerny T, Markova J, Ho AD, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiation therapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. J Clin Oncol. 2011; 29:4234-42.

4. Aleman BM, Raemaekers JM, Tirelli U, Bortolus R, van't Veer MB, Lybeert ML, et al. Involved-field radiation therapy for advanced Hodgkin's lymphoma. N Engl J Med 2003; 348:2396-2406.
5. Johnson PW, Radford JA, Cullen MH, Sydes MR, Walewski J, Jack AS, et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). J Clin Oncol. 2005; 23:9208-18.
6. Johnson PW, Sydes MR, Hancock BW, Cullen M, Radford JA, Stenning SP, et al. Consolidation radiation therapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). J Clin Oncol. 2010; 28:3352-9.
7. Loeffler M, Brosteanu O, Hasenclever D, Sextro M, Assouline D, Bartolucci AA, et al. Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease Overview Study Group. J Clin Oncol. 1998; 16: 818-29.
8. Engert A, Haverkamp H, Kobe C, Markova J, Renner C, Ho A, et al. Reduced-intensity chemotherapy and PET-guided radiation therapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial [published correction appears in Lancet. 2012 May 12;379(9828):1790]. The Lancet. 2012; 379:1791-9.
9. Kriz J, Reinartz G, Dietlein M, Kobe C, Kuhnert G, Haverkamp H, et al. Relapse analysis of irradiated patients within the HD15 trial of the German Hodgkin Study Group. Int J Radiat Oncol Biol Phys. 2015; 92:46-53.
10. Kobe C, Dietlein M, Franklin J, Markova J, Lohri A, Amthauer H, et al. Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. Blood. 2008; 112:3989-94.
11. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989; 7:1630.
12. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32:3059.

13. Younes A, Hilden P, Coiffier B, Hagenbeek A, Salles G, Wilson W, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017; 28: 1436-47.
14. Engert A, Schiller P, Josting A, Herrmann R, Koch P, Sieber M, et al. Involved-field radiation therapy is equally effective and less toxic compared with extended-field radiation therapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2003; 21:3601-8.
15. Sasse S, Klimm B, Görgen H, Fuchs M, Heyden-Honerkamp A, Lohri A, et al. Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiation therapy in early-stage Hodgkin's lymphoma. Ann Oncol. 2012; 23:2953-9.
16. Radford JA, Cowan R, Flanagan M, Dunn G, Crowther D, Johnson RJ, et al. The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkin's disease. J Clin Oncol. 1988; 6:940-6.
17. Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood. 1999; 94: 429-33.
18. Zaucha JM, Chauvie S, Zaucha R, Biggii A, Gallamini A. The role of PET/CT in the modern treatment of Hodgkin lymphoma. Cancer Treat Rev. 2019; 77:44-56.
19. Devizzi L, Maffioli L, Bonfante V, Viviani S, Balzarini L, Gasparini M, et al. Comparison of gallium scan, computed tomography, and magnetic resonance in patients with mediastinal Hodgkin's disease. Ann Oncol. 1997; 8:53-6.
20. Gallamini A, Rossi A, Patti C, Picardi M, Romano A, Cantonetti M, et al. Consoliข dation Radiation therapy 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; 38:3905-13.
21. Ricardi U, Levis M, Evangelista A, Gioia DM, Sacchetti GM, Gotti M, et al. Role of radiation therapy to bulky sites of advanced Hodgkin lymphoma treated with ABVD: final results of FIL HD0801 trial. Blood Adv. 2021; 5:4504-1