

Hindawi Publishing Corporation
Advances in Hematology
Volume 2011, Article ID 271595, 12 pages
doi:10.1155/2011/271595

Review Article

Prognostication and Risk-Adapted Therapy of Hodgkin's Lymphoma Using Positron Emission Tomography

Yvette L. Kasamon

Department of Oncology and Medicine, Johns Hopkins University School of Medicine, 1650 Orleans Street, Baltimore, MD 21231, USA

Correspondence should be addressed to Yvette L. Kasamon, ykasamo1@jhmi.edu

Received 2 August 2010; Accepted 10 October 2010

Academic Editor: Kensei Tobinai

Copyright © 2011 Yvette L. Kasamon. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The use of ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) for response assessment in lymphoma is now widespread. Prognostic information obtained from PET performed after two to three cycles of chemotherapy may guide more individualized, risk-adapted therapeutic strategies. Progress in the risk stratification of Hodgkin's lymphoma through midtreatment PET is reviewed, with a focus on management implications in newly diagnosed and relapsed disease. How to tailor treatment on the basis of the interim PET result is not yet defined but is the subject of ongoing trials.

1. Introduction

Strategies that minimize toxicity, without compromising disease control, are a leading area of research in Hodgkin's lymphoma (HL). Because the majority of HL patients are cured, investigations can now focus upon reducing treatment toxicities [1, 2]. However, a clear subset of patients has progressive or relapsed disease and may benefit from a preemptive, tailored approach. More accurate prognostication could identify such poor-risk patients, while sparing good-risk patients from the toxicities of overly intensive therapy.

In the assessment of treatment response, there are limitations in the prognostic information provided by computed tomography (CT). Residual masses are frequent after lymphoma therapy, particularly with initial bulky disease [3, 4]. Yet, it is recognized that their presence and size correlate poorly with outcome [3–5]. This underlies the response category of “complete remission unconfirmed” in the 1999 International Working Group criteria [6]. ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) enhances the ability to distinguish between viable tumor and fibrosis or necrosis in residual masses [7, 8]. Given this and the increasingly widespread use of PET in response assessment, PET has been integrated into the recently revised

response criteria for lymphoma [9, 10]. When performed midtreatment, PET also provides valuable information about the quality of the treatment response and ultimate prognosis in patients with aggressive lymphomas including HL. The prognostication of HL on the basis of early metabolic imaging with PET is reviewed and treatment implications considered.

2. Pretreatment Prognostic Indices in HL

The International Prognostic Score (IPS) remains the most commonly used scoring system for newly diagnosed, advanced HL [11]. This consists of seven pretreatment variables that independently predict inferior outcome: albumin <4 g/dL, hemoglobin <10.5 g/dL, male sex, age ≥ 45 years, stage IV disease, white blood cell count $\geq 15,000/\text{mm}^3$, and lymphocytopenia (lymphocyte count $<600/\text{mm}^3$ or $<8\%$ of the white blood cell count). Each adverse factor is similarly prognostic, reducing the 5-year freedom from progression (FFP) rate by approximately 8%, with the estimated 5-year FFP ranging from 84% with no risk factors to 42% with ≥ 5 factors in the original paper. The IPS has been utilized in the design and analysis of clinical studies and may guide the choice of chemotherapy in individual patients.

For early stage disease, cooperative groups have used other baseline criteria for risk stratification and treatment selection [1, 12–14]. Shared factors have included the degree of elevation in erythrocyte sedimentation rate, the number of involved regions, and the presence of bulky disease. Stage IIB is often regarded as advanced disease.

Such pretreatment indices are useful in characterizing groups of patients. However, they are less useful in the prognostication of an individual patient. Furthermore, these are static rather than dynamic parameters and do not provide information about the quality of the treatment response. In contrast, metabolic imaging performed early in the course of therapy provides useful, individualized information about the quality of response and about prognosis.

3. Posttreatment PET in HL

For PET scans performed after the end of chemotherapy or chemoradiation for HL, the negative predictive value (NPV, i.e., negative PET scan and no treatment failure) has been consistently high—approximately 90% [15–20]. This is despite some of the studies being restricted to patients with residual masses [15, 18, 20]. In contrast, the reported positive predictive value (PPV, i.e., positive PET scan and treatment failure) is weaker and varies widely, ranging from 26% to 74% in representative series [17–20]. As such, a positive posttreatment PET scan should be interpreted with particular caution, especially within two to three months of RT [9].

It must be kept in mind that, even in a reliably FDG avid tumor, a negative PET does not necessarily signify complete eradication of disease [21]. The limit of resolution of current PET systems for detecting tumor generally ranges between 0.5 and 1 cm [22, 23], which translates into an estimated 10^8 to 10^9 cells. Therefore, millions of viable tumor cells could persist despite the achievement of a negative PET scan [21]. This has substantial implications for the study of de-escalated therapy in patients with a negative interim PET.

4. Midtreatment PET and Prognosis in Newly Diagnosed HL

Earlier identification of chemoresistant disease, prior to treatment completion, would facilitate an individualized, risk-adapted strategy. Midtreatment (interim) metabolic imaging via FDG-PET has strong potential in this regard. In HL and aggressive B-cell non-Hodgkin's lymphoma (NHL), it has been repeatedly recognized that PET performed after only 2 or 3 cycles of chemotherapy provides valuable prognostic information. Early achievement of a negative PET (absence of abnormal FDG uptake concerning for tumor) is prognostically favorable, whereas persistent abnormal FDG uptake on early PET, even in the context of a CT response, raises concern for treatment failure [24]. PET performed after only one cycle also appears to have prognostic significance [25, 26].

Why can interim PET provide more valuable prognostic information than one at the end of therapy? An early PET

result may offer a window into the chemosensitivity of the tumor. As previously reviewed [21], cancers are usually not diagnosed until they reach a size of 10^{10} to 10^{11} cells. Chemotherapy kills tumor by first-order kinetics; that is, a given dose kills the same fraction, not the same number, of cells regardless of tumor size [27]. Thus, in the idealized setting, each cycle of chemotherapy must kill approximately 1.5 to 2 logs of tumor for a lymphoma to be cured after 6 cycles. Accordingly, most of the tumor cell kill should occur early—with the first 2 cycles [21]. A negative cycle 2 PET implies that the rate of tumor cell kill is sufficient to produce cure by the end of treatment, whereas a negative scan late in treatment does not distinguish between 4 logs of kill (PET remission) and the 10 or 11 logs of kill necessary for cure [21].

As in NHL, the literature on the prognostic significance of interim PET in newly diagnosed HL represents a mixture of prospective and retrospective studies (Table 1), utilizing variable scanning techniques and criteria for PET interpretation [25, 28–38]. In a meta-analysis of interim PET in 360 patients with newly diagnosed advanced HL, the sensitivity of interim PET was 0.81 (95% confidence interval, 0.72 to 0.89) and the specificity was 0.97 (95% confidence interval, 0.94 to 0.99); corresponding sensitivity and specificity for diffuse large B-cell lymphoma were 0.78 and 0.87 [24].

FDG-PET performed after 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) complements and is potentially superior to the IPS [39]. In the widely cited study by Gallamini et al. [31], 260 patients with poorer-risk HL were prospectively evaluated with cycle 2 PET, without change of therapy. The estimated 2-year progression-free survival was 95% in those with a negative interim PET, but only 13% in those with a positive interim PET. On univariate analysis, the cycle 2 PET result and the IPS were among the variables that were statistically significantly associated with treatment outcome. Notably, however, on multivariate analysis, only cycle 2 PET and the presence of stage IV disease were independently associated with outcome.

The majority of data on the prognostic significance of interim PET in HL is in patients with more advanced disease [31, 32, 36, 38]. Of these, the majority of patients had an IPS of <4 [24]. The prognostic value of interim PET in early stage, favorable disease is not well established. One would expect, given the greater pretest probability of early stage patients being cured, that the high NPV observed in advanced HL would also hold for early stage HL provided that treatment is not de-escalated. In contrast to the high NPV of interim PET, the observed PPV has been variable (Table 1). Furthermore, relatively few patients with positive interim PET have been studied (50 in the largest series) [31]. This is an important consideration when treatment intensification is contemplated on the basis of a positive PET, given the risk of greater toxicity with more intensive treatment.

A number of other factors may account for the observed variability in the PPV of interim PET. As in NHL, the variability is likely due in part to methodological differences among the studies. Variable (but mostly qualitative) criteria have been used in defining a positive scan, with borderline

TABLE 1: PET during first-line chemotherapy for Hodgkin's lymphoma.

Study	Prospective	No.	Stage	Chemo, ±RT	Cycles before PET	No. PET+ (%)	PPV	NPV	EFS, PET+	EFS, PET-	Median follow-up
Friedberg et al. 2004 [28]	yes	22	I-IV; 28% III-IV	Mostly ABVD	3	5 (23%)	80%	94%	—	—	24 mo
Hutchings et al. 2005 [29]	no	85	I-IV; 33% III-IV	Mostly ABVD	2-3	13 (15%) ^a	61.5%	94%	46% (2 y) 39% (5 y)	97% (2 y) 92% (5 y)	40 mo
Gallamini et al. 2006 [34]	yes	108	IIA with RF, IIB-IV; 46% III-IV	Mostly ABVD	2	20 (19%)	90%	97%	6% (2 y)	96% (2 y)	20 mo (mean)
Hutchings et al. 2006 [30]	yes	77	I-IV; 36% III-IV	Mostly ABVD	2	16 (21%) ^a	69%	95%	0% (2 y)	96% (2 y)	23 mo
		64			4	13 (20%)	85%	96%	19% (2 y)	96% (2 y)	23 mo
Zinzani et al. 2006 [32]	yes	40	IIB-IV; 48% III-IV	ABVD	2	8 (20%) ^b	100%	100%	—	—	18 mo
		40			4	7 (18%) ^b	100%	100%	—	—	18 mo
Kostakoglu et al. 2006 [25]	no	23	II-IV; 35% III-IV	ABVD	1	6 (26%)	83%	100%	17% (2 y)	100% (2 y)	20 mo
Querellou et al. 2006 [33]	no	44	IIA-IV; 63% III-IV	Mostly ABVD	3-4	— ^c	—	95% ^c	—	95% (1 y)	18 mo
Gallamini et al. 2007 [31]	yes	260 ^d	IIA with RF, IIB-IV; 47% III-IV	Mostly ABVD	2	50 (19%) ^a	86%	95%	13% (2 y)	95% (2 y)	26 mo
Sher et al. 2009 [35]	no	46	Mostly I-II	ABVD-based ^e	—	20 (43%)	15%	96%	85% (2 y)	96% (2 y) ^f	—
Markova et al. 2009 [36]	no	50	IIB with RF, III-IV; 78% III-IV	BEACOPP	4	14 (28%)	14% ^g	97% ^h	86% (2 y) ^g	97% (2 y)	25 mo
Furth et al. 2009 [37]	yes	40	I-IV; 48% III-IV	OEPA ⁱ	2	14 (35%)	14%	100%	86% (4 y)	100% (4 y)	46 mo
Avigdor et al. 2009 [38]	yes	45	IIB-IV; 93% III-IV	BEACOPP ^{esc} × 2, then ABVD ^j	2	13 (29%)	45%	87%	53% (4 y)	87% (4 y)	48 mo

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; EFS: event-free survival; esc: escalated; MRU: minimal residual uptake; NPV: negative predictive value; OEPA: vincristine, etoposide, prednisone, doxorubicin; PPV: positive predictive value; RF: risk factor(s); RT: radiation therapy. Definition of an event variably includes relapse or progression, incomplete remission, disease-related death, and/or any death; starting points for EFS estimates vary. Table modified from Kasamon et al. [21].

^aMRU cases were analyzed with PET- cases.

^bMRU cases (4 after cycle 2 PET, 3 after cycle 4 PET) were analyzed separately; 1 relapsed.

^c4/24 patients were PET+, 1 being newly diagnosed; 18/20 PET- patients were newly diagnosed.

^dIncludes previously reported patients [30, 34].

^eAll received radiation.

^fFor interim and post-chemotherapy PET- disease; 1/26 was interim PET-, post-chemotherapy PET+.

^g7/14 received RT, which was restricted to ≥ 2.5 cm, PET+ masses on post-chemotherapy imaging.

^hIncludes 1 non-relapse death.

ⁱPediatric study; 98% received RT.

^jResponse-adapted study; with or without additional therapy.

cases of “minimal residual uptake” [30] posing particular challenges as later discussed. There are also differences in image acquisition protocols and technique; for example, earlier studies used PET alone, in contrast to combination PET/CT.

In addition, false positive signals from inflammation are a leading consideration [40], as are other causes of false positive signals including infection, supraclavicular brown

fat, granulocyte colony stimulating factors in bone marrow disease [41], bony lesions, and in the case of posttherapy scans, thymic hyperplasia which can mimic mediastinal disease. False positives due to inflammation are possible in any type of tumor, but are a particular consideration in HL given its unique histopathology. In contrast to NHL, less than 1% of the tumor mass in HL is comprised of the malignant Hodgkin and Reed-Sternberg cells; rather, most of the tumor

is comprised of nonmalignant cells, with the nature of that cellularity having prognostic significance [42, 43]. This raises the question, what are the histologic underpinnings of a positive PET signal in HL?

Moreover, the prognostic utility of any criterion can be a moving target, depending on the effectiveness of the underlying regimen. Thus, the prognostic and predictive value of interim PET could vary depending on whether one receives ABVD versus BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) [39], or chemotherapy alone versus combined modality therapy. The PPV of interim PET may indeed be lower after BEACOPP [36, 39].

5. Risk-Adapted Strategies in Newly Diagnosed HL

Risk-adapted approaches in lymphoma utilizing interim PET are feasible and hold promise [13, 44–46]. Multicenter trials are in progress in patients with newly diagnosed, limited stage [47–49] and advanced stage HL [50–54], evaluating risk-adapted strategies based on the results of interim PET (Table 2). Most of these trials focus upon adult HL, although interim PET is also being investigated in pediatric HL [55].

5.1. Risk-Adapted Strategies in Limited Stage HL. In limited stage HL, a central question is whether therapy can be safely de-escalated or abbreviated, including through the omission of RT, in patients achieving a negative interim PET result during initial chemotherapy [47–49].

The prognostic information provided by early metabolic imaging may inform decisions about RT in limited stage HL. The role of using interim PET for this purpose cannot be considered standard but is in the process of being defined. Limited stage HL is traditionally treated with combined modality therapy. However, the effectiveness of RT for local control of HL must be balanced by the risks of late toxicities, including second malignancies and cardiovascular disease [56]. Such toxicities are leading causes of morbidity and mortality in patients who are cured of their lymphoma. Concerns about the late effects of RT have led to concerted efforts to define the minimum amount of radiation necessary to maintain cure rates. These include reduction in RT dose (e.g., from 30 to 20 Gray [14]) and the move from extended-field to involved-field [2] to, most recently, involved-node RT [57].

The appropriateness of chemotherapy alone for limited stage HL is a matter of debate. Chemotherapy alone has, however, emerged as a viable alternative to chemoradiation, at least in patients with nonbulky disease. A statistically significant overall survival difference has not been conclusively shown with the omission of RT in nonbulky, stage I or II HL [1, 58, 59]. A randomized study that found a difference in favor of RT had methodological limitations [60]. However, the risk of relapse has been higher with the omission of RT [1, 58]. In the HD6 trial of limited stage, nonbulky HL, the 5-year freedom-from progression after ABVD alone was 87%, versus 93% in the group that received

RT ($P = .06$) [1]. As such, a minority of patients are affected by the omission of radiation. Of note, the rapidity of the chemotherapeutic response may identify this subset, as the 5-year FFP was significantly better in those who achieved CR or unconfirmed CR by anatomic criteria after 2 cycles of ABVD (95% at 5 years, versus 81% in those who did not; $P = .007$) [1]. It is possible that early prognostication via interim PET may help to differentiate these subsets, thereby identifying who least stands to benefit from the addition of RT. The impact of this approach remains to be determined. In limited-stage HL, three large, multicenter, randomized trials are basing the radiation decision upon the results of PET performed after 2 or 3 cycles of ABVD (Table 2) [47–49]. All three trials investigate the omission of RT in patients who achieve a negative PET after 2 or 3 cycles of ABVD.

In terms of the number of chemotherapy cycles, caution is advised when considering de-escalating therapy on the basis of a negative interim PET result. The generally favorable outcomes of interim PET negative patients occurred following unabbreviated therapy. In the H10 trial involving PET after 2 ABVD cycles for stage I-II HL, additional chemotherapy is given to the PET negative patients who do not receive RT (Table 2) [49]. Notably, this trial includes patients with either favorable or unfavorable (including bulky) disease. In contrast, in the HD16 trial which is restricted to early favorable disease (stage I-II without risk factors), patients with a negative PET after 2 cycles of ABVD receive no further therapy in the experimental arm [48]. Similarly, in the RAPID trial which is restricted to nonbulky, stage IA or IIA disease, interim PET negative patients who are randomized to the no-radiation arm receive no further chemotherapy [47]. Particularly if RT is omitted, one risks undertreatment if an adequate course of systemic chemotherapy is not delivered, as a negative PET scan may not indicate absence of disease. The results of these trials are awaited. The early cessation of chemotherapy because of a negative interim PET cannot be supported outside of a clinical trial.

In the risk-adapted management of HL, an additional consideration is that resistance to radiation and resistance to chemotherapy often coexist. This is exemplified by the lower likelihood of radiation eradicating the tumor if relapse or progression occurs shortly (less than a year) after chemotherapy [61]. In addition, tumors that respond suboptimally to chemotherapy commonly relapse or progress within the radiation field. For example, in a retrospective study of 81 HL patients treated with Stanford V chemotherapy, 4 out of 6 patients with a positive PET before pre-planned RT relapsed; 3 of these relapses occurred within the radiation field and one at the margin [62]. RT may also increase the risk of toxicity from subsequent potentially curative therapies such as blood or marrow transplantation (BMT). As such, in patients with positive interim or postchemotherapy PET scans, RT should not necessarily be considered the appropriate next step. Although a true positive PET may identify a subset who stand to benefit from RT, a true positive PET might also identify a subset who stand *not* to benefit from RT.

TABLE 2: Current risk-adapted studies using interim PET in Hodgkin's lymphoma.

Study	Group	Projected accrual	Timing of PET	Treatment
Limited disease:				
RAPID trial [47]	UK NCRI	1600	After ABVD×3	PET−, randomize to RT versus no further therapy PET+, further ABVD + RT
HD16 [48]	GHSG	1100	After ABVD×2	Standard arm: RT regardless of PET Experimental: PET−, no further therapy Experimental: PET+, RT
H10 [49]	EORTC, GELA, IIL	1600	After ABVD×2	Standard arm: complete ABVD + RT regardless of PET Experimental: PET−, complete ABVD (no RT) Experimental: PET+, BEACOPPesc then RT
Advanced disease:				
HD18 [50]	GHSG	1500	After BEACOPPesc×2	PET−, randomize to 2 versus 6 more cycles (no RT) PET+, randomize to BEACOPPesc with versus without rituximab ^a
HD0607 [53]	GITIL	450	After ABVD×2	PET−, complete ABVD; if still PET−, randomize to RT versus no RT PET+, randomize to BEACOPPesc with versus without rituximab ^b
RATHL [51]	UK NCRI	1200	After ABVD×2	PET−, randomize to ABVD versus AVD (no RT) PET+, BEACOPP-14 or BEACOPPesc
HD0801 [52]	IIL	300	After ABVD×2	PET−, complete ABVD; if still PET−, randomize to RT versus no RT PET+, high-dose therapy with autologous BMT
S0816 [54]	SWOG intergroup	230	After ABVD×2	PET−, further ABVD PET+, BEACOPPesc ^c

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BMT: blood or marrow transplantation; EORTC: European Organization for Research and Treatment of Cancer; esc, escalated; GELA: Groupe d'Étude des Lymphomes de l'Adulte; GHSG: German Hodgkin Study Group; GITIL: Gruppo Italiano Terapie Innovative Nei Linfomi; IIL: Intergruppo Italiano Linfomi; NCRI: National Cancer Research Institute; RATHL: response-adapted therapy in Hodgkin lymphoma; RT: radiation therapy; SWOG: Southwest Oncology Group.

^aRT restricted to residual ≥ 2.5 cm, PET+ sites on end-of-chemotherapy imaging.

^bIf PET− after 4 cycles of BEACOPPesc \pm rituximab, changed to standard BEACOPP \pm rituximab.

^cStandard BEACOPP if human immunodeficiency virus positive.

5.2. Risk-Adapted Approaches in Advanced HL. In current risk-adapted trials for advanced HL based on metabolic imaging, the main questions are twofold: (a) whether treatment intensification improves outcome in interim PET positive patients and (b) whether toxicity can be minimized in interim PET negative patients (Table 2).

Improved prognostication could identify which HL patients can benefit the most from intensified but more toxic chemotherapy. Escalated BEACOPP is an effective first-line regimen that, compared to COPP-ABVD (cyclophosphamide-vincristine-procarbazine-prednisone-ABVD) and standard BEACOPP, confers superior FFP and overall survival rates at 5 years [63] and beyond [64] in advanced HL. However, it is also more toxic, including increased risk of acute hematologic toxicity, infertility, and myelodysplasia or leukemia [63]. Although escalated BEACOPP appears to be superior to ABVD in disease control [65, 66], its greater toxicity, combined with the ability to salvage relapsed patients [65], has hindered its widespread acceptance as the new standard of care.

In the interim PET positive patients, escalation of therapy from ABVD to a BEACOPP regimen is among the approaches under investigation [51, 53, 54]. In the first published

study of risk-adapted therapy in HL using interim metabolic imaging [13], 108 patients had therapy tailored using ⁶⁷Ga scintigraphy or PET performed after 2 cycles of standard or escalated BEACOPP. Pretreatment risk factors determined the initial regimen, with that regimen continued, escalated, or de-escalated according to the interim functional imaging result. Treatment failure occurred in 2% of patients with negative interim PET and 27% of patients with positive interim PET. Notably, 79% of the patients initially deemed high-risk had therapy reduced to standard BEACOPP, and overall survival rates were similar in the intermediate-risk and high-risk groups [13]. Although this approach has not been studied in a randomized fashion, the results demonstrate that, even among patients deemed to be high-risk by pretreatment indices, a minority require intensified upfront therapy.

The several ongoing trials involving change from ABVD to BEACOPP in advanced HL [51, 53, 54] will not directly prove the utility of this approach as compared with continued ABVD. They will, however, provide important data that, together with the H10 trial in limited stage HL (which has both standard and experimental arms) [49] will help answer this question. Two trials [50, 53] will also interestingly

address the contribution of rituximab, a drug that has activity in classical HL despite the usual absence of CD20 on Reed-Sternberg cells [67, 68].

In the interim PET negative patients, investigational approaches include reduction in the number of chemotherapy cycles, omission of bleomycin (given its risk of pulmonary toxicity), and omission of consolidative RT (Table 2). With respect to the latter, the role of RT in advanced stage HL is undefined [69–72] and practices vary. For example, in a randomized study of advanced stage HL patients achieving an anatomic complete remission to chemotherapy, there was no difference in 5-year survival, and there was a tendency toward inferior survival, with RT [69]. In a meta-analysis of chemotherapy versus chemoradiation for advanced HL, RT was associated with a significantly inferior overall survival [70]. On the other hand, a retrospective study in advanced HL found a progression-free and overall survival advantage to RT, despite more of the radiated patients having initial bulky disease and partial remissions after chemotherapy [72]. BEACOPP, as originally developed, included focal RT to sites of initial bulky disease or residual tumor [63]. More recently, end-of-chemotherapy PET scan has been utilized to limit RT to residually FDG avid masses after BEACOPP, with encouraging preliminary results [15]. The HD18 trial omits RT altogether in patients achieving a negative cycle 2 PET after escalated BEACOPP [50]. Other multicenter trials for advanced HL (HD0801, HD0607) are investigating RT omission in a randomized fashion in patients with negative interim and end-of-chemotherapy PET scans [52, 53].

6. Prognostication through Metabolic Imaging in Relapsed or Refractory HL

In patients with HL, high-dose therapy with BMT is reserved for the relapsed or refractory setting. Although an overall survival advantage has yet to be demonstrated, high-dose therapy with BMT prolongs event-free survival in patients with relapsed HL and is potentially curative [73]. In relapsed HL, autologous BMT is associated with a 5-year event-free survival of approximately 40%–50%, although late treatment failures occur [74–76].

In both HL and NHL, it is widely recognized that one of the leading determinants of outcome is the sensitivity of the tumor to salvage chemotherapy administered as a bridge to transplantation [74, 75, 77, 78]. Failure rates after BMT are excessive in the context of resistant relapse [79]. CT has been the standard imaging modality for determination of response, and therefore potential chemosensitivity and candidacy for transplantation, following salvage chemotherapy. However, a growing literature suggests that the presence of residual metabolic activity in the tumor prior to transplantation is prognostically significant and may be superior to anatomic response assessment (Table 3) [45, 80–84]. As reviewed previously [85], many of the studies of interim, pretransplantation PET are heterogeneous in terms

of disease (combination of HL and NHL, primary refractory and relapsed cases), design (retrospective, prospective), and metabolic response criteria. Table 3 summarizes selected studies of metabolic imaging performed after salvage chemotherapy, prior to high-dose therapy with autologous BMT, in patients with relapsed or refractory HL [45, 81–84]. The literature suggests that residual PET positive disease prior to transplantation portends worse outcomes. This is illustrated by a study by Moskowitz et al. [45], whose group previously found that initial remission under one year, active B symptoms, and extranodal disease were associated with inferior outcomes in relapsed HL. In patients who were chemoresponsive by CT criteria, there was no apparent difference in outcome according to the number of these risk factors provided that pretransplantation metabolic imaging (via gallium scintigraphy or PET) was negative [45].

How might this prognostic information be utilized? Further, prospective studies as to whether metabolic imaging complements pretreatment clinical risk scores in HL would be of interest [82]. Although PET may more accurately identify poor-risk patients who are less likely to benefit from autologous BMT, outcomes are far from all-or-none. The available literature does not support withholding transplantation to an otherwise appropriate, “responding” patient with HL on the basis of a positive interim PET. Whether, however, selected patients stand to benefit more from an alternative salvage approach such as allogeneic transplantation is a question that warrants further study. Rather than relying solely on the chemotherapy or chemoradiation in the preparative regimen, an allogeneic transplant offers the possibility of an immunologic attack against the tumor via a graft-versus-lymphoma effect [74]. This is especially attractive in a lymphoma that responds suboptimally to chemotherapy.

7. General Considerations in Analyzing the Midtreatment PET

For the prognostication of HL in clinical trials, performing an interim PET after two or three cycles of chemotherapy seems optimal (Tables 1 and 3). To avoid the transient fluctuations in FDG uptake that may occur after chemotherapy [86] and to permit the chemotherapy to take effect, an interim PET should be performed as close to the next cycle as possible. This consideration is balanced against the logistics of obtaining the centralized read promptly and keeping treatment on schedule, which is feasible [87].

In addition to causes of false positive and false negative results, a number of issues surround the interpretation of FDG PET scans that are highly relevant for prognostication. These include the criteria utilized for metabolic response and the reproducibility of the read, as briefly reviewed next.

7.1. Definition of Metabolic Response. A baseline PET is advisable to facilitate the evaluation of subsequent scans. Interim or posttherapy PET is most widely interpreted using visual (qualitative) criteria. Yet, FDG uptake lies on

TABLE 3: Selected studies of pretransplantation PET in relapsed/refractory Hodgkin's lymphoma.

Study	Prospective	Type of FI	No.	No. FI+ (%)	PPV	NPV	EFS, FI+	EFS, FI-	Median follow-up
Spaepen et al. 2003 [81]	no	PET	19	9 (47%)	78%	90%	—	—	—
Schot et al. 2007 [82]	yes	PET	23	5 (22%) NMR, 10 (43%) PMR	60% if NMR, 70% if PMR	75% if CMR, 30% if PMR	40% (2 y) if NMR, 37% if PMR	73% (2 y) if CMR	—
Jabbour et al. 2007 [83]	no	⁶⁷ Ga or PET	211	57 (27%)	74%	68%	23% (3 y)	69% (3 y)	34 mo for nonrelapsed pts
		PET	68	25 (37%)	72%	77%	—	—	—
Castagna et al. 2009 [84]	no	PET, after 2 cycles	24	10 (42%)	90%	93%	10% (2 y)	93% (2 y)	24 mo
		PET, after 4 cycles	24	6 (25%)	—	—	0% (2 y)	78% (2 y)	24 mo
Moskowitz et al. 2010 [45]	yes	⁶⁷ Ga or PET	105	41 (39%)	—	—	33% (4 y)	77% (4 y)	7 y in surviving pts

CMR: complete metabolic remission; EFS: event-free survival; FI: functional imaging; Ga: Gallium; NMR: no metabolic remission; NPV: negative predictive value; PMR: partial metabolic remission (residual intensity above background level); PPV: positive predictive value; pts, patients.

a continuum. A challenge in metabolic response assessment is the dichotomization of this continuous variable as either “positive” or “negative” for the purposes of response assessment, prognostication, and therapy. There has been variation among studies (including the ongoing studies of risk-adapted therapy) in what constitutes a “positive” or a “negative” result and the reference background against which tumor FDG uptake is compared (surrounding tissue, mediastinal blood pool, mediastinal blood pool plus normal liver). These criteria have not been validated. Particularly difficult are cases of low-level tumoral FDG uptake, just above background, that are deemed unlikely to represent malignancy but may [29]. The prognostic significance of such “minimal residual uptake” may vary depending on the pretest probability of treatment failure [88].

A standardized set of criteria for interim PET analysis is needed [89]. Without this, the results of the risk-adapted studies may be difficult to generalize. The International Harmonization Project criteria utilized for posttreatment response designation were not developed for, nor are recommended for, midtreatment response assessment [9]. These criteria may be prone to high rates of interim PET positivity; any activity above local background in a less than 2 cm mass including in normal size lymph nodes is considered positive (to account for effects of partial volume averaging), as is any activity above mediastinal blood pool in a larger mass [9]. A prospective trial is evaluating a cutoff of 1.5 times blood pool activity for differentiating between positive and negative results in NHL [90].

In addition to whether a PET is “positive,” the intensity of residual FDG uptake may have prognostic significance [44]. A 5-point scale (the Deauville criteria [91], based on the “London” criteria [88]) that captures gradations in FDG

uptake has been proposed for interim response assessment, with scores of 4 or 5 considered “positive”:

- (1) no uptake above background,
- (2) uptake \leq mediastinum,
- (3) uptake $>$ mediastinum but \leq normal liver,
- (4) uptake moderately $>$ liver,
- (5) uptake markedly $>$ liver and/or new disease.

International validation studies of the 5-point scale are in progress. As with any criteria that categorize a continuous variable, discriminating subtle differences between FDG uptake in tumor as compared to mediastinum or liver may be challenging. Differences in outcome in patients with a score of 2 versus 3 will be of particular interest in studies of interim PET. For the purposes of prognostication and clinical trial planning, what should define a positive or a negative interim PET result? This is not yet known, but may depend upon the risks of the planned intervention. For instance, if intensification (with risks of overtreatment and greater toxicity) is considered on the basis of a positive interim PET, a conservative approach to PET interpretation may be prudent, with borderline cases scored as negative [44]. If de-escalation is considered on the basis of a negative PET, it may be prudent to score such cases as positive so as to avoid undertreatment.

Semiquantitative assessments using standardized uptake values (SUVs) may complement visual criteria, at least in NHL [92, 93], but have not been shown to be superior to qualitative assessments. This clearly warrants further study,

however, as PET is inherently a quantitative imaging method [94]. Criteria for response assessment in solid tumors based on SUVs have been proposed [94].

7.2. Reproducibility of the PET Read. Discordance in the PET interpretation is a recognized concern, even if performed by expert nuclear medicine physicians. The interobserver variability is exemplified by an expert panel's analysis of interim PET scans in diffuse large B-cell lymphoma, wherein there was only moderate agreement using predefined visual criteria including the London criteria [95]. Additionally, no consensus could be reached in 9 of 12 discordant cases, with sites of para-aortic disease, spleen, and bone posing particular difficulty [95]. In a multicenter trial for stage II–IV HL, concordance in reads among four centers has been preliminarily studied using the London criteria [88]. Very good agreement (kappa statistic, 0.85) was found for a conservative reading ("positive" defined as a score of 4 or 5), and good agreement (kappa statistic, 0.79) for a sensitive reading ("positive" defined as a score of 3, 4, or 5) [88]. Other investigations of the reproducibility of PET reads in multicenter trials are in progress. Given the potential for greater interobserver reproducibility of semiquantitative measures [94, 96], further efforts to develop and validate semiquantitative criteria are encouraged. The reproducibility of the PET interpretation is key if treatment decisions are rendered on the basis of the PET result. Coupled with the need for standardized, reproducible reporting is the clear need for quality-control measures and consistent scanning techniques in multicenter trials [97].

8. Conclusions

In HL, as in NHL, early prognostication through interim PET clearly has the potential to guide optimal treatment. The metabolic imaging result has changed the definitions of disease response and chemosensitivity. However, many methodological and management questions remain. Although it is tempting to incorporate interim PET scanning into routine practice [98], such imaging is best performed on a clinical trial. How to manage the result is not yet established, but will be clarified through ongoing and planned clinical trials.

Acknowledgment

This work supported by the National Institutes of Health (K23 CA124465 to Y. L. Kasamon).

References

- [1] R. M. Meyer, M. K. Gospodarowicz, J. M. Connors et al., "Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group," *Journal of Clinical Oncology*, vol. 23, no. 21, pp. 4634–4642, 2005.
- [2] A. Engert, P. Schiller, A. Josting et al., "Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy 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," *Journal of Clinical Oncology*, vol. 21, no. 19, pp. 3601–3608, 2003.
- [3] J. A. Radford, R. A. Cowan, M. Flanagan et al., "The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkin's disease," *Journal of Clinical Oncology*, vol. 6, no. 6, pp. 940–946, 1988.
- [4] A. Surbone, D. L. Longo, V. T. DeVita Jr. et al., "Residual abdominal masses in aggressive non-Hodgkin's lymphoma after combination chemotherapy: significance and management," *Journal of Clinical Oncology*, vol. 6, no. 12, pp. 1832–1837, 1988.
- [5] M. Jochelson, P. Mauch, and J. Balikian, "The significance of the residual mediastinal mass in treated Hodgkin's disease," *Journal of Clinical Oncology*, vol. 3, no. 5, pp. 637–640, 1985.
- [6] B. D. Cheson, S. J. Horning, B. Coiffier et al., "Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas," *Journal of Clinical Oncology*, vol. 17, no. 4, pp. 1244–1253, 1999.
- [7] M. E. Juweid, G. A. Wiseman, J. M. Vose et al., "Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography," *Journal of Clinical Oncology*, vol. 23, no. 21, pp. 4652–4661, 2005.
- [8] G. Jerusalem, Y. Beguin, M. F. Fassotte 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*, vol. 94, no. 2, pp. 429–433, 1999.
- [9] M. E. Juweid, S. Stroobants, O. S. Hoekstra et al., "Use of positron emission tomography for response assessment of lymphoma: consensus of the imaging subcommittee of international harmonization project in lymphoma," *Journal of Clinical Oncology*, vol. 25, no. 5, pp. 571–578, 2007.
- [10] B. D. Cheson, B. Pfistner, M. E. Juweid et al., "Revised response criteria for malignant lymphoma," *Journal of Clinical Oncology*, vol. 25, no. 5, pp. 579–586, 2007.
- [11] D. Hasenclever and V. Diehl, "A prognostic score for advanced Hodgkin's disease," *The New England Journal of Medicine*, vol. 339, no. 21, pp. 1506–1514, 1998.
- [12] C. Fermé, H. Eghbali, J. H. Meerwaldt et al., "Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease," *The New England Journal of Medicine*, vol. 357, no. 19, pp. 1916–1927, 2007.
- [13] E. J. Dann, R. Bar-Shalom, A. Tamir et al., "Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome," *Blood*, vol. 109, no. 3, pp. 905–909, 2007.
- [14] A. Engert, A. Plütschow, H. T. Eich et al., "Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma," *The New England Journal of Medicine*, vol. 363, no. 7, pp. 640–652, 2010.
- [15] C. Kobe, M. Dietlein, J. Franklin 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*, vol. 112, no. 10, pp. 3989–3994, 2008.
- [16] K. Spaepen, S. Stroobants, P. Dupont et al., "Can positron emission tomography with ¹⁸F-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who

- need additional therapy from others in whom additional therapy would mean avoidable toxicity?" *British Journal of Haematology*, vol. 115, no. 2, pp. 272–278, 2001.
- [17] M. de Wit, K. H. Bohuslavizki, R. Buchert, D. Bumann, M. Clausen, and D. K. Hossfeld, "18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma," *Annals of Oncology*, vol. 12, no. 1, pp. 29–37, 2001.
- [18] M. R. Weihrauch, D. Re, K. Scheidhauer et al., "Thoracic positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease," *Blood*, vol. 98, no. 10, pp. 2930–2934, 2001.
- [19] H. Mocikova, P. Obrtlíkova, B. Vackova, and M. Trneny, "Positron emission tomography at the end of first-line therapy and during follow-up in patients with Hodgkin lymphoma: a retrospective study," *Annals of Oncology*, vol. 21, no. 6, pp. 1222–1227, 2010.
- [20] Z. Molnar, Z. Simon, Z. Borbenyi et al., "Prognostic value of FDG-PET in Hodgkin lymphoma for posttreatment evaluation. Long term follow-up results," *Neoplasma*, vol. 57, no. 4, pp. 349–354, 2010.
- [21] Y. L. Kasamon, R. J. Jones, and R. L. Wahl, "Integrating PET and PET/CT into the risk-adapted therapy of lymphoma," *Journal of Nuclear Medicine*, vol. 48, no. 1, pp. 19S–27S, 2007.
- [22] J. L. Humm, A. Rosenfeld, and A. Del Guerra, "From PET detectors to PET scanners," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 30, no. 11, pp. 1574–1597, 2003.
- [23] M. Tatsumi, C. Cohade, Y. Nakamoto, E. K. Fishman, and R. L. Wahl, "Direct comparison of FDG PET and CT findings in patients with lymphoma: initial experience," *Radiology*, vol. 237, no. 3, pp. 1038–1045, 2005.
- [24] T. Terasawa, J. Lau, S. Bardet et al., "Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review," *Journal of Clinical Oncology*, vol. 27, no. 11, pp. 1906–1914, 2009.
- [25] L. Kostakoglu, S. J. Goldsmith, J. P. Leonard et al., "FDG-PET after 1 cycle of therapy predicts outcome in diffuse large cell lymphoma and classic Hodgkin disease," *Cancer*, vol. 107, no. 11, pp. 2678–2687, 2006.
- [26] W. Römer, A.-R. Hanauske, S. Ziegler et al., "Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose," *Blood*, vol. 91, no. 12, pp. 4464–4471, 1998.
- [27] H. E. Skipper, F. M. Schabel Jr., and W. S. Wilcox, "Experimental evaluation of potential anticancer agents. Xiii. On the criteria and kinetics associated with "curability" of experimental leukemia," *Cancer Chemotherapy Reports. Part 1*, vol. 35, pp. 1–111, 1964.
- [28] J. W. Friedberg, A. Fischman, D. Neuberg et al., "FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo Hodgkin lymphoma: a blinded comparison," *Leukemia & Lymphoma*, vol. 45, no. 1, pp. 85–92, 2004.
- [29] M. Hutchings, N. G. Mikhaeel, P. A. Fields, T. Nunan, and A. R. Timothy, "Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma," *Annals of Oncology*, vol. 16, no. 7, pp. 1160–1168, 2005.
- [30] M. Hutchings, A. Loft, M. Hansen et al., "FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma," *Blood*, vol. 107, no. 1, pp. 52–59, 2006.
- [31] A. Gallamini, M. Hutchings, L. Rigacci et al., "Early interim 2-[¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study," *Journal of Clinical Oncology*, vol. 25, no. 24, pp. 3746–3752, 2007.
- [32] P. L. Zinzani, M. Tani, S. Fanti et al., "Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients," *Annals of Oncology*, vol. 17, no. 8, pp. 1296–1300, 2006.
- [33] S. Querellou, F. Valette, C. Bodet-Milin et al., "FDG-PET/CT predicts outcome in patients with aggressive non-Hodgkin's lymphoma and Hodgkin's disease," *Annals of Hematology*, vol. 85, no. 11, pp. 759–767, 2006.
- [34] A. Gallamini, L. Rigacci, F. Merli et al., "The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease," *Haematologica*, vol. 91, no. 4, pp. 475–481, 2006.
- [35] D. J. Sher, P. M. Mauch, A. Van Den Abbeele, A. S. LaCasce, J. Czerminski, and A. K. Ng, "Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy," *Annals of Oncology*, vol. 20, no. 11, pp. 1848–1853, 2009.
- [36] J. Markova, C. Kobe, M. Skopalova et al., "FDG-PET for assessment of early treatment response after four cycles of chemotherapy in patients with advanced-stage Hodgkin's lymphoma has a high negative predictive value," *Annals of Oncology*, vol. 20, no. 7, pp. 1270–1274, 2009.
- [37] C. Furth, I. G. Steffen, H. Amthauer et al., "Early and late therapy response assessment with [¹⁸F]fluorodeoxyglucose positron emission tomography in pediatric Hodgkin's lymphoma: analysis of a prospective multicenter trial," *Journal of Clinical Oncology*, vol. 27, no. 26, pp. 4385–4391, 2009.
- [38] A. Avigdor, S. Bulvik, I. Levi et al., "Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin's lymphoma," *Annals of Oncology*, vol. 21, no. 1, pp. 126–132, 2010.
- [39] A. Gallamini, S. Viviani, V. Bonfante et al., "Early interim FDG-PET during intensified BEACOPP therapy for advanced-stage Hodgkin disease shows a lower predictive value than during ABVD," *Haematologica*, vol. 92, suppl. 1, supplement 1, pp. 143–144, abstract 0392, 2007.
- [40] P. Castellucci, P. Zinzani, M. Pourdehnad et al., "18F-FDG PET in malignant lymphoma: significance of positive findings," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 32, no. 7, pp. 749–756, 2005.
- [41] Y. Sugawara, S. J. Fisher, K. R. Zasadny, P. V. Kison, L. H. Baker, and R. L. Wahl, "Preclinical and clinical studies of bone marrow uptake of fluorine-18-fluorodeoxyglucose with or without granulocyte colony-stimulating factor during chemotherapy," *Journal of Clinical Oncology*, vol. 16, no. 1, pp. 173–180, 1998.
- [42] C. Steidl, T. Lee, S. P. Shah et al., "Tumor-associated macrophages and survival in classic Hodgkin's lymphoma," *The New England Journal of Medicine*, vol. 362, no. 10, pp. 875–885, 2010.
- [43] E. D. Hsi, "Biologic features of Hodgkin lymphoma and the development of biologic prognostic factors in Hodgkin lymphoma: tumor and microenvironment," *Leukemia & Lymphoma*, vol. 49, no. 9, pp. 1668–1680, 2008.
- [44] Y. L. Kasamon, R. L. Wahl, H. A. Ziessman et al., "Phase II study of risk-adapted therapy of newly diagnosed, aggressive

- non-Hodgkin lymphoma based on midtreatment FDG-PET scanning," *Biology of Blood and Marrow Transplantation*, vol. 15, no. 2, pp. 242–248, 2009.
- [45] C. H. Moskowitz, J. Yahalom, A. D. Zelenetz et al., "High-dose chemo-radiotherapy for relapsed or refractory Hodgkin lymphoma and the significance of pre-transplant functional imaging: research paper," *British Journal of Haematology*, vol. 148, no. 6, pp. 890–897, 2010.
- [46] K. Dunleavy, R. F. Little, S. Pittaluga et al., "The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma," *Blood*, vol. 115, no. 15, pp. 3017–3024, 2010.
- [47] "PET scan in planning treatment in patients undergoing combination chemotherapy for stage IA or stage IIA Hodgkin lymphoma (a randomised phase III trial to determine the role of FDG-PET imaging in clinical stages IA/IIA Hodgkin's disease)," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00943423>.
- [48] "HD16 for early stage Hodgkin lymphoma (HD16 for early stages-treatment optimization trial in the first-line treatment of early stage Hodgkin lymphoma; treatment stratification by means of FDG-PET)," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00736320>.
- [49] "Fludeoxyglucose F 18 PET scan-guided therapy or standard therapy in treating patients with previously untreated stage I or stage II Hodgkin's lymphoma (the H10 EORTC/GELA/IIIL randomized intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stage I/II Hodgkin's lymphoma)," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00433433>.
- [50] "HD18 for advanced stages in Hodgkin's lymphoma," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00515554>.
- [51] "Fludeoxyglucose F 18-PET/CT imaging in assessing response to chemotherapy in patients with newly diagnosed stage II, stage III, or stage IV Hodgkin lymphoma (a randomized phase III trial to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin lymphoma)," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00678327>.
- [52] "High-dose chemotherapy and stem cell transplantation, in patients PET-2 positive, after 2 courses of ABVD and comparison of RT versus no RT in PET-2 negative patients (HD0801) (Early salvage with high dose chemotherapy and stem cell transplantation in advanced stage Hodgkin's lymphoma patients with positive PET after two courses of ABVD [PET-2 positive] and comparison of RT versus no RT in PET-2 negative patients)," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00784537>.
- [53] "Positron emission tomography (PET)-adapted chemotherapy in advanced Hodgkin Lymphoma (HL) (HD0607) (multicenter clinical study with early treatment intensification in patients with high-risk Hodgkin lymphoma, identified as FDG-PET scan positive after 2 conventional ABVD courses)," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00795613>.
- [54] "Fludeoxyglucose F 18-PET/CT imaging and combination chemotherapy with or without additional chemotherapy and G-CSF in treating patients with stage III or stage IV Hodgkin lymphoma (a phase II trial of response-adapted therapy of stage III-IV Hodgkin lymphoma using early interim FDG-PET imaging)," July 2010, <http://www.clinicaltrials.gov/ct2/show/NCT00822120>.
- [55] "Combination chemotherapy and radiation therapy in treating young patients with newly diagnosed Hodgkin lymphoma (a non-randomized phase III study of response adapted therapy for the treatment of children with newly diagnosed high risk Hodgkin lymphoma)," August 2010, <http://www.clinicaltrials.gov/ct2/show/NCT01026220>.
- [56] B. M. P. Aleman, A. W. van den Belt-Dusebout, W. J. Klokmann, M. B. van't Veer, H. Bartelink, and F. E. van Leeuwen, "Long-term cause-specific mortality of patients treated for Hodgkin's disease," *Journal of Clinical Oncology*, vol. 21, no. 18, pp. 3431–3439, 2003.
- [57] T. Girinsky, R. van der Maazen, L. Specht et al., "Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines," *Radiotherapy and Oncology*, vol. 79, no. 3, pp. 270–277, 2006.
- [58] H. Eghbali, P. Brice, G. Creemers et al., "Comparison of three radiation dose levels after EBVP regimen in favorable supradiaphragmatic clinical stages (CS) I-II Hodgkin's lymphoma (HL): preliminary results of the EORTC-GELA H9-F trial," *Blood*, vol. 106, no. 11, abstract 814, 2005.
- [59] D. J. Straus, C. S. Portlock, J. Qin et al., "Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease," *Blood*, vol. 104, no. 12, pp. 3483–3489, 2004.
- [60] S. Laskar, T. Gupta, S. Vimal 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?" *Journal of Clinical Oncology*, vol. 22, no. 1, pp. 62–68, 2004.
- [61] K. A. Fox, S. M. Lippmann, and J. R. Cassady, "Radiation therapy salvage of Hodgkin's disease following chemotherapy failure," *Journal of Clinical Oncology*, vol. 5, no. 1, pp. 38–45, 1987.
- [62] R. Advani, L. Maeda, P. Lavori et al., "Impact of positive positron emission tomography on prediction of freedom from progression after Stanford V chemotherapy in Hodgkin's disease," *Journal of Clinical Oncology*, vol. 25, no. 25, pp. 3902–3907, 2007.
- [63] V. Diehl, J. Franklin, M. Pfreundschuh et al., "Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease," *The New England Journal of Medicine*, vol. 348, no. 24, pp. 2386–2395, 2003.
- [64] A. Engert, V. Diehl, J. Franklin et al., "Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study," *Journal of Clinical Oncology*, vol. 27, no. 27, pp. 4548–4554, 2009.
- [65] A. M. Gianni, A. Rambaldi, P. Zinzani et al., "Comparable 3-year outcome following ABVD or BEACOPP first-line chemotherapy, plus pre-planned high-dose salvage, in advanced Hodgkin lymphoma (HL): a randomized trial of the Michelangelo, GITIL and IIL cooperative groups," *Journal of Clinical Oncology*, vol. 26, no. 20s, abstract 8506, 2008.
- [66] M. Federico, S. Luminari, E. Iannitto et al., "ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 gruppo italiano Per lo studio dei linfomi trial," *Journal of Clinical Oncology*, vol. 27, no. 5, pp. 805–811, 2009.
- [67] A. Younes, J. Romaguera, F. Hagemester et al., "A pilot study of rituximab in patients with recurrent, classic Hodgkin disease," *Cancer*, vol. 98, no. 2, pp. 310–314, 2003.

- [68] R. J. Jones, C. D. Gocke, Y. L. Kasamon et al., "Circulating clonotypic B cells in classic Hodgkin lymphoma," *Blood*, vol. 113, no. 23, pp. 5920–5926, 2009.
- [69] B. M. P. Aleman, J. M. M. Raemaekers, U. Tirelli et al., "Involved-field radiotherapy for advanced Hodgkin's lymphoma," *The New England Journal of Medicine*, vol. 348, no. 24, pp. 2396–2406, 2003.
- [70] M. Loeffler, O. Brosteanu, D. Hasenclever et al., "Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease," *Journal of Clinical Oncology*, vol. 16, no. 3, pp. 818–829, 1998.
- [71] C. J. Fabian, C. M. Mansfield, S. Dahlberg et al., "Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease: a Southwest Oncology Group randomized study," *Annals of Internal Medicine*, vol. 120, no. 11, pp. 903–912, 1994.
- [72] P. W. Johnson, M. R. Sydes, B. W. Hancock, M. Cullen, J. A. Radford, and S. P. Stenning, "Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519)," *Journal of Clinical Oncology*, vol. 28, no. 20, pp. 3352–3359, 2010.
- [73] N. Schmitz, B. Pfistner, M. Sextro et al., "Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial," *The Lancet*, vol. 359, no. 9323, pp. 2065–2071, 2002.
- [74] G. Akpek, R. F. Ambinder, S. Piantadosi et al., "Long-term results of blood and marrow transplantation for Hodgkin's Lymphoma," *Journal of Clinical Oncology*, vol. 19, no. 23, pp. 4314–4321, 2001.
- [75] A. R. Yuen, S. A. Rosenberg, R. T. Hoppe, J. D. Halpern, and S. J. Horning, "Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent or refractory Hodgkin's disease," *Blood*, vol. 89, no. 3, pp. 814–822, 1997.
- [76] N. Schmitz, H. Haverkamp, A. Josting et al., "Long term follow up in relapsed Hodgkin's disease (HD): updated results of the HD-R1 study comparing conventional chemotherapy (cCT) to high-dose chemotherapy (HDCT) with autologous haemopoietic stem cell transplantation (ASCT) of the German Hodgkin Study Group (GHSG) and the Working Party Lymphoma of the European Group for Blood and Marrow Transplantation (EBMT)," *Journal of Clinical Oncology*, vol. 23, no. 16S, abstract 6508, 2005.
- [77] T. Philip, C. Guglielmi, A. Hagenbeek et al., "Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma," *The New England Journal of Medicine*, vol. 333, no. 23, pp. 1540–1545, 1995.
- [78] N. Wadehra, S. Farag, B. Bolwell et al., "Long-term outcome of Hodgkin disease patients following high-dose busulfan, etoposide, cyclophosphamide, and autologous stem cell transplantation," *Biology of Blood and Marrow Transplantation*, vol. 12, no. 12, pp. 1343–1349, 2006.
- [79] T. Philip, J. O. Armitage, and G. Spitzer, "High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma," *The New England Journal of Medicine*, vol. 316, no. 24, pp. 1493–1498, 1987.
- [80] L. S. Poulou, L. Thanos, and P. D. Ziakas, "Unifying the predictive value of pretransplant FDG PET in patients with lymphoma: a review and meta-analysis of published trials," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 37, no. 1, pp. 156–162, 2010.
- [81] K. Spaepen, S. Stroobants, P. Dupont et al., "Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation," *Blood*, vol. 102, no. 1, pp. 53–59, 2003.
- [82] B. W. Schot, J. M. Zijlstra, W. J. Sluiter et al., "Early FDG-PET assessment in combination with clinical risk scores determines prognosis in recurring lymphoma," *Blood*, vol. 109, no. 2, pp. 486–491, 2007.
- [83] E. Jabbour, C. Hosing, G. Ayers et al., "Pretransplant positive positron emission tomography/gallium scans predict poor outcome in patients with recurrent/refractory Hodgkin lymphoma," *Cancer*, vol. 109, no. 12, pp. 2481–2489, 2007.
- [84] L. Castagna, S. Bramanti, M. Balzarotti et al., "Predictive value of early 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) during salvage chemotherapy in relapsing/refractory Hodgkin lymphoma (HL) treated with high-dose chemotherapy," *British Journal of Haematology*, vol. 145, no. 3, pp. 369–372, 2009.
- [85] Y. L. Kasamon and R. L. Wahl, "FDG PET and risk-adapted therapy in Hodgkin's and non-Hodgkin's lymphoma," *Current Opinion in Oncology*, vol. 20, no. 2, pp. 206–219, 2008.
- [86] J. M. Engles, S. A. Quarless, E. Mambo, T. Ishimori, S. Y. Cho, and R. L. Wahl, "Stunning and its effect on 3H-FDG uptake and key gene expression in breast cancer cells undergoing chemotherapy," *Journal of Nuclear Medicine*, vol. 47, no. 4, pp. 603–608, 2006.
- [87] M. Meignan, E. Itti, S. Bardet et al., "Development and application of a real-time on-line blinded independent central review of interim PET scans to determine treatment allocation in lymphoma trials," *Journal of Clinical Oncology*, vol. 27, no. 16, pp. 2739–2741, 2009.
- [88] S. F. Barrington, W. Qian, E. J. Somer et al., "Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 37, no. 10, pp. 1824–1833, 2010.
- [89] M. Meignan, "Interim PET in lymphoma: a step towards standardization," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 37, no. 10, pp. 1821–1823, 2010.
- [90] G. J. Kelloff, D. M. Sullivan, W. Wilson et al., "FDG-PET lymphoma demonstration project invitational workshop," *Academic Radiology*, vol. 14, no. 3, pp. 330–339, 2007.
- [91] M. Meignan, A. Gallamini, M. Meignan, A. Gallamini, and C. Haioun, "Report on the first international workshop on interim-PET-scan in lymphoma," *Leukemia & Lymphoma*, vol. 50, no. 8, pp. 1257–1260, 2009.
- [92] C. Lin, E. Itti, C. Haioun et al., "Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis," *Journal of Nuclear Medicine*, vol. 48, no. 10, pp. 1626–1632, 2007.
- [93] E. Itti, C. Lin, J. Dupuis et al., "Prognostic value of interim 18F-FDG PET in patients with diffuse large B-cell lymphoma: SUV-based assessment at 4 cycles of chemotherapy," *Journal of Nuclear Medicine*, vol. 50, no. 4, pp. 527–533, 2009.
- [94] R. L. Wahl, H. Jacene, Y. Kasamon, and M. A. Lodge, "From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors," *Journal of Nuclear Medicine*, vol. 50, no. 1, pp. 122S–150S, 2009.

- [95] S. J. Horning, M. E. Juweid, H. Schöder et al., “Interim positron emission tomography scans in diffuse large B-cell lymphoma: an independent expert nuclear medicine evaluation of the Eastern Cooperative Oncology Group E3404 study,” *Blood*, vol. 115, no. 4, pp. 775–777, 2010.
- [96] H. A. Jacene, S. Lebolleux, S. Baba et al., “Assessment of interobserver reproducibility in quantitative 18F-FDG PET and CT measurements of tumor response to therapy,” *Journal of Nuclear Medicine*, vol. 50, no. 11, pp. 1760–1769, 2009.
- [97] S. F. Barrington, J. E. Mackewn, P. Schleyer et al., “Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma,” *Annals of Oncology*, September 2010.
- [98] R. T. Hoppe, F. H. Advani, W. Z. Ai et al., “NCCN practice guidelines in oncology - Hodgkin lymphoma, v.2.2010,” August 2010, http://www.nccn.org/professionals/physician_gls/PDF/hodgkins.pdf.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

