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End-of-treatment but not interim PET scan predicts outcome in nonbulky limited-stage Hodgkin's lymphoma

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Background: Early interim positron emission tomography (PET) scans appear powerfully predictive of outcome in Hodgkin's lymphoma (HL), particularly in advanced-stage disease where it has been predominantly studied. The prognostic value of interim PET in limited-stage patients with nonbulky disease has not been well established.
Patients and methods: Ninety-six patients with nonbulky limited-stage HL were identified who had interim and end-of-treatment PET scans. Response rate, overall survival (OS), and progression-free survival (PFS) were calculated.
Results: Four-year PFS and OS for the entire cohort were 88% and 97%, respectively. Interim PET did not predict outcome, with PFS in positive and negative patients 87% versus 91% ($P = 0.57$), respectively. End-of-treatment PET result was predictive of outcome, with PFS of 94% in end PET-negative patients versus 54% in end PET-positive patients ($P < 0.0001$). Four-year OS was 100% in end PET-negative patients and 84% in end PET-positive patients ($P < 0.0001$).
Conclusions: Interim PET scans were not predictive of outcome, compared with scans carried out at completion of therapy. End-of-treatment PET was highly predictive of PFS and OS, regardless of interim PET result. In this low-risk patient population, even patients with interim positive PET scans show a favorable prognosis.
Key words: FDG-PET, HL, Hodgkin's disease, interim, prognosis, staging

introduction

Classical Hodgkin's lymphoma (cHL) carries one of the most favorable prognoses in oncology. Treatment is guided by clinical stage, with limited-stage patients experiencing cure rates approximating 90% and advanced-stage patients experiencing cure rates of 75%, on average [1–4]. 2-[Fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET) scanning has emerged as an important tool in the initial staging, remission assessment, and prognostication of Hodgkin's lymphoma (HL). In particular, PET scans early in the course of therapy appear to be powerfully predictive of outcome, particularly in advanced-stage disease where the prognostic value of PET has been predominantly studied [5–10]. The value of interim PET scans in the 20%–25% of limited-stage patients who present with nonbulky disease has not been well elucidated [1, 11–13].

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Treatment of limited-stage disease continues to evolve with current efforts focused on preserving high rates of cure while minimizing potentially devastating late effects of radiation and chemotherapy. Recent data show that many patients with limited-stage disease will not benefit from consolidative radiation [3, 14–16], although a small minority of patients will still relapse and die due to omission of radiotherapy from their treatment plan. Presently, there is no validated way to identify patients who may benefit preferentially from treatment intensification early in their course of therapy. Here, we present a retrospective analysis from two academic lymphoma centers on the prognostic value of both interim and end-of-treatment PET scans in patients with nonbulky limited-stage HL treated with a combination of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), with or without radiation.

materials and methods

study design

We queried our institutional review board-approved comprehensive clinicopathological database of hematologic malignancy patients at the

Massachusetts General Hospital Cancer Center and Dana-Farber Cancer Institute for all adult HL patients diagnosed and treated at our institutions with available PET imaging from 1 January 2000 through 31 December 2008. One hundred fifty-five cases were identified. Subjects were then selected for inclusion in our analysis if they had limited-stage nonbulky disease (defined as mass <10 cm or less than one-third of the intrathoracic diameter for mediastinal disease), had cHL histology, had received ABVD chemotherapy, and had both interim PET imaging after two to four cycles of treatment and end-of-treatment PET imaging. All subjects had to have cHL; nodular lymphocyte predominant HL was excluded. Ninety-six subjects met the inclusion criteria and are included in the analysis.

central radiology review

For each FDG–PET study, 10–20 mCi FDG was administered i.v. and images were obtained after a radiopharmaceutical uptake period of ∼60 min. Whole-body FDG–PET images were acquired from the base of the skull to the mid-thighs using a PET or a combined PET–computed tomography scanner. All PET images were corrected for detector efficiency, attenuation, scatter, decay, and random coincidences. Two nuclear medicine physicians (KZ and DI) evaluated each PET study for evidence of FDG-avid disease, with the final result based on consensus. Interim and end-of-treatment PET studies were graded on a four-point scale for likelihood of residual metabolically active disease. A grade of 0 indicated there was no evidence of FDG-avid lymphoma. A grade of 1 indicated, that although there was abnormal radiotracer uptake, the PET study was likely negative for FDG-avid neoplastic disease. A grade of 2 indicated an indeterminate study. A grade of 3 indicated the PET was likely positive for FDG-avid neoplastic disease, whereas a grade of 4 indicated there was definite FDG-avid neoplastic disease. There were two indeterminate PET studies, one interim PET and one PET carried out at the end of treatment, which were included in the positive group at the time of analysis. Therefore, for the purposes of analysis, PET studies with grade 0 or 1 were considered negative for FDG-avid lymphoma, whereas PET studies with grades 2–4 were considered positive for FDG-avid lymphoma.

statistical analysis

Primary end points were overall survival (OS) and progression-free survival (PFS). OS was defined as time from initial pathological diagnosis to death from any cause. PFS is defined as the time from diagnosis to progression or death from any cause. Kaplan–Meier estimates of PFS and OS were calculated along with their corresponding 95% confidence intervals, and significance was tested with the log-rank test. The overall response rate (ORR) was defined as the number of subjects with either complete response (CR) or partial response (PR) according to the revised response criteria for malignant lymphoma [17]. Comparison of CR rate between treatment groups was analyzed using Fisher's exact test with a two-sided significance level of 0.05. Primary refractory disease was defined as progressive disease on treatment or relapse within 3 months of completing therapy.

results

patient characteristics

Patient characteristics are summarized in Table 1. The median age was 34 (range 18–77 years). Seventeen (18%) patients were ≥50 years old, 22 (23%) presented with 'B' symptoms, and 8 (8%) had involvement of more than three nodal sites. Erythrocyte sedimentation rate was not available for most patients. The majority of patients had Ann Arbor [18] stage II disease (88%). Seventy-two (75%) patients had nodular sclerosis cHL, with 9 (9%) having mixed cellularity and 15 (16%) having cHL not otherwise specified. A majority of patients had interim PET carried out after cycle 2 (43%) or cycle 3 (47%). Forty-one (43%) patients received six cycles of ABVD without radiation therapy as part of the initial treatment plan. Fifty-four (56%) received combined modality therapy with four to six cycles of ABVD followed by involved-field radiotherapy at 30–36 Gy. Given the retrospective nature of this study, treatment was determined by physicians in consultation with their patients and was not prospectively mandated.

Table 1. Patient characteristics

	All patients, $N = 96$ (%)
Sex	
Male	44 (46)
Female	52 (54)
Age, median (range), years	34 (18–77)
Follow-up, median (range), months	46 (6–107)
Risk factors	
Age ≥50 years	17 (18)
B symptoms	22 (23)
> 3 nodal sites	8 (8)
Stage	
IA	11 (11)
IB	1 (1)
IIA	63 (66)
IIB	21 (22)
Histological type	
NS	72 (75)
MC	9 (9)
CHL, nos	15 (16)
Timing of interim PET	
Cycle 2B	41 (43)
Cycle 3A	6 (6)
Cycle 3B	45 (47)
Cycle 4A	4 (4)
Treatment	
ABVD ×4	1 (1)
ABVD ×6	41 (43)
ABVD ×4 + IFRT	25 (26)
ABVD ×6 + IFRT	29 (30)

ABVD, Adriamycin, bleomycin, vinblastine, and dacarbazine; cHL, classical Hodgkin's lymphoma; IFRT, involved-field radiotherapy; MC, mixed cellularity; NS, nodular sclerosis; nos, not otherwise specified; PET, positron emission tomography.

outcome

The ORR for all patients was 98%, with a CR rate of 86%. At a median follow-up of 46 months (range 6–107), PFS and OS for the entire cohort were 88% and 97%, respectively (Figure 1). The inclusion of planned consolidative radiation did not predict outcome, with univariate analysis of both PFS and OS showing no difference between radiated versus nonradiated patients with 4-year PFS 91% versus 90% ($P = 0.95$) and 4-year OS 98% versus 100% ($P = 0.89$), respectively.

The results of PET imaging are presented in Figure 2. Seventy-nine (82%) patients had a negative interim PET scan,

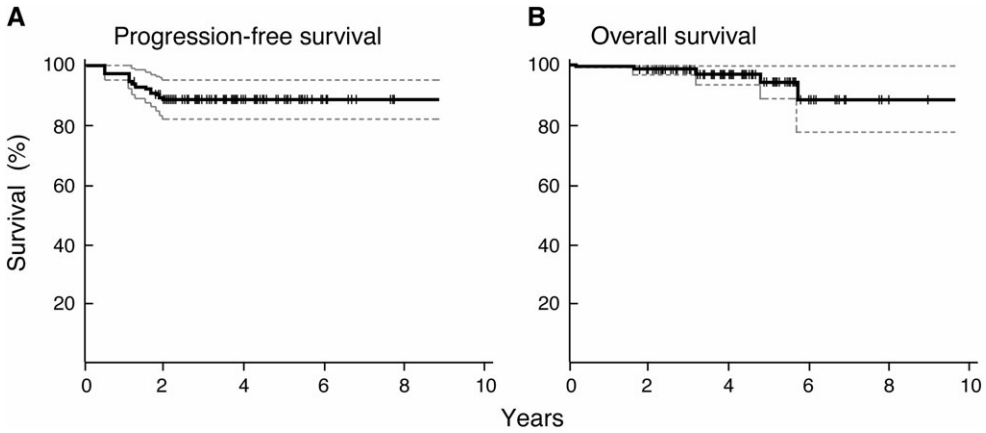

Figure 1. (A) Progression-free survival and (B) overall survival for the entire cohort.

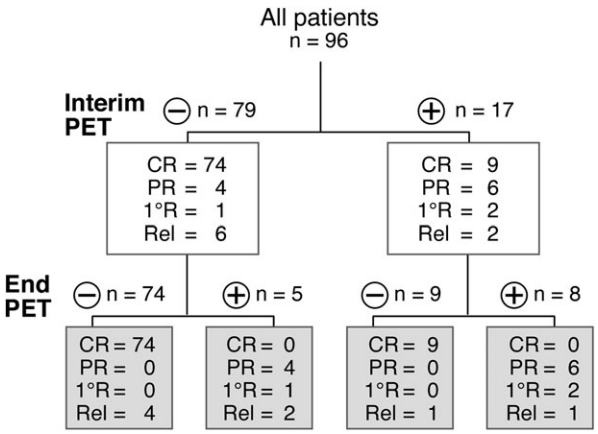

Figure 2. Flow chart showing clinical outcome for results according to interim PET. 1°R, primary refractory disease defined as persistent disease or relapse within 3 months of completing therapy; CR, complete response; PET, positron emission tomography; PR, partial response; REL, relapses occurring >3 months after completion of therapy.

whereas 17 (18%) were positive. Among the 79 interim PET-negative patients, 74 (94%) went on to have a negative end-of-treatment PET scan, whereas 5 patients turned PET positive at the end of treatment. Among the 17 patients with a positive interim PET scan, 9 (53%) subsequently went negative at the end of treatment, whereas 8 remained PET positive. The ORR was 100% in patients with a negative interim PET scan, compared with 88% in those who were interim positive ($P = 0.03$). Seventy-four of 79 patients (93%) in the interim PET-negative group achieved CR at the end of therapy compared with 9 of 17 patients (53%) with a positive interim scan ($P = 0.0001$). Three patients had primary refractory disease apparent within 1 month of completing initial therapy. Eight patients relapsed after achieving CR, five of whom had received prior radiation as part of their initial treatment; one relapse occurred outside the radiation field.

Interim PET scan did not predict outcome, with univariate analysis of both PFS and OS showing no difference between the two groups with 4-year PFS 87% versus 91% ($P = 0.57$) and 4-year OS 87% versus 100% ($P = 0.09$) (Figure 3A). End-of-treatment PET, however, was predictive of outcome. At a follow-up of 4 years, the PFS for end PET-negative patients was 94%, compared with 54% for end PET-positive patients ($P < 0.0001$) (Figure 3B). OS was similarly better in end PET-negative patients, with 100% remaining alive compared with 84% with positive PET at end of treatment ($P < 0.0001$).

Nine patients converted from an interim positive scan to a negative PET scan at the end of treatment, with a 4-year PFS of 89% and OS of 100%. Five patients converted from an interim negative scan to an end positive scan, with a 4-year PFS of 40% and OS of 100% (Figure 4A and B).

discussion

We present a retrospective analysis of the role of interim and end-of-treatment PET imaging in predicting outcome in patients with limited-stage nonbulky cHL. We found that interim PET results were not strongly predictive of outcome, compared with scans carried out at completion of therapy. Patients who were interim PET positive but converted to end PET negative did as well as those who were both interim and end negative without intensification of chemotherapy. End-of-treatment PET was highly predictive of PFS and OS, with 4-year OS of 100% for end PET-negative patients, regardless of interim PET status. For the entire cohort, no progression was seen after 24 months, suggesting that late relapses are unlikely in this low-risk population. Notably, even end PET-positive patients did well with a 4-year OS of 84%, indicative of both false-positive rates of PET scans and the efficacy of salvage therapies available for relapsed low-risk patients.

Several studies to date have evaluated the role of interim PET imaging in patients with cHL, with or without bulky disease; all studies have shown that interim PET result predicts PFS [5–10]. None of these studies, however, correlated interim PET result with end-of-treatment PET scan, and only one of these studies specifically reported results in limited-stage patients [6]. That study included only 31 limited-stage patients, of whom 5 had a positive interim PET scan. Only 1 of 31 limited-stage patients in that series relapsed. Given the small patient number and lack of events, predictive value of interim PET in this cohort could not be interpreted. Our study differs from previous reports in that it is confined to limited-stage patients with non-bulky disease, and that we correlate interim PET results with

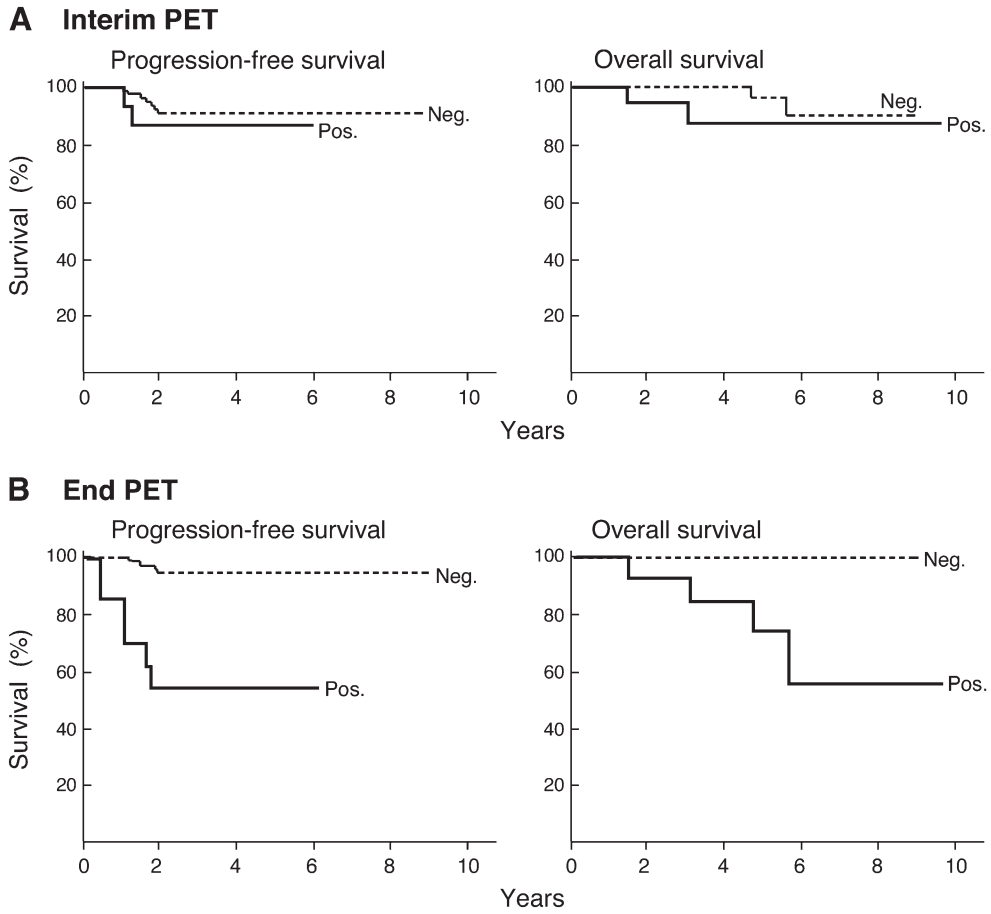

Figure 3. Survival by PET result. (A) Progression-free survival (PFS) of interim PET positive versus negative ($P = 0.57$). Overall survival (OS) of interim PET positive versus negative ($P = 0.09$). (B) PFS of end PET positive versus negative ($P < 0.0001$). OS of end PET positive versus negative ($P < 0.0001$). Neg., negative; PET, positron emission tomography; Pos., positive.

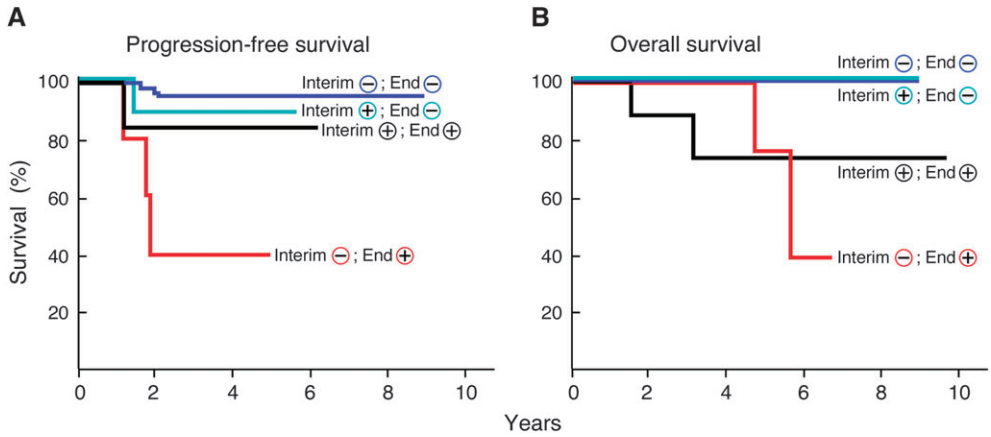

Figure 4. (A) Progression-free survival and (B) overall survival by both interim and end PET results.

end-of-treatment PET scan. Given results of prior series that included predominantly advanced-stage patients, it is likely that the predictive value of interim PET imaging is stronger in advanced-stage and higher risk patients as compared with our low-risk population. Our data show that the achievement of complete PET remission at the end of therapy is the critical predictor of outcome.

A key finding of our study is the poor value of the interim PET scan to predict patient outcome in this low-risk population. Nine of the 17 patients with positive interim PET scans went on to achieve a CR without escalation in chemotherapy, with only one relapse in this group. Notably, patients with a positive interim PET scan were more likely to receive consolidative radiation, 15 of 17 (88%) compared with

43 of 79 (54%) of interim PET-negative patients ($P = 0.01$), so this may have contributed to their favorable outcome. Two of nine patients in our series who turned interim PET positive to end PET negative did not receive radiation and remain free of disease. Analysis of consolidative radiation in the entire cohort, however, did not show an impact on outcome. It may be that among patients with nonbulky localized disease, consolidative radiation can be selectively targeted to only those patients who are interim PET-positive, but our data include too few patients to draw definitive conclusions and this is a question best addressed by a prospective randomized trial.

In our data, the ability to achieve a CR on PET scan at the end of therapy rather than after two to three cycles of chemotherapy is the most important radiographic prognostic factor in nonbulky limited-stage disease. The observation in previous studies that interim PET is powerfully predictive of outcome has led some to modify treatment programs based on that interim PET scan result, but no randomized trial published to date validates that approach. Our data show that outcome remains favorable even for patients in our series with a positive interim PET scan. Approximately half of patients in our series who were interim PET positive converted to PET negative at end of treatment without intensification of systemic therapy and experienced similar outcomes as their interim PET-negative counterparts. One reason for the encouraging OS for patients in our series regardless of PET scan result may be the availability of curative therapy at relapse, particularly in low-risk patients. An additional reason may be a higher rate of false-positive PET uptake on interim scans that are carried out within 2 weeks of prior chemotherapy exposure, although this has not been definitely established in cHL. In a prospective trial of another aggressive lymphoma, diffuse large B-cell lymphoma, only 5 of 38 patients with a positive interim PET scan had biopsy-proven persistent disease [19]. End-of-treatment PET scans will typically be carried out 4–6 weeks after completion of therapy, potentially allowing for reduction in treatment-related inflammation and a decreased false-positive rate. Only 3 of the 13 patients with positive end-of-treatment PET scans had biopsies in our population, all of which were positive for cHL; no biopsies were carried out for interim PET positivity in our series. Whether therapy can be de-escalated for low-risk patients with early negative PET scans also remains an unanswered question worthy of prospective investigation.

To our knowledge, this is the first report on the value of interim PET scans specifically in limited-stage nonbulky HL. The study is limited by its retrospective nature as well as the nonuniform timing of PET scans, although all radiology was centrally reviewed by two nuclear radiologists who concurred on interpretations. Application of consolidative radiation was also nonuniform, making the role of radiation difficult to assess in this analysis. Despite limitations, our study yields valuable observations. The interim PET was not predictive of either PFS or OS in these low-risk patients, although end-of-treatment PET response was highly predictive. We confirm the strong negative predictive value of both interim and end-of-treatment PET scans and also show that low-risk patients with positive interim PET scans may achieve a CR at the end of therapy and enjoy an excellent prognosis without treatment intensification. Patients with either positive or negative interim PET scans in our study show a favorable OS, and no relapses were observed in any patient after 2 years. Treatment decisions based on interim functional imaging data are worthy of ongoing investigation and are best addressed in the context of prospective clinical trials.

disclosure

There are no relevant conflicts of interests to disclose.

references

1. Ferme C, Eghbali H, Meerwaldt JH et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007; 357(19): 1916–1927.
2. Canellos GP, Anderson JR, Propert KJ et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992; 327(21): 1478–1484.
3. Meyer RM, Gospodarowicz MK, Connors JM 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. J Clin Oncol 2005; 23(21): 4634–4642.
4. Federico M, Luminari S, Iannitto E 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. J Clin Oncol 2009; 27(5): 805–811.
5. Gallamini A, Hutchings M, Rigacci L 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. J Clin Oncol 2007; 25(24): 3746–3752.
6. Hutchings M, Loft A, Hansen M et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006; 107(1): 52–59.
7. Zinzani PL, Tani M, Fanti S et al. Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients. Ann Oncol 2006; 17(8): 1296–1300.
8. Advani R, Maeda L, Lavori P et al. Impact of positive positron emission tomography on prediction of freedom from progression after Stanford V chemotherapy in Hodgkin's disease. J Clin Oncol 2007; 25(25): 3902–3907.
9. Kobe C, Dietlein M, Franklin J 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(10): 3989–3994.
10. Furth C, Steffen IG, Amthauer H 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. J Clin Oncol 2009; 27(26): 4385–4391.
11. Noordijk EM, Carde P, Dupouy N et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 2006; 24(19): 3128–3135.
12. Bonadonna G, Bonfante V, Viviani S et al. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. J Clin Oncol 2004; 22(14): 2835–2841.
13. Hutchings M, Mikhaeel NG, Fields PA et al. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. Ann Oncol 2005; 16(7): 1160–1168.
14. Straus DJ, Portlock CS, Qin J 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 2004; 104(12): 3483–3489.
15. Canellos GP, Abramson JS, Fisher DC, LaCasce AS. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. J Clin Oncol 2010; 28(9): 1611–1615.
16. Rueda A, Olmos D, Viciana R, Alba E. Treatment for relapse in stage I/II Hodgkin's lymphoma after initial single-modality treatment. Clin Lymphoma Myeloma 2006; 6(5): 389–392.
17. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25(5): 579–586.
18. Lister TA 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(11): 1630–1636.
19. Moskowitz CH, Schoder H, Teruya-Feldstein J et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced-stage diffuse large B-cell lymphoma. J Clin Oncol 2010; 28(11): 1896–1903.