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Scientific Article

Importance of baseline PET/CT imaging on radiation field design and relapse rates in patients with Hodgkin lymphoma

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Abstract

Purpose: This study analyzed the impact of pretreatment positron emission tomography/computed tomography (PET/CT) scans on involved site radiation therapy (ISRT) field design and pattern of relapse among patients with Hodgkin lymphoma (HL).

Methods and materials: Thirty-seven patients with stage I or II HL who received first-line chemotherapy followed by consolidative ISRT to all initial sites of disease were enrolled in an institutional review board–approved outcomes-tracking protocol between January 2009 and December 2014. Patients underwent standard-of-care follow-up. Relapse-free survival (RFS) was evaluated using a Kaplan-Meier analysis and cohort comparisons using a χ^2 test.

Results: Thirty-one patients underwent (PET/CT) scans before chemotherapy and 6 did not because of a lack of insurance (n = 2), inpatient chemotherapy administration (n = 2), scheduling conflicts (n = 1), and unknown reasons (n = 1). The median follow-up was 46 months, and the 4-year RFS rate was 92%. Patients without pretreatment PET imaging were more likely to experience disease relapse (4-year RFS, 97% vs. 67%; $P = .001$). Among the 6 patients who did not receive a baseline PET/CT scan, all 3 recurrences occurred in lymph node regions outside of, but immediately adjacent to, the radiation field.

Conclusions: Patients with stage I/II HL who receive ISRT without pretreatment PET/CT scans appear to have an increased risk for relapse in adjacent nodal stations just outside the radiation field. A larger cohort with a longer follow-up is needed to confirm these findings.

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Introduction

Hodgkin lymphoma (HL) is a common cause of cancer in adolescents and young adults (AYA) and is the leading malignancy among adolescents aged 15 to 19 years.[1] The majority of patients who are treated with combined chemo- and radiation therapy (RT) are cured.[2–5] However, long-term survivors experience an increased incidence of late adverse effects, most notably cardiovascular events and secondary malignancies, as a result of previous chemoradiation exposure.[6] These late adverse effects are the impetus behind efforts to reduce radiation exposure to organs at risk by decreasing the prescribed radiation dose, decreasing the size of the radiation fields,[7] and using radiation techniques that create radiation dose distributions that better conform to the targeted tumor volume.[8]

Historically, patients with HL were staged by an exploratory laparotomy, which included a liver biopsy, splenectomy, and sample biopsies of abdominal lymph nodes. With advancements in imaging technology, noninvasive anatomic computed tomography (CT) imaging has supplanted the need for invasive staging. Positron emission tomography (PET)/CT has further refined the staging and radiation target delineation and often leads to smaller radiation treatment field designs.[7,9]

Involved site and involved node RT limit the radiation target volume to only what is seen on the PET/CT in contrast to the previously used involved field, which included other contiguous nodes in the involved region.[10,11] However, prechemotherapy PET/CT scans are essential for the development of these more-tailored radiation fields.[7,9]

Unfortunately, the AYA population is at risk for being uninsured or underinsured, which may affect the ability for timely staging of PET/CT scans and/or treatment. In the present study, we investigate the association between baseline PET/CT scans in designing radiation fields and the pattern of relapses among patients with HL.

Methods and materials

Fifty-seven consecutive patients with classical HL diagnosed between January 2009 and August 2015 who were treated with combined chemotherapy and RT and consented to enrollment in an institutional review board–approved institutional outcomes tracking protocol were evaluated. One patient was excluded because of composite HL and non-HL, 6 patients were excluded because of treatment of relapse disease, and 13 were excluded for advanced stage III/IV disease. The 37 remaining patients made up the cohort for the present study of early-stage (I/II) HL. Thirty-one of the patients had a PET/CT scan before starting chemotherapy (median time from diagnosis, 8 days; range, −5 days to 28 days), including 13 with complete diagnostic CT and/or magnetic resonance imaging (MRI) scans of the neck, chest, abdomen, and pelvis, and 19 with incomplete CT and/or MRI scans, including 14 with missing neck scans, 16 lacking abdomen/pelvis scans, and 3 lacking chest scans.

Two of the 6 patients without PET/CT imaging had a PET/CT scan performed within 5 days after chemotherapy initiation. Four patients had complete CT/MRI body imaging, but one patient was missing the neck scan, and one was missing the chest, abdomen, and pelvis scan (ie, patient only had a neck CT scan). The reasons for not receiving pretreatment PET/CT imaging included not having insurance (n = 2), not having coverage for PET/CT scans as an inpatient during chemotherapy initiation (n = 2), scheduling conflicts (n = 1), and an unknown reason unrelated to insurance coverage (n = 1). Patient, disease, and treatment characteristics and pretreatment PET/CT imaging status are listed in Table 1.

All patients received first-line chemotherapy before consolidative RT at our institution. A total of 29 adult patients received adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy over 2 (n = 3), 3 (n = 2), 4 (n = 12), or 6 cycles (n = 12) as first-line chemotherapy. Seven pediatric patients received 4 cycles

Table 1 Patient characteristics and disease factors (n = 37)

Patient Characteristics	PET scan (n = 31), No. of Patients (%))	No PET scan (n = 6), No. of Patients (%)	χ^2 (*P*-value)
Male	9 (29%)	4 (66%)	.157
Female	22 (71%)	2 (33%)	
Pediatric	7 (23%)	0	.571
Adult	24 (77%)	6 (100%)	
Bulky	16 (52%)	4 (66%)	.667
Non-bulky	15 (48%)	2 (33%)	
B Symptoms	6 (19%)	4 (66%)	.0347
No B Symptoms	25 (81%)	2 (33%)	
Stage			
I	5 (16%)	0	.567
II	26 (84%)	6 (100%)	
Risk level			
Stage IA/IIA	15 (48%)	1 (17%)	.206
Stage I/II B and/or bulky	16 (52%)	5 (83%)	
Chemotherapy			
ABVD	23 (74%)	6 (100%)	.317
ABVE-PC	7 (23%)	0	
VAMP	1 (3%)	0	
RT Dose			
≤30.6 Gy	23 (74%)	3 (50%)	.335
>31 Gy	8 (26%)	3 (50%)	

ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; ABVE-PC, adriamycin, bleomycin, vincristine sulfate, etoposide, prednisone, cyclophosphamide; PET, positron emission tomography; RT, radiation therapy; VAMP, vincristine sulfate, adriamycin, methotrexate, prednisone.

of adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) and one pediatric patient received 4 cycles of vincristine, adriamycin, methotrexate, and prednisone as first-line chemotherapy.

All available prechemotherapy imaging was used for treatment planning. At treatment simulation, attempts were made to reproduce the patient position during the prechemotherapy PET/CT scan to increase the accuracy of the involved site target delineation and RT treatment planning. Simulation included a 3-dimenstional CT scan with contrast and either a free-breathing 4-dimensional CT scan or 3 consecutive breath-hold 3-dimensional scans if the disease was located in the mediastinum or abdomen. Prechemotherapy PET/CT and/or CT imaging was fused with the planning simulation scans to assist with target delineation. The gross tumor volume, clinical target volume, and planning target volume were contoured in accordance with the International Lymphoma Radiation Oncology Group guidelines.[7] For patients without prechemotherapy PET/CT or complete diagnostic CT imaging, the field design was modified in an attempt to account for the uncertainties regarding the pretreatment extent of involvement. All nearby organs at risk were contoured and evaluated to ensure that proper dose constraints were met.

Patients were evaluated weekly for potential toxicities throughout their treatment course. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), Versions 3 and 4. Patients were assessed 1 month after completion of RT, then every 3 months for the first 2 years after treatment, and annually thereafter. Imaging was performed semiannually with a PET/CT or CT scan for the first 2 years after treatment. Patients underwent routine laboratory tests (complete blood count, erythrocyte sedimentation rate test, and thyroid function tests) every 3 months for 2 years, then semiannually for 5 years, and then annually.[12]

Statistical analysis

Differences in the characteristics of the patients who underwent pretreatment PET/CT imaging and those who did not were evaluated using a Fisher's exact test (a nonparametric χ^2 test). Relapse-free survival (RFS) was estimated with the Kaplan-Meier product limit method and defined as the development of a relapse of HL from the start of chemotherapy. A log-rank test was used to evaluate the impact of pretreatment PET/CT scan on rates of recurrence. A P-value $<.05$ was considered significant for all analyses.

Results

The median follow-up for the entire cohort was 46 months. The median age at diagnosis was 28 years (range, 7-73 years) with 20 patients who were aged $\leq$30 years and 30 patients aged $\leq$40 years. During follow-up, 4 recurrences developed (3 within 12 months of follow-up), with one recurrence in a patient with pretreatment PET/CT scans and 3 in patients without pretreatment PET/CT scans. Patients without pretreatment PET/CT imaging had an increased risk of relapse compared with those with pretreatment PET/CT scans (4-year RFS rate, 67% vs 97%; $P = .001$). The one recurrence among the 31 patients who received prechemotherapy PET/CT scans was in a pediatric patient with stage IIB bulky HL who was treated with 25.5 Gy after ABVE-PC chemotherapy. The patient experienced both an out-of-field recurrence in the lung and an in-field recurrence within the site of bulky mediastinal disease, which was shown to have residual CT abnormalities after chemotherapy.

All 3 recurrences among the 6 patients who did not receive prechemotherapy PET/CT scans occurred in patients with stage IIB bulky disease treated to 39.6 to 45 Gy after 6 cycles of first-line ABVD chemotherapy after interim PET/CT scans demonstrated an incomplete response. All recurrences developed in areas outside of, but adjacent to, the radiation treatment fields (Figs 1 and 2), raising the concern of possible inadequate field coverage. These out-of-field recurrences included right cervical neck relapse after radiation to the mediastinal region alone despite a PET/CT scan 5 days after chemotherapy initiation that was considered negative within the neck, cardiophrenic lymph node relapse after mediastinal and cervical radiation, and para-aortic node relapse after bilateral neck, axilla, and mediastinal radiation. None of these 3 recurred in sites of bulky disease nor in sites with residual CT abnormalities after chemotherapy. Two of the recurrences occurred completely outside of the radiation field, with an expected dose of <1 Gy. The third recurrence developed 5 years after treatment, with the center of the recurrence being outside of the radiation field (expected dose <1 Gy) but with the most inferior extent of the recurrence abutting the treatment field in an area that received approximately 25 to 30 Gy of radiation. None of the 6 patients without pretreatment PET/CT imaging experienced an in-field treatment failure.

Discussion

Innovations in radiation therapy have allowed for smaller treatment fields that decrease radiation-associated toxicities while maintaining the current rates of disease control in patients with HL. Most notably, advancements in modern imaging have improved disease localization, which allows for a decrease in the volume of tissue irradiated, and novel radiation delivery techniques have allowed for the possibility of sparing nearby critical structures. However, smaller treatment fields increase the

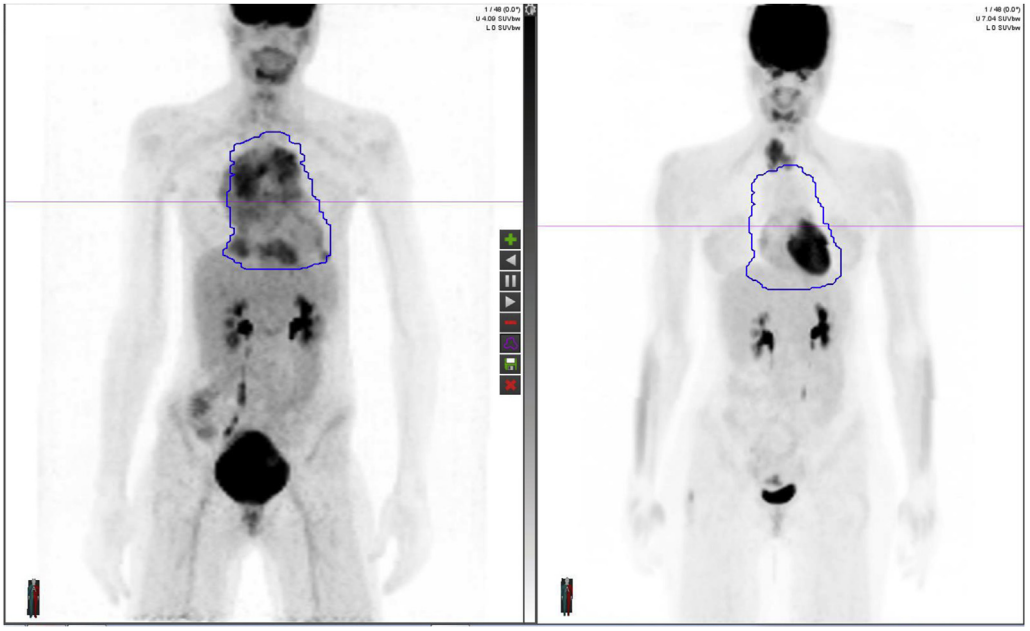

Figure 1 Positron emission tomography (PET)/computed tomography (CT) scan 4 days after the start of chemotherapy with adriamycin, bleomycin, vinblastine, and dacarbazine with the CT simulation clinical target volume (CTV) in blue superimposed after fusion (left). PET/CT scan 5 years later with the CT simulation CTV in blue superimposed after fusion with a new PET-positive relapse in the right medial neck, just superior to the previously treated field (right).

risk of marginal misses. Because HL predominantly recurs at sites of previous disease involvement, it is critical to obtain complete pretreatment anatomic and functional imaging to ensure that the extent of disease is delineated as accurately as possible, which will affect both disease control and late normal tissue effects.

PET/CT scans have recently become the gold standard in determining the extent of HL, with a specificity and sensitivity that is superior to that of CT scans alone.[13,14] Studies have shown that the addition of PET/CT scans, compared with using only pretreatment contrast-enhanced CT scans, can alter the staging in 10% to 30% of patients with HL. In most cases, the addition of PET/CT demonstrates additional sites of involvement that are not appreciated on simple anatomic imaging.[14–17] Our study suggests a higher rate of disease progression in patients without pretreatment PET/CT that is related to inadequate field size. Almost universally, the reason for not obtaining a pretreatment PET/CT scan has been related to insurance coverage or hospital reimbursement.

Pretreatment PET/CT scans are especially important from the perspective of radiation oncologists. With a greater specificity and sensitivity, functional imaging can elucidate numerous involved sites, which could drastically alter the design of the radiation treatment field.[18,19] HL predominately recurs in sites of previous disease involvement. RT has been shown to be the most effective single modality for local control of HL. Therefore, using the most optimal imaging to ensure complete radiation coverage is essential.[20] Girinsky et al demonstrated that the addition of a pretreatment PET/CT scan commonly alters both the interpretation of the primary tumor burden and the nodal involvement.[21] A PET/CT scan altered the size of the gross tumor volume in 86% of patients, most of whom saw an increase in gross tumor volume. Along with the difference in the primary tumor burden, the addition of pretreatment PET scans also elucidates additional lymph node disease in 70% of patients. These discrepancies ultimately lead to significant differences in the final planned treatment volumes.[22]

The importance of pretreatment PET/CT scans and their superiority to contrast-enhanced CT alone has been well understood and has allowed for the development of modern radiation treatment design, such as involved node and involved site RT. These modern treatment designs allow for the most conformal radiation treatments and minimize the dose to nearby healthy tissue. These approaches are at risk for missing involved areas, however; if complete pretreatment anatomic and functional imaging is not performed, it can lead to disease progression in unirradiated sites, as in the present study.

Furthermore, as new field design techniques are used in an attempt to further minimize the ISRT treatment field to address only residual disease after chemotherapy and to eliminate rapidly responding sites of involvement, it is important to recognize that patients without pretreatment PET/CT scans in the study relapsed in areas of non-bulky, rapidly responding disease with no residual CT scan abnormalities. This finding is concerning because of the potential of more frequent treatment failures with

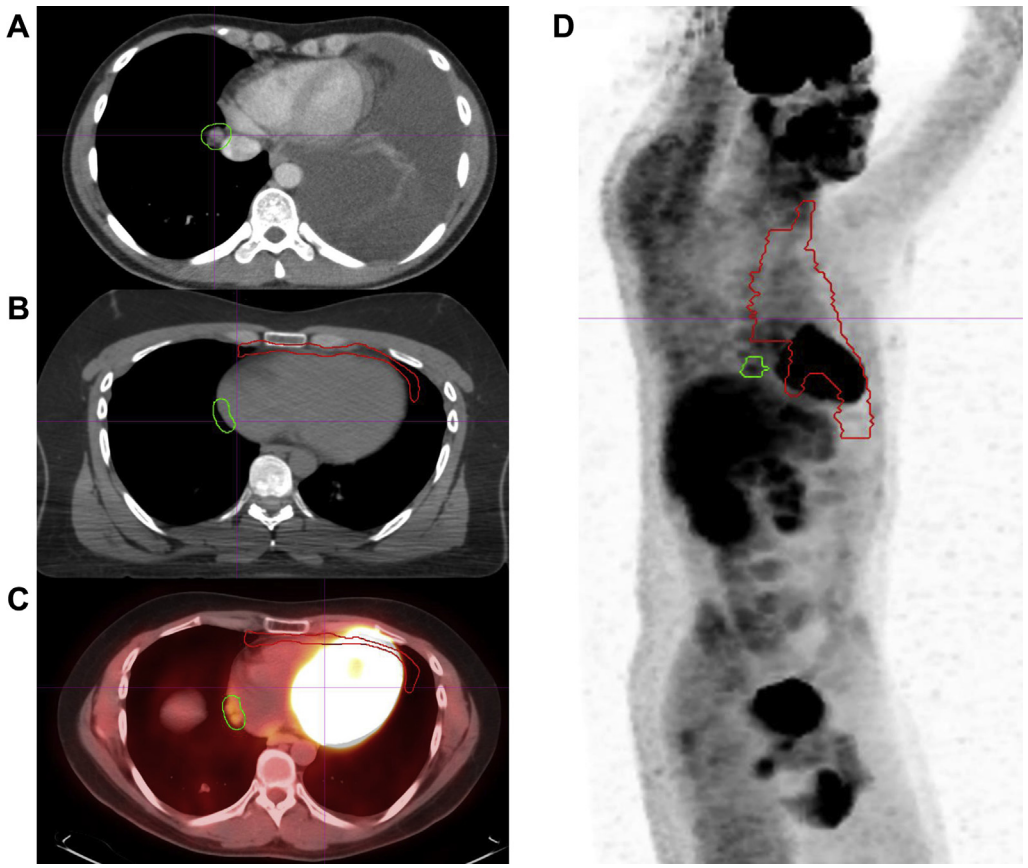

Figure 2 (A) Prechemotherapy computed tomography (CT) scan for a patient in the no-positron emission tomography (PET) group with the right posterior cardiophrenic node circled in green, which was seen on one transverse image and not reported in the CT report. (B) Transverse image from CT simulation with the clinical target volume (CTV) in red and the future area of relapse in green. (C, D) Postradiation PET/CT scan for the same patient with the CTV in red and the site of relapse in green in the same cardiophrenic space as seen in (A).

continued attempts to minimize volumes. Consequently, a careful analysis of patterns of failure will be needed in ongoing and future studies with smaller radiation target volumes.

Our study helps to support the National Comprehensive Cancer Network guidelines by indicating the need for prechemotherapy PET/CT imaging in staging all patients with HL. In evaluating why our patients did not receive pretreatment imaging, the most common reason was lack of insurance (n = 2), followed by chemotherapy initiation during inpatient admission with the decision to get a PET/CT scan after discharge from the hospital (n = 2), scheduling conflicts (n = 1), and unknown reasons that were unrelated to insurance (n = 1). Ironically, just as the AYA population is at an increased risk for developing HL, they are also at the highest risk for lacking or having inadequate health insurance. In the present study, 79% of patients were under 40 years of age and considered to be either pediatric or AYA patients. With respect to cancer care, several studies have demonstrated that unfavorable insurance status in AYA patients with cancer is associated with a delay in diagnosis,[23] increased risk of distant disease at presentation,[24] decreased DFS,[25] and decreased overall survival.[6]

Recent studies have examined the relationship between insurance and disease outcomes for patients with HL and found that a lack of insurance is associated with an increased delay in diagnosis, thereby increasing the risk for more advanced disease at presentation.[24,26] In addition, uninsured AYA patients, once diagnosed, experience an increased lag time from diagnosis to treatment[23,25,27] and when treated, they are less likely to receive comprehensive medical care or care that adheres to standard guidelines.[28,29] All of these issues portend worse outcomes.

One study by Parikh et al[30] recently compared outcomes to insurance status for 45,777 patients with HL, representing >75% of all HL diagnoses, treated from 1998 to 2011. They reported that patients with an unfavorable insurance status (no insurance or Medicaid) had a 5-year overall survival rate of 54% compared with a 5-year overall survival rate of 87% for their favorably insured peers. Furthermore, patients with an unfavorable insurance status had a significantly increased likelihood of not receiving chemotherapy within 30 days of diagnosis

and not receiving RT at all,[30] both of which were correlated with a decreased overall survival.

Yet, the literature also suggests that when patients are given equal access to comprehensive care, the differences in overall and event-free survival are nullified.[13,14] Studies in Canada, which has universal healthcare, also confirm the lack of difference between various socioeconomic status groups and races when given comparable comprehensive treatment.[31] The recent passing of the Affordable Care Act in the United States extended the possibility of attaining health insurance to this vulnerable population. Despite these great advances in healthcare coverage, many AYA patients remain uninsured. This population must be targeted because they are at the greatest risk for receiving inadequate treatment, such as pretreatment imaging.

Although statistically significant differences were observed between subgroups of patients with and without complete pretreatment anatomic and functional imaging, our patient population is small, limiting our ability to conduct a multivariate analysis. Consequently, further research, with greater patient accrual and longer follow-up, is needed to confirm our findings.

Conclusions

Our report examines the effect of not performing a PET/CT scan prior to initiating chemotherapy in patients with HL. As radiation fields continue to become smaller and more precise, we must ensure that patients receive complete imaging to properly treat the full extent of disease. In the treatment of AYA patients with HL, patients are at a higher risk if they lack insurance and encounter significant barriers to receiving pretreatment PET/CT imaging. Patients who do not receive complete staging are at an unnecessary, and in some instances preventable, risk for recurrence. Therefore, we recommend that PET/CT scans be performed in all patients with HL before chemotherapy is administered in order to responsibly treat this curable disease.

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