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A Prospective Study of ^{18}F FDG-PET with CT Co-Registration for Radiation Treatment Planning of Lymphomas and other Hematologic Malignancies

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Abstract

Purpose—This prospective single-institution study examines the impact of positron emission-tomography (PET) using 2- ^{18}F fluoro-2-deoxyglucose and CT scan radiation treatment planning (TP) on target volume definition in lymphoma.

Methods and Materials—118 patients underwent PET/CT TP during 6/2007-5/2009. Gross tumor volume (GTV) was contoured on CT-only and PET/CT studies by radiation oncology (RO) and nuclear medicine (NM) for 95 patients with positive PET scans. Treatment plans and dose-volume histograms were generated for CT-only and PET/CT for 95 evaluable sites. Paired t-test statistics and Pearson correlation coefficients were used for analysis.

Results—70 (74%) patients had non-Hodgkin lymphoma, 10 (11%) had Hodgkin lymphoma, 12 (10%) plasma-cell neoplasm, and 3 (3%) other hematologic malignancies. Forty-three (45%) presented with relapsed/refractory disease. Forty-five (47%) received no prior chemotherapy. The addition of PET increased GTV as defined by RO in 38 patients (median, 27%; range, 5-70%) and decreased GTV in 41 (median, 39.5%; range, 5-80%). The addition of PET increased GTV as defined by NM in 27 patients (median, 26.5%; range, 5-95%) and decreased GTV in 52 (median, 70%; range, 5-99%). Intra-observer correlation between CT-GTV and PET-GTV was higher for RO than for NM (0.94, $P < .01$ vs. 0.89, $P < .01$). Based on Bland-Altman plots, the PET-GTVs

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defined by RO were larger than NM. On evaluating clinical TPs, only four (4%) patients had inadequate target coverage (D95<95%) of the PET-GTV defined by NM.

Conclusions—Significant differences between RO and NM volumes were identified when PET was co-registered to CT for radiation planning. Despite this, the PET-GTV defined by RO and NM received acceptable prescription dose in nearly all patients. However, given the potential for a marginal miss, consultation with an experienced PET reader is highly encouraged when delineating PET/CT volumes, particularly for questionable lesions and to assure complete and accurate target volume coverage.

Keywords

PET planning; lymphoma radiation; radiation treatment planning for lymphoma

Introduction

Positron emission-tomography (PET) using 2-[¹⁸F] fluoro-2-deoxyglucose (FDG-PET) scanning can complement CT anatomic information by localizing metabolically active tumor cells. PET scanning is widely recognized as essential for lymphoma staging in both Hodgkin (HL) and non-Hodgkin lymphomas (NHL) and is also now routinely used to assess chemotherapy response. PET as an adjunct to CT to identify initial or residual disease has led to its incorporation into radiation-treatment (RT) planning for lymphomas (1-4, 5).

Accurate target-volume delineation has become an essential component of radiation-field design due to treatment strategies that now incorporate reduced radiation-field sizes and targeted conformal therapies (1, 6, 7). In particular, radiation using involved node RT (INRT) or involved site RT (ISRT) restricts RT to the initially involved nodes with a margin, thus requiring more precision in identifying involved disease. In fact, pretreatment positron-emission tomography (PET) is required for the application of the ISRT or INRT principles to early-stage HL and NHL (1, 3, 4, 7). It is unfortunately often logistically difficult to acquire a PET prechemotherapy in the RT position. Therefore, ISRT guidelines consider limitations in radiation planning. ISRT similarly restricts RT to the initially involved lymph nodes but allows for a larger margin to account for uncertainties (1). Multiple studies have demonstrated that target-volume alterations can occur when PET is obtained at the time of simulation for HL. Few studies, however, specifically examine PET for radiation planning in a predominantly NHL population including other hematologic malignancies.

The implications on target-volume delineation may differ for HL and NHL. Most studies examining the use of PET for radiation planning in HL fuse pretreatment PET scans obtained in the treatment position to post-treatment CT simulation scans because PET is often negative at completion of chemotherapy. In NHL, patients are often referred for definitive therapy and in that case are likely to have positive PETs at time of radiation (e.g., mucosa-associated lymphoid tissue [MALT] or follicular lymphomas). And while the sensitivity and specificity of PET is well defined in HL, its utility is more controversial for low-grade NHL (8-10). This study is unique in that all patients had a positive PET at time of simulation.

We previously performed a retrospective study analyzing the volume changes that occur when PET is incorporated into CT for radiotherapy planning of HL and NHL (2). However, this prior pilot study was limited in patient numbers and did not utilize a standardized PET technique. Here we present the results of the first prospective study to examine the impact of PET radiation planning in a predominantly NHL population and incorporate an analysis of the variability in target definition between nuclear medicine physicians (NMP) and radiation oncologists (RO).

Materials and Methods

A single-institution prospective study was approved by the Institutional Review Board (IRB). 118 consecutive patients with pathologically confirmed lymphoma were referred for PET/CT radiation-treatment planning at XXXXXXXX (XXXXXX) from June 2007 to June 2009 (Table 1). All patients were simulated with PET and CT in the treatment position using immobilization in the same imaging session with a standardized technique recommended by NMPs as outlined below. Ninety-five patients had PET-positive disease at time of simulation and were included in the analysis. Sample size was determined in consultation with the study statistician to have 90% power to detect a change in treatment volume of 5% or greater. Twenty-three patients with negative PET scans at the time of radiation planning were excluded.

Patient simulation

All patients were imaged with a dedicated PET/CT scanner (Discovery ST, GE) in the Department of Radiation Oncology in the appropriate treatment position with immobilization. Patients were instructed to fast for 6 hours and a finger-stick blood glucose sample was obtained. Per protocol, FDG was not injected if the glucose was >200 mg/dL. ^{18}F FDG-PET was injected with an activity of 12 mCi ($\pm 10\%$). A spiral CT scan with intravenous contrast was acquired with 3 mm-thick slices from the mid skull to the upper thigh to be used for both PET attenuation correction and RT planning. CT scan information was then automatically co-registered to the PET scan information using the Advantage SimMD software available on the GE Discovery ST scanner with rigid body registration. A NMP diagnostically evaluated all PET/CT scans acquired. An isocenter was set at time of simulation and patients were tattooed to define the coordinate system for treatment planning.

Treatment planning

For all patients with PET-positive findings, each treatment volume was contoured on CT alone (blinded to the PET scan at simulation) and on co-registered PET/CT by three ROs and three NMPs using clinical information and radiologic interpretations of prior scans by institutional radiologists. Using qualitative and quantitative standardized uptake value (SUV) analysis as defined by our co-investigator NMP (XX), the PET-positive areas were incorporated in the GTV in addition to any suspicious CT abnormality. The windowing level for contouring was set at a baseline threshold of 40% maximum SUV per the recommendation of nuclear medicine. In addition, both the NMPs and ROs had access to PET/CT diagnostic reports for the PET volume and, therefore, clinical judgment could be incorporated to identify PET positive areas that should be included in the final volume. For

example, tumor that was clearly seen on CT scan, but not contained with the volume encompassed by the 40% threshold of maximum SUV, was still incorporated into GTV. Therefore, non-FDG avid but CT positive areas were included in GTV. The GTV edge was defined by using the anatomic data from the CT. The clinical target volume (CTV) encompassed questionable lymph node sites in proximity to the GTV. CTV was expanded to a planning target volume (PTV) by a standard margin of 0.5-1 cm depending on treatment site and immobilization to account for setup error using ICRU guidelines. Treatment decisions were made outside the study context.

Quantitative volume analysis of the GTV, as defined by the ROs and NM physicians, on both the CT and co-registered PET/CT scans, were performed. Forty treatment sites were initially planned using conventional fields and 49 with conformal techniques including intensity-modulated radiotherapy or 3D conformal RT. Six patients underwent simulation but did not proceed with radiation due to advanced disease found at the time of treatment planning.

Statistical analysis

The mean, median, and range were used to describe patient and treatment characteristics. Scatterplots were created and done in R, an open-source statistical program. In each scatterplot each point represents a single patient. For example, to evaluate GTV, each point represents a patient's GTVs from the CT and PET scans and a line of unity was defined where, for example, CT GTV volume equals PET/CT GTV volume. These scatterplots describe the correlation between tumor volumes on CT and PET (Fig. 1). Bland-Altman plots are used to display agreement between volumes. Paired t-test statistics and Pearson correlation coefficients were additionally used for analysis.

Results

Of the 95 patients with positive PET scans at the time of simulation, new FDG-avid sites were identified in 2 NHL patients, resulting in the addition of a RT site that was outside of the field initially planned. Another 6 patients were not treated due to extensive disease PET/CT simulation that was not apparent on pre-RT imaging. All patients not proceeding with treatment were diagnosed with NHL. Eighty-nine patients proceeded to RT after PET/CT simulation.

RO treatment volume changes using PET vs CT

The addition of PET increased RO-defined GTV in 38 patients (median, 27%; range, 5-70%). PET reduced GTV in 41 patients (median, 39.5%; range, 5-80%) (Fig. 1). In 4 patients, the GTV increased by >50% when with PET and decreased by >50% in 16 patients (Table 2). The addition of PET resulted in either a target volume change or change in overall treatment plan in a total of 87 patients.

Radiation oncology treatment volume changes by histology

Eighteen patients presented with diffuse large B-cell lymphoma (DLBCL). For DLBCL, incorporation of PET increased GTV by >5% in 6 (33%) patients and decreased GTV by >5% in 5 (28%) patients. Thirty-seven patients presented with an indolent lymphoma of

follicular or MALT subtype. For indolent lymphoma, PET increased GTV by >5% in 8 (22%) patients. For indolent lymphoma, GTV decreased by >5% in 12 patients (32%) with PET. GTV-RO increased by >5% in five of nine HL patients (56%). In total, PET led to clinically significant change in GTV size in 11 patients (61%) with DLBCL and 20 patients (54%) with an indolent lymphoma.

Nuclear medicine treatment volume changes using PET vs CT

The addition of PET increased NM-defined GTV in 27 patients (median, 26.5%; range, 5-95%). PET also reduced GTV in 52 patients (median, 70%; range, 5-99%). In 50% of patients, NM-defined GTV using PET was smaller by a median of 75%, implying there may be potential for significant volume reductions using PET. The addition of PET resulted in a clinically meaningful change in treatment volume as contoured by NMPs in 79 patients.

Comparison of RO and NMP Treatment Volumes

Based on Bland-Altman plots, the PET-GTVs defined by RO were overall larger than NM (Fig. 2). The absolute median difference in the size of the PET-GTV between RO and NM was 12.5 cm³ (interquartile, 5.3-48.5, $P < .01$). The CT-GTVs defined by RO were also overall larger than NM (Fig. 2). The absolute median difference in the size of the CT-GTV was 13.3 cm³ (interquartile, 3.8-41.2, $P < .01$) (Fig. 3). The intra-observer correlation between CT- and PET-GTV was higher for RO than NM (0.94 [$P < .01$] vs. 0.89 [$P < .01$]) and there was overall better inter-observer correlation between RO (XX, XX, XX) and NM (XX, XX, XX) with CT (0.96, $P < .01$) than with PET (0.89, $P < .01$). An illustrative case example is depicted in Fig. 4.

Treatment planning

All patients were replanned using both CT and PET/CT PTVs as defined by RO. Dose-volume histograms were generated for all sites using all volumes. A radiation-treatment plan was created using the RO-generated PTV using CT information alone. This plan was then superimposed on the PET PTV to determine whether target coverage of the PET PTV was adequate. In 24 patients, the D₉₅ of the PET volume was <95% with CT, and in 20 the D₉₅ was <90%, implying inadequate coverage.

The RO RT plan was also overlaid on the NMP-defined volumes to examine NMP target coverage. In only four patients, it would have been inadequate.

The impact on normal structures was analyzed. 262 normal structures at risk were contoured on both the CT and PET/CT simulation scans. The mean dose to 20 (8%) normal structures decreased by >5% in 15 patients using the plan generated with RO-derived PET PTV. The mean dose to 13 (5%) normal structures increased by >5% in 10 patients using the PET PTV plan. In all patients, dose-tolerance constraints were met without sacrificing PTV coverage in both CT and PET-based plans.

Discussion

¹⁸F-DG-PET scan is the standard of care in the diagnostic workup for multiple lymphoma subtypes. Smaller RT fields are becoming standard for HL and NHL to reduce toxicity, and therefore adequate imaging at the time of staging is essential to delineate treatment sites requiring RT. ¹⁸F-DG-PET images can be co-registered to CT simulation scans to utilize this information and design informed radiation fields.

Use of PET/CT is considered important for conformal therapy and essential for implementing ISRT or INRT (1, 4, 7). As a result, studies on PET/CT planning for lymphoma have focused on HL and its application for the design of the INRT field treated post-chemotherapy (5). Patients who receive combined-modality radiation often have negative PETs after complete response to chemotherapy. Therefore, optimal candidates for PET/CT simulation include those referred for radiation as the primary treatment including patients with NHL histology, partial responders to chemotherapy who are not candidates for further systemic treatment but may still be curable (e.g., elderly patients), and patients with relapsed/refractory disease referred for salvage high-dose chemoradiation. In our prior retrospective work, we performed a hypothesis-generating analysis of the impact of PET/CT on treatment planning primarily in NHL and found that PET resulted in a change in treatment field for the majority of patients (2). Here we present the results of a prospective IRB-approved study confirming the impact of PET on treatment-field definition primarily in NHL. We did not evaluate the influence of prechemotherapy PET on treatment-field definition in PET-negative patients on post-chemotherapy PET, which is often the case for combined modality when patients are referred for consolidative radiation. This scenario was beyond the scope of this study and is the subject of a new protocol within the collaborative group setting.

Impact of PET on RO Volume Definition

In this study, PET had a significant impact on RT volumes, causing >5% variance (either increasing or decreasing volume) in nearly all patients (89%) and a change in management in 8 patients (8%). In our prior study, treatment volume increased in most patients with PET, which is consistent with other reports in the literature (2, 4, 5). However, with the accrual of additional patients, treatment volumes decreased in 43% and increased in 40% with PET. Clear factors to predict whether volumes increased or decreased with PET did not emerge but it was apparent that PET played a significant role in delineating volumes in the majority of patients with both NHL and HL. The sensitivity and specificity of PET varies according to histologic lymphoma subtype (8, 11, 12). There were a number of patients with different histologies in our study and all had positive PET scans at simulation. Most were referred for definitive RT alone, in contrast to patients in most other studies who receive RT post-chemotherapy. Despite the variability in the utility of FDG PET/CT for staging in indolent lymphomas, PET/CT clearly impacted the design of radiation-treatment volumes in patients with MALT and follicular lymphomas. In these subtypes, treatment volumes either increased or decreased in 54% of patients. PET/CT impacted RT volumes in 61% of patients with aggressive NHL, such as DLBCL. Therefore, although most studies highlight the importance of PET treatment planning in HL, this study demonstrates that PET should also be utilized in

patients with NHL, particularly for PET-positive scans at simulation. This is particularly important as FDG PET/CT may not have the same utility in staging of indolent lymphomas as intermediate/aggressive lymphomas (12). However, our study suggests that, despite the questionable use of PET in the staging of MALT and follicular lymphomas, PET was useful in radiation-treatment field design in $\approx 50\%$ of patients.

A Comparison of NMP and RO Volume Definition

Multiple factors may influence FDG uptake and confound interpretation of PET findings. Windowing level, image resolution, patient preparation (e.g., blood glucose levels and uptake time), and patient motion (e.g., breathing) may affect reproducibility of images. Attention to technical factors regarding PET and CT fusion are also necessary. The IAEA has a series of recommendations in an expert report on PET and PET/CT for RT planning to maintain quality in RT (13). Our study uniquely restricts the analysis to patients PET-positive at the time of simulation. Also, all patients were scanned in treatment position in contrast to acquiring a simulation in diagnostic radiology and then fusing it to the simulation scan. To standardize the windowing level, we selected a threshold with the recommendation of our NMP co-investigators. Therefore, guidelines for window setting were applied and the volume edge was defined by using anatomic data from the CT component due to blurred edge using PET. The uniformity of fusion and interpretation technique is a strength of this study and reduces the potential errors and differences in treatment volumes that can occur due to simple technical differences between scans. We also held a contouring workshop for the NMP co-investigators to review the RO approach to delineating RT volumes for this study and we only asked that the NMP radiologists designate the gross tumor. Given the relative uniformity in PET/CT treatment-planning technique, we chose to compare the volumes delineated by the study NMPs with those by the ROs. Interestingly, significant differences between RO and NM treatment volumes were identified when PET was co-registered to CT for radiation planning.

Overall, RO volumes were significantly larger than NM volumes and CT volumes correlated better between RO and NM than did PET. The study NMPs were more likely to consider exclusion of anatomic CT abnormality for negative PETs whereas ROs included all CT abnormalities for positive and negative PETs. Multiple studies have highlighted that PET/CT information should be used to include areas not detected on CT but not to exclude FDG-negative CT abnormalities, as those sites may harbor microscopic disease. However, there may be clinical scenarios where PET scan may help to discern normal anatomic processes (e.g., atelectasis) from malignant processes. These findings highlight the potential variability in PET interpretation and emphasize the difficulties in defining the treatment volume without pathologic correlation.

Despite these differences, the ^{18}F FDG-PET-GTV defined by both RO and NM received acceptable prescription doses in nearly all patients. Without pathologic correlates, there is an underlying assumption that the RO is correctly identifying the PET sites that should be included within the radiation-treatment field. Based upon our findings, interpretation of involved treatment sites by RO and NM may differ. Therefore, given the potential for a marginal miss, consultation with an experienced PET reader is highly encouraged when

delineating PET/CT target volumes particularly for questionable lesions and to assure complete and accurate target volume coverage.

Conclusions

This study demonstrates the significant impact of PET in the treatment-volume definition of both HL and NHL patients. Although significant differences were identified in RO-delineated treatment volumes compared with NMs, the RO volume nearly always encompassed the NM volume and, therefore, the prescription dose coverage was adequate in nearly all patients. INRT was not utilized in this study. In the INRT era, differences in volume interpretation and design and its impact on target-dose coverage may be far more significant as there is little margin for error compared with historically larger IFRT fields. Also, new guidelines for ISRT will encourage the use of FDG-PET/CT in treatment planning. ISRT employs larger margins than INRT and therefore allows for patients being in a different position at the time of PET/CT than at CT simulation. This study also highlights the importance of multidisciplinary review of imaging to delineate treatment volumes particularly in the era of conformal therapy and in the absence of defined, standardized window settings for radiation planning. Clinical judgment is ultimately required to design treatment fields incorporating both gross tumor and areas suspicious for microscopic extension of disease. Without long-term clinical follow-up to correlate clinical outcomes with the volumes designed using PET/CT radiation planning, it will be difficult to understand the full impact of PET on RT design. This prospective study continues to collect clinical outcomes information to correlate patterns of relapse with PET/CT RT field design.

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SUMMARY

This prospective single-institution study examines the impact of FDG-PET and CT scan radiation treatment planning on target volume definition in lymphomas. Contours and treatment plans were generated on CT-only and PET/CT studies by radiation oncology and nuclear medicine for 95 patients with positive PET scans. Significant differences between GTVs were identified when PET was co-registered to CT planning. Consultation with an experienced PET reader is highly encouraged when delineating volumes in lymphomas.

Fig. 1. Scatterplot demonstrating the correlation of radiation oncologist–delineated positron-emission tomography (PET) and computed tomography (CT) gross tumor volumes (cm³) in log scale.

Fig. 2.

Bland-Altman plot, a method of data-plotting used to analyze the agreement between the gross tumor volume (GTV) measurements by radiation oncology (RO) and nuclear medicine (NM). Demonstrates extent of agreement between RO and NM for volumes delineated on PET (A) and CT (B). For both CT and PET, RO delineated larger volumes overall than NM.

Label	Mean	Lower Quartile	Median	Upper Quartile
Absolute Difference GTV CT Volumes	41.1	3.8	13.3	41.2
Absolute Difference GTV PET Volumes	55.8	5.3	12.5	48.5
Absolute % Difference GTV CT Volumes	52.4	7.1	19.9	46.9
Absolute % Difference GTV PET Volumes	99.8	10.9	24.2	73.5

Fig. 3. Absolute difference and absolute percent difference in gross tumor volumes (GTV) volumes delineated by nuclear medicine (NM) and radiation oncologists (RO) on computed tomography (CT) and positron-emission tomography (PET), respectively.

Fig. 4.

Comparison of nuclear medicine and radiation oncology (RO) volumes in a case example of a patient with non-Hodgkin's lymphoma with paraspinal disease; on the CT scan (left), the RO-CT contour (pink), RO-PET contour (green,) and NM-PET contour (red) is depicted. On the PET (right), RO-CT contour (green), RO-PET contour (yellow), and NM-PET (pink) contour is depicted. The case demonstrates how radiation oncology incorporates both the CT and PET abnormality in the final contour and nuclear medicine defines the PET contour strictly by the location of FDG-avid disease.

Table 1

Patient characteristics

Characteristic	N
Gender	
Male	50
Female	45
Age	
Median	61
Range	20-93
Radiation dose (Gy)	
Median	30
Range	6-66
Chemotherapy	
Yes	50
No	45
Relapsed or refractory	43
Histology	
Non-Hodgkin lymphoma	70
Hodgkin lymphoma	10
Plasma cell neoplasm	12
AML	1
Other	2
Subtype	
Non-Hodgkin lymphoma	
Follicular	24
Diffuse large B-cell	18
Marginal zone	13
Mantle cell	4
Low-grade B-cell NOS	3
SLL/CLL	3
Bronchial associated lymphoid tissue	1
Burkitt's lymphoma	1
Plasmablastic lymphoma	1
Mycosis fungoides	1
Adult T-cell HTLV-1+	1
Hodgkin lymphoma	
Nodular sclerosing	6
Lymphocyte predominant	3
Lymphocyte rich	1
Plasma cell neoplasm	
Solitary plasmacytoma	4
Multiple myeloma	8

Characteristic	N
AML	1
Other	
Langerhans cell histiocytosis	2
Treatment approach	
Definitive	48
Palliative	37
Pre/post-transplant	4
No RT	6
Prior RT to involved site	
Yes	5
No	90
Conventional vs. 3D plan	
Conventional	40
3D plan	49
No RT	6

Abbreviation: 3D = three dimensional; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; HTLV-1 = human T-lymphotropic virus type I; NOS = not otherwise specified; RT = radiation therapy; SLL = small lymphocytic lymphoma.

Table 2

PET/CT GTV alteration relative to CT-based treatment planning

GTV-RO		GTV-NM	
Change	Number of Patients	Change	Number of Patients
Increase in GTV			
>5%-10%	5	>5%-10%	2
>10-20%	12	>10-20%	5
>20-50%	17	>20-50%	16
>50%	4	>50%	4
Total increase	38	Total increase	27
Decrease in GTV			
>5%-10%	6	>5%-10%	5
>10-20%	7	>10-20%	7
>20-50%	12	>20-50%	10
>50%	16	>50%	30
Total decrease	41	Total decrease	52
Change in GTV			
±5%	10	±5%	10

GTV = gross tumor volume