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Patterns of Use and Survival Outcomes of Positron Emission Tomography for Initial Staging in Elderly Follicular Lymphoma Patients

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Abstract

The role of positron emission tomography (PET) in the initial assessment of follicular lymphoma (FL) has been a topic of debate. We examined the patterns of utilization of PET-staging in FL and assessed the association of PET with survival. Using the SEER-Medicare database, we identified 5,712 patients diagnosed with first primary FL between 2000 and 2009. Older age, African-American race, poor performance status, B-symptoms, and history of anemia were negatively associated with PET-staging. Receipt of PET-staging was positively associated with treatment at institutions affiliated with research networks and with residence in areas with higher concentrations of nuclear medicine specialists. PET was associated with improved lymphoma-related [HR 0.69, 95% CI 0.58-0.82] and overall [HR 0.75, 95% CI 0.68-0.83] survival. Our findings substantiate the use of PET as the standard-of-care for imaging in FL patients. Further investigation is warranted to identify mechanisms underlying the apparent survival advantage associated with PET-staging in FL.

Keywords

positron emission tomography; follicular lymphoma; patterns of care; neoplasm staging

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Introduction

Collectively, lymphoid neoplasms are the fourth most common cancer and the sixth leading cause of cancer death in the United States. In 2016, 136,960 new lymphoid neoplasms are expected in the United States making this group of cancers the fourth most common cancer and the sixth leading cause of cancer death in the United States.[1]

Follicular lymphoma (FL) accounts for approximately 13,900 cases in the United States, has a median age at diagnosis of 60 years, is characterized by an indolent clinical course, and is usually considered incurable.[2-6] Imaging studies at initial diagnosis may contribute to the management of FL through identification of stage or bulk, guidance of biopsy, assessment of disease in proximity to critical structures, detection of histological transformation to aggressive lymphoma, and prediction of outcomes. [¹⁸F] Fluoro-2 deoxyglucose (FDG)-positron emission tomography (PET) is a functional imaging modality with the potential for greater sensitivity and negative predictive value in FDG-avid malignancies. Consequently, PET has emerged as a useful tool for initial staging in aggressive lymphomas and has been incorporated into current guidelines for staging and response assessment.[7-11] However, the clinical benefits of PET in the initial staging and management of indolent lymphomas such as FL have been debated.

PET has demonstrated a distinct advantage over computerized tomography (CT) in the selection of appropriate limited-stage FL patients for radiation therapy (RT).[12] However, early studies demonstrated a high level of concordance between PET and CT in ascertaining clinical stage and a moderate potential of PET to alter management decisions in patients with discordant tests.[13,14] Other concerns related to PET included: false positive results in the presence of infection, inflammation, sarcoidosis, or brown fat;[15,16] false negative findings due to variability in technique and FDG avidity across FL subgroups;[8,14,17,18] and operator, reader, and equipment variability.[17] In 2007, a working group at the International Harmonization Project (IHP) was convened to develop consistent trial parameters across study groups.[19] Commenting that the above concerns regarding the use of PET had been addressed, the working group recommended the use of PET for clinical trials that had response rate as a major endpoint.[19] An overt shift in clinical opinion occurred in 2014 with the revision of the NCCN guidelines in favor of PET for staging and pre-treatment evaluation in FL.[7]

In summary, for a long period after Medicare approved PET for reimbursement in 1998, considerable uncertainty prevailed regarding the role of PET in the initial assessment of FL. In such an environment, non-clinical factors, such as reimbursement incentives, physician-ownership of imaging facilities, and the public relations value of owning and using advanced medical technologies, also may have influenced variation in the use of PET for cancer and other conditions.[20,21] Although currently there is a consensus in favor of PET-staging in FL, it remains to be seen how the increased uptake of PET has impacted survival. In this study, we examined the relationship between clinical and non-clinical factors and the use of PET and the impact of PET-staging on survival in a large population of Medicare beneficiaries with FL.

Materials and Methods

Data Source and Study Population

We used the Surveillance, Epidemiology, and End Results (SEER) registry data from 2000 through 2009 linked to Medicare claims data through 2011. The SEER program is a National Cancer Institute (NCI)-sponsored epidemiologic surveillance system of population-based tumor registries that routinely seek to collect demographic and clinical information on all incident cases that occur in persons residing in SEER areas.[22] Medicare is the primary health insurer for 93% of the U.S. population aged 65 years and older.

SEER registry data were used to identify patients with a histologically confirmed first primary diagnosis of FL based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes (Supplemental Table I).[23] Exclusion criteria are displayed in Figure 1.

Study Variables

The primary variables of interest were receipt of PET scans (PET or PET/CT scans) for initial staging, all-cause survival, and lymphoma-specific survival. We defined initial staging scans as any scans received during the index month of follow-up through six months after the start date of follow-up, and before the receipt of any cancer-directed treatment. Healthcare Common Procedure Coding System (HCPCS) codes in the Medicare carrier and outpatient claims files were searched to identify PET scans (Supplemental Table I). Patients were observed until death or the end of observations. All-cause mortality was ascertained from the Medicare data (complete till 12/31/2011) and cause-specific mortality was determined from the SEER data (complete till 12/31/2009).

Patient age, sex, race/ethnicity, region of residence (Northeast, Midwest, South, or West), marital status, year of diagnosis, cause of death, census tract-level characteristics (education, poverty, and metropolitan/urban/rural status), FL stage, histopathology, B-symptoms, and nodal or extranodal primary site of involvement were identified from the SEER data.

We assigned patients to a poor performance status group if they had durable medical equipment claims for oxygen, wheelchairs or related supplies or skilled nursing facilities, home health agencies, or hospice claims.[24] We also adjusted for whether patients had a recent history of anemia and used the Klabunde's modification of the Charlson comorbidity index based on claims in the year before diagnosis (Supplemental Table I).[25,26]

FL-directed treatment strategies were identified using ICD, 9th Revision, Clinical Modification (ICD-9-CM) Diagnosis; ICD-9-CM Procedural; Current Procedural Terminology (CPT); HCPCS; and revenue centers codes (Supplemental Table I) on inpatient, outpatient and physician claims. We categorized patients into the following groups based on the first treatment received: chemo (chemotherapy +/- RT), R-chemo (rituximab + chemo +/- RT), RT (alone or in combination with rituximab), and R-monotherapy (rituximab alone). Those who did not receive any FL-directed treatment within the first six months of diagnosis were categorized into the observation group, a common strategy utilized for frontline management of FL with an indolent behavior and low tumor burden.[27]

We assigned patients to hospitals based on the most frequently occurring provider number (hospital ID) from hospital outpatient and inpatient claims with the primary diagnosis code for FL in a one-year window centered on the date of diagnosis. Subsequently, we used the Hospital File included with the SEER-Medicare data to classify these facilities as teaching hospitals (or not) or as members of any of the following NCI Clinical Trials Cooperative Groups (NCTCGs): Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group (NCCTG), and American College of Radiology Imaging Network (ACRIN).

Local density of nuclear medicine specialists and medical oncologists (lowest tertile, middle tertile, and highest tertile) was categorized by aggregating the county-level health workforce data from the 2005 Area Health Resources File [28] to the patients' Hospital Referral Region (HRR). The Dartmouth Atlas divides the United States into 306 HRRs on the basis of patterns of care for Medicare patients.[29] We assigned each patient to an HRR using the county of residence.

Statistical Analysis

Patterns of PET-staging—We examined the associations between patient characteristics and receipt of one or more staging PET scans using multivariable logistic regression.

Descriptive Survival Analysis and Standard Multivariable Cox Regressions

Kaplan-Meier (KM) survival curves and log-rank tests were used to compare the survival distribution in the PET and no-PET groups. Survival time was measured from the date of diagnosis. For analysis of lymphoma-specific survival, patients who died of other causes were censored at death.

All-cause and lymphoma-specific survival were modeled using unadjusted and multivariable Cox proportional hazards regressions with PET-staging as the independent variable of interest. Adjustments were made for FL stage, management strategy, and other covariates noted above. This adjusted model is referred to hereafter as the standard Cox model.

It is possible that patients who received PET-staging also had better prognosis on account of imbalances in observed and/or unobserved factors. We attempted to counter these potential biases using propensity score- and instrumental variable-based approaches.

Propensity Score-Based Survival Analysis—Our propensity score (PS)-based survival analysis attempted to limit bias by adjusting for potential imbalance in observed covariates between the PET and no-PET groups. A PS for each patient was calculated using multivariable logistic regressions, with PET-staging as the dependent variable, and adjusting for the same set of variables as in the standard Cox model. These propensity scores formed the basis of a one-to-one matching of patients in the PET group to those in the no-PET group using a caliper width of 0.005. Alternatively, we weighted each individual observation in the standard Cox model by the mean-standardized inverse of probability of PET-staging, given the patient's covariates.

Instrumental Variable-Based Survival Analysis—Instrumental variable-based methods seek to account for both observed and unobserved factors that potentially influence selection into intervention groups of interest, thus providing a potentially more reliable causal inference than PS-based approaches. Our instrument was a measure of local area (HRR) proclivity for PET-staging that we constructed based on the two-step methodology described by Hadley et al (Supplemental Content).[30,31] The instrument is valid based on the theory that patients in regions with high rates of PET-staging are more likely to undergo PET-staging but that region itself does not independently affect survival rates apart from its effect on PET-staging. We compared the balance of patient characteristics across the median of the instrument to determine how well the instrument balanced the observed prognostic factors.

The instrumental variable analyses were carried out using two-stage residual inclusion models (2SRI).[32] The first stage was a multivariable logistic regression predicting PET-staging as a function of the instrument and the set of covariates in the standard Cox model. The second stage was a multivariable Cox regression model that adjusted for PET-staging, the residual of prediction from the first stage, and the remaining covariates in the standard model.

Sensitivity Analyses—While FL stage and management strategy are important predictors of survival, these variables may be altered by the results of the PET scan. Therefore, we repeated our survival analyses, excluding FL stage and management strategy from all adjustments. Additionally, patterns and survival outcomes of PET-staging were analyzed in the subset of patients diagnosed in 2006-2009, when the rates of PET-staging had stabilized.

All p-values were two-sided and the value of type 1 error was set to 0.05 for all significance tests. We used SAS (version 9.4; SAS Institute Inc., Cary, NC) and Stata (version 13; StataCorp LP, College Station, TX) statistical software for all analyses.

Results

The study sample consisted of 5,712 patients (Table I). The mean age at diagnosis was 75.5 years. Approximately 77% of patients were under 80 years of age, 93% were Caucasian, and 58% were female. Approximately 44% of the patients in this cohort underwent PET-staging (n = 2,490). Management strategies, stratified by stage and receipt of PET, are displayed in Supplemental Table II. The use of PET-staging increased sharply during the study period, reaching 60% of all patients diagnosed by 2006 (Figure 2).

Multivariable logistic regression (Table II) showed that the receipt of PET-staging was negatively associated with age ≥ 80 years (odds ratio [OR] 0.57, 0.48-0.68), poor performance status (OR 0.53, 0.45-0.64), presence of B-symptoms (OR 0.73, 0.59-0.88), and history of anemia (OR 0.72, 0.53-0.97), suggesting that patients with shorter expected survival were less likely to receive PET-staging. African-American race was negatively associated with the receipt of PET (OR 0.68, 0.47-0.98) but patients with high comorbidity scores were no less likely to undergo PET-staging. Patients with grade 3 FL (OR 1.74, 1.48-2.06) more commonly received PET-staging.

Management setting also significantly influenced the use of PET. Patients who were evaluated at NCTCG-member hospitals were more likely to receive PET-staging (OR 1.22, 1.07-1.39). Compared with the lowest tertile of HRR-density of nuclear medicine specialists, patients in the highest tertile (OR 1.35, 1.14-1.61) were more likely to receive PET-staging. As expected, the effect of NCTCG membership diminished as PET-use stabilized over time (2006-2009). However, the concentration of nuclear medicine specialists continued to be a significant predictor of PET-staging over the stable PET-use period (Supplemental Table III).

There were 2,430 patients (43%) who died during the follow-up. The median duration of follow-up was 4.70 years. Seventy-three percent of deaths were lymphoma-related. Patients who received PET-staging had increased all-cause (overall survival, OS) and lymphoma-specific survival (LSS, Figure 3). PET-staging was associated with more favorable OS (hazard ratio [HR] 0.75, 0.68-0.83) and LSS (HR 0.69, 0.58-0.82) in the standard multivariable Cox models (Table III). The global proportional hazards assumption was assessed using the Wald test, and Schoenfeld residuals were assessed to check the proportional hazards assumption for individual covariates. No violations were detected. Complete results from the standard Cox models are displayed in Supplemental Table IV.

All covariates were balanced in the PS-matched samples. In the instrumental variable analysis, our selected instrument was strongly associated with receipt of PET-staging (partial F-statistics 155.5 in the all-cause survival sample and 144.2 in the lymphoma-specific survival sample) and was not a significant predictor of survival. However, some differences in covariate balance—including for FL-stage, comorbidity index, treatment strategy, and performance status—persisted between those above and below the median value of the instrument (Supplemental Table V). Survival estimates of PET-staging from PS-matched and inverse probability weighted Cox models were similar to the standard multivariable Cox models, and the survival benefit of PET-staging was further supported by the instrumental variable models (Table III). Our sensitivity analyses confirmed all our main results except that the impact of PET on all-cause survival was not statistically significant at the 5% level in the alternative instrumental variable model that did not control for FL-stage and management strategy (Supplemental Table VI).

Discussion

In this retrospective study examining the patterns of uptake of PET-staging in a large, nationally representative cohort of newly diagnosed FL patients, we found that the rate of PET-staging increased sharply after Medicare began coverage in 1998, despite the lack of expert consensus around the role of PET in the initial management of FL at that time. That said, our results suggest that PET-staging is more likely to be used when physicians believe that it will have an impact on management decisions—as evidenced by lower rates among patients with a poorer performance status, older patients, and patients who presented with B-symptoms. Our findings may reflect the patterns of belief regarding the benefits of PET as a prognostic tool to stratify patients based on expectations about outcomes as clinical data about the impact of PET were emerging.

An important contribution of the present study is the examination of the influence of management-setting and local healthcare markets on the use of PET-staging. We found that the propensity to use PET-staging during this period was greater in the NCTCG-member hospitals. Since advanced imaging is included in the protocol for initial work-up and follow-up in many cancer-related clinical trials, such institutions are expected to be early acquirers of PET-equipment. In a fee-for-service system, hospitals with on-site PET facilities not only have a financial incentive to use them, but over time, the use of PET may get incorporated into the practice culture of these hospitals. Similar findings on the influence of research networks on diffusion of innovations have been reported previously.[33] Another important factor influencing the use of PET-staging was the local concentration of nuclear medicine specialists. These specialists are likely to be concentrated in regions with greater availability of PET equipment or potential for referral arrangements.

The relationship between PET-staging and survival was consistently positive and significant across various specifications of the survival model. As the distribution of treatment strategies in Supplemental Table II suggest, an accurate assignment of FL stage may alter the prognostic evaluation of some patients following diagnosis and possibly induce a decision to treat or modify the intensity of treatment. Accordingly, an analysis of the NCCN database showed that patients who underwent PET-staging were more likely to receive early treatment and anthracycline-based chemotherapy.[34] Although the preliminary estimates of upstaging as a result of PET were low ($\approx 10\%$),[13,14] a recent analysis of 142 patients from the FOLL05 trial showed that 62% of FL patients conventionally diagnosed as stage II were upstaged to stage III or IV as a result of PET.[35] A small proportion of patients also may be downstaged by PET, leading to treatment with curative intent. In addition, several studies have demonstrated that the standardized uptake value, a relative measure of FDG uptake derived from PET, may be useful in identifying histologic transformation—a dramatic event often requiring immediate systemic therapy.[36,37] Estimates of incidence of histological transformation in FL vary from 10 to 70 percent.[38-43] Other uses of PET that may influence survival include determining the field of radiation for RT and identifying occult transformation in patients with increased risk for histological transformation using PET-guided biopsy. Conversely, differences in the incidence in occult transformation between the arms of our study could have influenced our findings.

Given the results from our survival analyses and the multiple modes through which PET may influence initial treatment and survival, it would be logical to conclude that some patients may have been sub-optimally treated as a consequence of not receiving PET-staging.

That said, our study has limitations in identifying and sorting out these pathways. Although initial management and FL stage are important predictors of survival, these variables may be altered by PET. Inclusion of these variables in the main model, as well as in the propensity-score and IV calculations, may bias the effect of PET on survival. Specifically, if PET improves survival mainly through more accurate staging or smarter choice of management strategy, then the total effect PET may be reflected in the ensemble of estimated coefficients. To check whether the inclusion of stage and initial management potentially biased our survival estimates of PET, we estimated alternative models that omitted FL stage and initial

management from all calculations. The results from these alternative specifications are comparable to the main models, suggesting that bias through the above mechanism was unlikely. Both results in conjunction suggest that PET may improve survival not mainly through improvement in staging accuracy or selection of initial management approach but through alternative mechanisms. In particular, a baseline PET scan may enable more adequate post-treatment response evaluation and aid in the selection of appropriate downstream management strategies in the PET group. Correspondingly, in the current study, the proportion of patients who had at least one PET scan following the end of front-line therapy was higher in the PET group (67%) as compared to the no-PET group (25%). It is also possible that patients receiving a baseline PET scan are more likely to receive additional scans downstream, resulting in more effective second and third line therapy than those receiving CT alone. Evidence in favor of this latter mechanism is provided by data from the National LymphoCare study that have shown that PET response after rituximab containing induction therapy is an independent predictor of survival.[44]

A potential concern is that our modeling approaches regard PET-staging and the selection of treatment strategies as statistically independent decisional outcomes. In reality, it is possible that healthier patients were more likely to be staged with PET and treated with chemoimmunotherapy—an important driver of all-cause survival in our multivariable Cox models—and those who were expected to be treated with R-chemo were more likely to receive PET-staging as a baseline investigation to facilitate post-treatment evaluation. In the above cases, the survival advantage of PET may be attributable partly to the selection effects on treatment. Given our inability to ascertain, based on SEER-Medicare data alone, how PET-staging may have impacted treatment strategy and how anticipated treatment strategy and unmeasured prognostic indicators may have impacted the decision to perform PET-staging, we advise caution in interpreting the results of survival analyses from this study. Although SEER-Medicare is one of the richest sources of utilization and survivorship information in the United States, a limitation of using this data is that our results are only generalizable to fee-for-service Medicare beneficiaries.

Concerns have been raised about whether the rapid rise in imaging expenditures is justified by improvement in patient outcomes or whether the increasing use of advanced imaging is largely revenue-driven. Evidence-based medicine entails the use of new technology based on peer-review published evidence of clinical benefit derived from reducing complications of therapy or additional diagnostic tests, or from improving quality of life or survival. However, new diagnostic technologies often are adopted based on demonstration of improved diagnostic accuracy alone because high level data required for a clear demonstration of benefit for patients is difficult to generate. A step toward filling this evidence gap is the CMS Coverage with Evidence Development program that provides medical benefits coverage for services that contribute to emerging evidence regarding their clinical benefits. [45] This approach allows CMS to make novel technologies available in a controlled fashion and simultaneously generate data to assess their appropriate use.

A critical issue concerning the increased use of PET-staging is whether this resulted in fewer FL patients being under-treated or over-treated. Prospective and retrospective datasets with detailed clinical, patient-, and provider-level information may be useful in answering such

questions. Although some prospectively collected data exist demonstrating that PET can help distinguish differences in OS for patients with FL, randomized clinical trials such as ECOG 2408 will provide data for secondary analyses once they become mature.[46]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Figure 3.

Table I
Baseline characteristics of the study population stratified by the receipt of PET-staging

	No-PET (CT alone) group (n=3,222)	PET or PET/CT group (n=2,490)	p value	Total (n=5,712)
Patient Characteristics				
Age				
Mean (median, SD)	76.0 (75, 6.8)	74.7 (74.0, 6.2)		75.5 (75.0, 6.6)
66-70 yr	827 (25.7)	749 (30.0)	<0.0001	1,576 (27.6)
71-75 yr	820 (25.4)	689 (27.7)		1,509 (26.4)
76-80 yr	733 (22.8)	567 (22.8)		1,300 (22.8)
> 80 yr	842 (26.1)	485 (19.5)		1,327 (23.2)
Race				
Caucasian	2,977 (92.4)	2,314 (92.9)	0.1228	5,291 (92.6)
African American	109 (3.4)	62 (2.5)		171 (3.0)
Others	136 (4.2)	114 (4.6)		250 (4.4)
Sex				
Male	1,323 (41.1)	1,085 (43.6)	0.0565	2,408 (42.2)
Female	1,899 (58.9)	1,405 (56.4)		3,304 (57.8)
Marital Status				
Married	1,791 (55.6)	1,501 (60.3)	0.0018	3,292 (57.6)
Others	1,237 (38.4)	854 (38.7)		2,091 (36.6)
Unknown	194 (6.0)	135 (5.4)		329 (5.8)
Year of Diagnosis				
2000-2002	1,299 (40.3)	211 (8.5)	<0.0001	1,510 (26.4)
2003-2005	1,069 (33.2)	812 (32.6)		1,881 (32.9)
2006-2009	854 (26.5)	1,467 (58.9)		2,321 (40.6)
Region				
Northeast	610 (18.9)	600 (24.1)	<0.0001	1,210 (21.2)
Midwest	565 (17.5)	251 (10.1)		816 (14.3)
West	1,224 (38.0)	946 (38.0)		2,170 (38.0)
South	823 (25.5)	693 (27.8)		1,516 (26.5)
Residence				
Metropolitan	2,550 (79.1)	2,064 (82.9)	0.0017	4,614 (80.8)
Urban	228 (7.1)	144 (5.8)		372 (6.5)
Less Urban/Rural	444 (13.8)	282 (11.3)		726 (12.7)
% in Census Tract with Less Education than High School Diploma				
< 25	2,397 (74.4)	1,915 (76.9)	0.0286	4,312 (75.5)
25	825 (25.6)	575 (23.1)		1,400 (24.5)
% in Census Tract Living in Poverty				
< 5	1,038 (32.2)	865 (34.7)	0.0993	1,903 (33.3)
5-7	427 (13.2)	349 (14.0)		776 (13.6)

	No-PET (CT alone) group (n=3,222)	PET or PET/CT group (n=2,490)	p value	Total (n=5,712)
7-12	746 (23.2)	550 (22.1)		1,296 (22.7)
> 12	1,011 (31.4)	726 (29.2)		1,737 (30.4)
Lymphoma Characteristics				
Grade				
1 or 2	1,730 (53.7)	1,190 (22.9)	<0.0001	2,920 (51.1)
3	450 (14.0)	504 (20.2)		954 (16.7)
Not specified	1,042 (32.3)	796 (31.9)		1,838 (32.2)
Stage				
I/II	1,522 (47.2)	1,223 (49.1)	0.3703	2,745 (48.0)
III/IV	1,478 (45.9)	1,102 (44.3)		2,580 (45.2)
Unknown	222 (6.9)	1,65 (6.6)		387 (6.8)
Primary Site				
Nodal	2,736 (84.9)	2,034 (81.7)	0.0011	4,770 (83.5)
Extra-nodal	486 (15.1)	456 (18.3)		942 (16.5)
Measures of Baseline Health Status				
NCI Comorbidity Index				
0	1,975 (61.3)	1,549 (62.2)	0.6335	3,524 (61.7)
1	813 (25.2)	626 (25.1)		1,439 (25.2)
2	434 (13.5)	315 (12.7)		749 (13.1)
Performance Status				
Good	2,665 (82.7)	2,217 (89.0)	<0.0001	4,882 (85.5)
Poor	557 (17.3)	273 (11.0)		830 (14.5)
History of Anemia				
Present	175 (5.4)	78 (3.1)	<0.0001	253 (4.4)
Absent	3,047 (94.6)	2,412 (96.9)		5,459 (95.6)
B-Symptoms				
Present	412 (12.8)	258 (10.5)	<0.0001	672 (11.8)
Absent	1,518 (47.1)	1,417 (56.9)		2,935 (51.4)
Unrecorded	1,292 (40.1)	813 (32.7)		2,105 (36.8)
Features of Management Setting				
NCI Clinical Trials Cooperative Group Membership[§]				
No	1,253 (38.9)	969 (38.9)	0.9836	2,222 (38.9)
Yes	1,969 (61.1)	1,521 (61.1)		3,490 (61.1)
Teaching Hospital				
No	1,619 (50.3)	1,187 (47.7)	0.0533	2,806 (49.1)
Yes	1,603 (49.7)	1,303 (52.3)		2,906 (50.9)
Local Density of Nuclear Medicine Specialists[#]				
1 st tertile (lowest)	1,118 (34.7)	819 (32.9)	0.2174	1,937 (33.9)
2 nd tertile	1,155 (35.9)	890 (35.7)		2,045 (35.8)

	No-PET (CT alone) group (n=3,222)	PET or PET/CT group (n=2,490)	p value	Total (n=5,712)
3 rd tertile (highest)	949 (29.5)	781 (31.4)		1,730 (30.3) (17.7)
Local Density of Medical Oncologists[#]				
1 st tertile (lowest)	1,099 (34.2)	751 (30.2)	0.0060	1,850 (32.4)
2 nd tertile	1,107 (34.4)	921 (37.0)		2,028 (35.5)
3 rd tertile (highest)	1,016 (31.5)	818 (32.9)		1,834 (32.1) (17.7)
Management Strategy				
Chemo	440 (13.7)	121 (4.9)	<0.0001	561 (9.8)
R-Chemo	717 (22.2)	955 (38.3)		1,672 (29.3)
RT (+/- R)	358 (11.1)	312 (12.5)		670 (11.7)
R alone	457 (14.2)	373 (15.0)		830 (14.5)
Missing chemo agents	241 (7.5)	86 (3.5)		327 (5.7)
Observation	1,009 (31.3)	643 (25.8)		1,652 (29.0)

[§] Assigned based on the frequency of outpatient and inpatient claims bearing diagnosis codes of follicular lymphoma in the follow-up period

[#] Derived from county-level health workforce data from the 2005 Area Health Resources File aggregated to the patients' Hospital Referral Region (HRR)

Abbreviations: PET, Positron Emission Tomography; SD, standard deviation; NCI, National Cancer Institute; Chemo, Chemotherapy; R, rituximab; RT, involved-field radiation therapy

Table II
Results from multivariable logistic regression with receipt of PET-staging as the dependent variable

OR (95% CI)	
Patient Characteristics	
Age	
66-70 yr	Reference
71-75 yr	0.89 (0.76-1.05)
76-80 yr	0.86 (0.73-1.02)
> 80 yr	0.57 *** (0.48-0.68)
Race	
Caucasian	Reference
African American	0.68 * (0.47-0.98)
Others	1 (0.74-1.34)
Sex	
Male	Reference
Female	1.01 (0.89-1.15)
Marital Status	
Others	Reference
Married	1.12 (0.98-1.27)
Unknown	0.96 (0.73-1.26)
Year of Diagnosis	
2000-2002	Reference
2003-2005	5.13 *** (4.30-6.14)
2006-2009	12.78 *** (10.67-15.30)
Region	
Midwest	Reference
Northeast	2.50 *** (2.03-3.07)
South	2.53 *** (1.99-3.21)
West	1.79 *** (1.46-2.19)
Residence	
Less Urban/Rural	Reference
Urban	1.01 (0.75-1.35)
Metropolitan	1.10 (0.89-1.35)
% in Census Tract with Less Education than High School Diploma	
25	Reference
<25	1.25 * (1.04-1.50)
% in Census Tract Living in Poverty	

OR (95% CI)	
< 5	Reference
5-7	1.15 (0.95-1.39)
7-12	1.08 (0.91-1.29)
> 12	1.13 (0.92-1.38)
<i>Lymphoma Characteristics</i>	
Grade	
1 or 2	Reference
3	1.74 *** (1.48-2.06)
Not specified	0.98 (0.86-1.12)
Primary Site	
Nodal	Reference
Extra-nodal	1.26 ** (1.07-1.48)
<i>Measures of Baseline Health Status</i>	
NCI Comorbidity Index	
0	Reference
1	1.03 (0.89-1.19)
>2	0.95 (0.79-1.15)
Performance Status	
Good	Reference
Poor	0.53 *** (0.45-0.64)
History of Anemia	
Absent	Reference
Present	0.72 * (0.53-0.97)
B-Symptoms	
Absent	Reference
Present	0.73 *** (0.59-0.88)
Unrecorded	0.95 (0.83-1.09)
<i>Features of Management Setting</i>	
Teaching Hospital[§]	
No	Reference
Yes	1.01 (0.88-1.15)
NCI Clinical Trials Cooperative Group Membership[§]	
No	Reference
Yes	1.22 ** (1.07-1.39)
Local Density of Nuclear Medicine Specialists[#]	
1 st tertile (lowest)	Reference
2 nd tertile	1.08 (0.93-1.26)

OR (95% CI)	
3 rd tertile (highest)	1.35 ^{***} (1.14-1.61)
Local Density of Medical Oncologists[#]	
1 st tertile (lowest)	Reference
2 nd tertile	1.10 (0.94-1.28)
3 rd tertile (highest)	1.04 (0.88-1.23)

[§] Assigned based on the frequency of outpatient and inpatient claims bearing diagnosis codes of follicular lymphoma in the follow-up period

[#] Derived from county-level health workforce data from the 2005 Area Resource File aggregated to the patients' Hospital Referral Region (HRR)

* p<0.05,

** p<0.01,

*** p<0.001

Abbreviations: PET, positron emission tomography; OR, odds ratio; CI, confidence interval; NCI, National Cancer Institute

Table III
Cox proportional hazards models comparing survival in PET group to the no-PET group (referent) by analytic method

Model Type	All-Cause Survival HR (95% CI)	Lymphoma-Specific Survival HR (95% CI)
Unadjusted	0.63 (0.58 - 0.69)	0.56 (0.48 - 0.66)
Standard Multivariable *	0.75 (0.68 - 0.83)	0.69 (0.58 - 0.82)
1:1 PS Matched (Caliper Width 0.005) *	0.74 (0.65 - 0.84)	0.63 (0.51 - 0.78)
IP Weighted *	0.74 (0.69 - 0.80)	0.71 (0.63 - 0.81)
IV 2 Stage Residual Inclusion Analysis *	0.60 (0.37 - 0.98)	0.37 (0.17 - 0.82)
Standard Multivariable Years 2006 Onward *	0.64 (0.54 - 0.75)	0.51 (0.36 - 0.73)

* Controlled for patient demographic and census tract characteristics; geographic region; year of diagnosis; FL grade; FL stage; primary site of involvement; comorbidity index; performance status; presence of B-symptoms; recent history of anemia; management strategy; and features of the management-setting

Abbreviations: CI, confidence interval; PS, propensity score; IP, inverse probability; IV, instrumental variable