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Follicular Lymphoma in the Medicare Population: Determinants and Outcomes of Management Approaches

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Abstract
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By

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Recent advances that have changed the management paradigm for follicular lymphoma (FL) include positron emission tomography (PET)-staging and the monoclonal antibody, rituximab (R). However, there is lack of consensus on the optimal management of FL. The three chapters of this dissertation use the linked Surveillance, Epidemiology, and End Results-Medicare data to examine the determinants and outcomes of management approaches in FL.

In Chapter 2, we study the factors associated with the use of PET-staging in FL and examine the extent to which the variations in PET use are influenced by physician preferences, availability, access, and reimbursement policies. Our findings of widespread use of PET-staging in FL, along with the socio-demographic, local and regional variations in its use underscore the importance of non-clinical factors in the utilization of new technology.

In Chapter 3, we examine the effect of clinical and non-clinical factors on management patterns in FL, given the clarity of guidelines (or lack thereof) and the status of emerging evidence. We find that involved field radiation therapy for stage I/grade 1-2 disease was not the standard approach despite the National Comprehensive Cancer Network (NCCN) recommending this use, but treatment with R + chemotherapy (R-chemo) or single-agent R was common, even though observation is a reasonable approach in these patients. Most grade 3 patients received upfront R-chemo even in the absence of clear recommendations in the NCCN guidelines. Our findings emphasize that emerging evidence and financial incentives of providers may play a more important role in determining treatment patterns in FL than guideline recommendations.

In Chapter 4, we examine the relationship between R-chemo use and PET-staging, and the implications of the PET-R-chemo interface on survival. We find a possible bi-directional association between PET-staging and R-chemo use. Patients who received PET-staging or R-chemo (or both) had longer survival than those who received neither, with the PET + R-chemo group having the most superior outcomes. Our findings motivate future research into the role of PET-staging in informing surveillance or treatment decisions and the influence of PET-staging on survival outcomes in FL.

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CHAPTER 1: Introduction

Follicular lymphoma (FL) is a complex disease showing a varied pattern of clinical presentations and clinical outcomes. FL is mainly seen as an incurable disease, although the survival of patients with FL has improved considerably over the last 30 years. The major advance in the management of FL in the past decades has been the introduction of immunotherapy. The role of advanced imaging in the assessment and management of lymphoma is also evolving. However, there is lack of consensus on the optimal management of FL and considerable variations in care and outcomes have been reported.[1] Therefore, it is important to identify the mechanisms that underlie the diversity in management decisions in FL and examine how management decisions influence survival outcomes.

The three chapters of this dissertation use a large, nationally representative dataset to examine to examine how management decisions in FL are influenced by medical, socioeconomic, and demographic characteristics of the patient; organizational characteristics of the treating facility; and availability of healthcare resources. Finally, by carefully characterizing and controlling for selection bias, we estimate the impact of management approaches on survival outcomes in FL.

We proceed by providing a clinical overview of FL in section 1.1; descriptions of innovation in therapeutic and imaging technology in sections 1.2 and 1.3; a summary of the three chapters in section 1.4; and finally, conclusions and implications of our findings in section 1.5.

1.1 Clinical Overview:

Non-Hodgkin lymphoma (NHL) was diagnosed in 70,800 individuals in the United States (U.S.) in 2014 and is the seventh most common cancer among males and the sixth most common cancer among females.[2] Follicular lymphoma (FL) is the second most common subtype of NHL.[1,3,4] Follicular lymphoma typically follows an indolent clinical course, characterized by serial relapses that are associated with decreasing response to cytotoxic therapy. Management strategies for FL include expectant observation, multi-agent chemotherapy with or without immunotherapy, immunotherapy, and radiotherapy—alone or in combination with systemic agents.

The Ann Arbor classification system (which was developed for Hodgkin's lymphomas) divides FL into four stages (I-IV) based on radiological inspection of the extent of spread.[5,6] Stage I and a small proportion of stage II patients represent localized FL and are commonly asymptomatic. The majority of patients are diagnosed with advanced stage disease (stage III-IV).[1,7] Clinical presentation and behavior of FL also varies by the histological grade. According to the WHO classification, FL is subdivided into 4 histological subtypes—1, 2, 3A, and 3B.[8] While grades 1, 2 are clinically similar and follow a typically indolent clinical course, the status of FL grade 3 (especially grade 3B) as an indolent or aggressive neoplasm is a subject of debate in the scientific community.[9,10]

1.2 Innovation in Imaging:

An important prerequisite for appropriate management of FL is an accurate identification of FL stage at diagnosis. Computerized tomography (CT) imaging of chest, abdomen and pelvis is routinely performed at the time of diagnosis to assign stage. Currently, a more sensitive imaging technique, [^{18}F] Fluoro-2 deoxyglucose (FDG)-positron emission tomography (PET), is also commonly used for staging FL. A PET scan

is a functional imaging tool that plays a critical role in staging and response evaluation in many malignancies and was approved for reimbursement by Medicare in 1998. Unlike older imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) scans that rely on the size of lesions, the fundamental basis for PET is increased cellular activity of malignant cells. FDG is absorbed and metabolized at a higher rate by most malignant cells and appears as bright areas in PET scans. Therefore PET has greater sensitivity and negative predictive value in FDG-avid malignancies such as FL.

Initial PET staging is particularly useful for an accurate identification of stage I and limited stage II FL patients as candidates for immediate radiotherapy. PET also has been found to be useful in assessment of treatment response.[11] To this end, pre-therapy PET scans may facilitate the interpretation of post-therapy PET scans.[12,13] Another role of PET is in selecting an appropriate site for biopsy if FL is suspected to be transforming to an aggressive type of lymphoma.[14,15] Histological transformation of indolent lymphoma is a dramatic event that occurs in 5–10%, carries a poor prognosis, and requires intensified management.[16]

1.3 Innovation in Treatment:

Historically, follicular lymphoma was recognized as a radiotherapy sensitive disorder with an often indolent course. Indeed, for a long time, radiotherapy was the treatment of choice for all types of lymphoma and response to radiation was even utilized as a diagnostic criterion for tumors not accessible for histologic study.[17] Drug development for FL is complicated by the commonly indolent, asymptomatic behavior of the disease and the difficulty in predicting prognosis in individual FL patients, such that many patients may not require any treatment. Two retrospective studies done in 1979 and 1984 suggested

that immediate systemic treatment offered no improvement in overall survival in low-grade FL[18,19] and later randomized trials confirmed these findings.[20,21] A major milestone was reached with the introduction of immunotherapy with rituximab (R), which is now a standard part of treatment in FL.

Rituximab is a genetically engineered monoclonal antibody that was approved for reimbursement by the Medicare program in 1997 for treatment of cancer. Rituximab may be administered as a single agent (R-mono) or in combination with chemotherapy (R-chemo). The use of R as a part of frontline chemo-immunotherapy regimens increased as several trials showed significant survival benefits offered by R-chemo compared to chemotherapy alone.[22-24] However, no trial has compared observation (watch and wait) to immediate R-chemo yet. The single trial that compared R-mono to expectant observation in asymptomatic patients reported delayed time to initiation of chemotherapy in the R-mono group but no difference in overall survival in the two groups.[25] Thus observation is still a viable approach for many asymptomatic patients.

1.4 The Three Chapters

FL shows a varied pattern of clinical presentations and clinical outcomes and little consensus exists on the optimal diagnostic workup and management. Important topics of scientific debate in FL include: the role of PET-staging in initial management and response evaluation and the impact of PET-staging on survival outcomes; the role of expectant observation in the post-rituximab era; the role of involved-field radiation therapy (IFRT) with curative intent in localized FL; and the optimal management of grade 3 patients. The three chapters that follow use the linked Surveillance, Epidemiology, and End Results-

Medicare database, created by the National Cancer Institute, to examine the determinants and outcomes of management approaches in FL.

Chapter 2: Patterns of Use of Positron Emission Tomography for Initial Staging in Elderly Follicular Lymphoma Patients:

Often in the medical world, new diagnostic technologies are adopted based only on demonstration of improved diagnostic accuracy and without a clear demonstration of benefit for patients. The emphasis on technology is such that many observers note the existence of a "technological imperative"—a tendency to utilize technology because it exists rather than because it is a better approach.[26] New technology comes with financial perks as well, especially in a favorable reimbursement environment. The use of PET-staging in FL may be a case in point.

Greater sensitivity of PET notwithstanding, there is limited evidence that PET-staging alters management decisions in a substantial proportion of FL patients in order to justify the use of PET-staging as a baseline investigation. Moreover, it is also unclear whether the advantages of PET-staging in FL outweigh the important concerns associated with it, including: false positive results in the presence of infection, inflammation;[27,28] false negative findings due to variability in technique;[12,14,29-31] and substantial operator, reader, and equipment variability.[12] Although clinical practice guidelines and expert opinions are changing currently in favor of PET-staging in FL,[32,33] there is evidence of widespread use of PET-staging in the US even before these changes came into effect.[34] The paucity of evidence on the effectiveness of PET-staging for FL and concerns about the unwarranted use of imaging motivated our analyses of patterns of use of PET-staging in Chapter 2. We sought to determine the factors associated with PET use, and to examine the extent to which

the variations in PET use are influenced by non-clinical factors such as physician and patient preferences, availability, access, and reimbursement policies.

We found widespread use of PET-staging in the FL population. Adoption of PET-staging varied across geographical regions, socio-economic strata, institution types, and residence in areas with greater availability of nuclear medicine specialists.

Chapter 3: Variations in the Management of Follicular Lymphoma: the Role of Clinical Practice Guidelines in Shaping Management Decisions:

A lack of trials comparing outcomes of the various therapeutic options for FL has made therapeutic decision-making a complex process. As a result, considerable variations in care and outcomes have been reported.[1,35,36]

Adherence to professional guidelines and recommendations is emphasized to mitigate undesirable variations in care. Several guidelines exist for the diagnosis and management of FL as well, including the commonly used guidelines from the National Comprehensive Cancer Network (NCCN). However, given the numerous treatment options available now and the paucity of clinical trials comparing these options to one another, the NCCN guidelines do not provide clear guidance on which approach is better.

There is some amount of clarity in the NCCN guidelines about the management of patients with localized disease (stage I-limited stage II/grade 1-2) but no recommendation that is applicable to grade 3 patients.[33] Because of the high radio sensitivity of FL and the potential for cure, the NCCN guidelines recommend involved field radiation therapy (IFRT) as the preferred approach for these patients.[33] But the data on which the recommendation for IFRT is based are from the 1990's, when different downstream treatment strategy and staging methods were employed.[37-39] Substantial progress has been

achieved in the last two decades, particularly through the introduction of rituximab and the refinement of diagnostic workup, such that the appropriateness of immediate IFRT as the recommended approach can now be challenged. On the other hand, the confusion about the classification of grade 3 as an indolent or aggressive disease may drive the use of R-chemo even in the absence of guideline recommendations.

In Chapter 3, we examine the patterns of care in two subpopulations of FL patients—those with stage I/grade 1-2 FL and those with grade 3 FL. Our selected subpopulations of FL patients are on two extremes as regards the clarity in the NCCN guidelines. While the guidelines recommend IFRT as the preferred approach for stage I/grade1-2 patients, there are no guidelines recommendations that can be applied for grade 3 FL. Our aims are: 1) to identify clinical and non-clinical factors that influence management approaches in FL; 2) to examine how clarity and the perceived validity or relevance of clinical guidelines affect clinical practice, given the ongoing emergence of evidence; and 3) to discuss how the observed patterns of care relate to gaps in the evidence base about the efficacy of candidate management approaches, alignment of physicians' financial incentives, and possible lapses in risk communication.

We found that IFRT in stage I/grade 1-2 disease was not the standard approach despite NCCN recommending this use. Systemic treatment with R-chemo or R-mono in stage I/grade 1-2 patients was very common, even though observation is a reasonable approach in these patients. On the other hand, most grade 3 patients received upfront R-chemo even in the absence of clear recommendations in the NCCN guidelines.

Chapter 4: Survival Outcomes in Follicular Lymphoma and the Role of Positron Emission Tomography (PET)-Staging:

Chapter 4 is a comprehensive inquiry into the relationship between R-chemo use and PET-staging, and possible implications of the PET-R-chemo interface on survival in FL. We develop a detailed conceptual model showing how PET-staging impacts survival mainly through its effect on selection of R-chemo as the initial treatment, but also by being associated with better execution of initial treatment and assessment of treatment response. Indeed, it is the possible role of PET in assessment of treatment response that complicates the analysis of survival outcomes of PET-staging. An implication of this latter role is that many physicians may order PET-staging if treatment with R-chemo is expected to begin soon after diagnosis. The initial staging scan in such a situation would not direct the choice of treatment (which would have been determined) induce treatment but rather serve as a baseline comparator for post-treatment PET scans. Thus, an inquiry into the survival outcomes of PET-staging that ignores the possible bi-directional relationship between PET-staging and R-chemo may yield biased estimates. We find confirmation in the first step of our analysis that the relationship between PET and R-chemo is likely bidirectional. In response, we create "management packages" using combinations of indicators variables for PET-staging and R-chemo and then analyze the survival outcomes associated with patients' receipt of these packages, while adjusting for selection bias based on observed and unobserved confounders using modern econometric techniques.

In all analyses, we found that packages with PET-staging and/or R-chemo were associated with better survival as compared to the no PET + others group (patients who neither received PET-staging nor R-chemo). There was also a gradient in the survival outcomes, although statistically insignificant, such that the PET + R-chemo group had the best survival, followed by PET + others and then by no PET + others.

1.5 Conclusions and Implications:

The widespread use of PET-staging in FL, along with the socio-demographic, local and regional variations in its use underscore the importance of non-clinical factors in the utilization of new technology. The patterns of use of PET-staging described in Chapter 2 motivate future research into the role of PET-staging in informing surveillance or treatment decisions. The use of PET-staging in FL should be driven by peer-review published evidence of clinical benefit derived from reducing the complications of therapy or additional diagnostic tests or improving quality of life or survival. There is also need to develop better financial incentives for physicians and hospitals to provide more cost-effective care.

The diverse patterns of care in stage I/grade 1-2 FL patients described in chapter 3 emphasize the need for systematic comparisons of management approaches in patients with localized disease. It is challenging to conduct randomized trials focused on a small subset of patients with stage I/limited stage II FL, who have long-term survival regardless of the given treatment. Therefore, other innovative prospective designs must be explored and the quality of retrospective data must be improved. While the controversy regarding the classification of grade 3 may take time to resolve, there is a need to include more grade 3 patients in clinical trials.

In Chapter 3, we draw important conclusions about the PET-treatment interface, including a possible bi-directional relationship between PET-staging and R-chemo use and the positive impact of PET-staging on survival in FL. However, the limitations of using observational data to examine outcomes of staging or diagnostic tests are also underscored.

The three chapters have several limitations as retrospective, claims-based analyses. Nevertheless, they represent first, large-scale, population-based analyses of patterns of care in FL and the first retrospective study examining survival outcomes of PET-staging in a large cohort of FL patients.

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CHAPTER 2:
Patterns of Use of Positron Emission Tomography for Initial Staging in Elderly Follicular Lymphoma Patients

2.1 Introduction

Non-Hodgkin lymphoma (NHL) was diagnosed in 70,800 individuals in the United States (U.S.) in 2014 and is the seventh most common cancer among males and the sixth most common cancer among females.[1] Follicular lymphoma (FL) accounts for approximately 15-30% of adult NHL in Western countries, is characterized by an indolent clinical course, and is usually incurable.[2-5] 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 prognosis. Unlike computerized tomography (CT) that relies on the size of lesions, the fundamental basis for [^{18}F] fluoro-2 deoxyglucose (FDG)-positron emission tomography (PET) is identifying the increased metabolic activity of malignant cells. PET offers the potential for greater sensitivity and negative predictive value in FDG-avid malignancies and has emerged as a useful supplementary imaging tool for initial staging in aggressive lymphomas.[6-8]

However, there is limited evidence of the clinical benefits of PET in the initial staging and management of FL. PET has demonstrated a distinct advantage over CT in the selection of appropriate limited-stage FL patients for involved-field radiation therapy (IFRT) but PET and CT were found to be concordant in determining clinical stage in 80%-90% of cases and PET altered management decisions in less than 10% of patients in whom tests were discordant.[9,10] Other concerns related to PET include: false positive results in the presence of infection, inflammation, sarcoidosis, or brown fat;[11,12] false negative

findings due to variability in technique and FDG avidity across FL subgroups;[6,10,13-15] and substantial operator, reader, and equipment variability.[14] Given these limitations, the International Harmonization Project, which was initiated to develop recommendations regarding imaging for lymphomas, did not include pretreatment PET scans for FL in its 2007 recommendations.[16] The National Comprehensive Cancer Network guidelines also did not provide advice on the use of PET-staging FL.[17] Despite the lack of evidence on the effectiveness of PET-staging for FL and concerns about the unwarranted use of imaging in general,[18] clinical opinion shifted in favor of the use of PET for staging and pretreatment evaluation in FL.[19]

Non-clinical factors, such as reimbursement incentives, physician-ownership of imaging facilities, and the public relations value of owning and using advanced medical technologies, may contribute to the use of PET scanning for FL patients and regional variation in the use of advanced imaging techniques for cancer and other conditions. We sought to study the patterns of PET utilization for staging in FL, to determine the factors associated with PET use, and to examine the extent to which the variations in PET use are influenced by non-clinical factors such as physician and patient preferences, availability, access, and reimbursement policies.

2.2 Materials and Methods

2.2.1 Data Sources and Study Population

We used the Surveillance, Epidemiology, and End Results (SEER) registry data from 2000 through 2009 linked to Medicare claims data through 2010. 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.[20] Medicare is the primary health insurer for 97% of the U.S. population aged 65 years and older. Medicare claims data provide valuable information on healthcare services delivered to beneficiaries.

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 9695 (FL Grade 1), 9691 (FL Grade 2), 9698 (FL Grade 3), and 9690 (FL not otherwise specified).[21] We excluded patients who were < 66 years old or of an unknown age at diagnosis; were diagnosed at autopsy or who died within 6 months of diagnosis; had interrupted Medicare Part A or B coverage or were enrolled in a health maintenance organization (HMO) at least one year prior through 6 months after diagnosis; had another diagnosis of cancer within 6 months of being diagnosed with FL; had chemotherapy, immunotherapy, or radiotherapy claims preceding the date of diagnosis by more than 45 days (deemed as patients with erroneous dates of diagnosis); had missing census tract information; or had no carrier, hospital outpatient or inpatient claims with a primary diagnosis of FL in a 1 year window centered on the diagnosis (Figure 2.1).

2.2.2 Study Variables

Since SEER data provide only the month and year of diagnosis, we used the 15th day of the month of diagnosis as the start date for follow-up. The primary variable of interest was receipt of PET scans (PET scans or dual PET/CT scans) for initial staging. We defined initial staging scans as any PET 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 treatment. We identified claims for PET scans in the Medicare carrier and outpatient claims files as those with the following comprehensive list of Healthcare Common Procedure Coding System (HCPCS) codes: 78608-78816, G0125, G0126, G0163-G0165, and G0210-G0235. A more restrictive list of codes that excluded PET codes for other malignancies led to 48 fewer patients in the PET group. We included the following patient characteristics: age, sex, race/ethnicity, region of residence (Northeast, Midwest, South, or West), marital status, year of diagnosis, and census tract characteristics of residence (education, poverty, and metropolitan/urban/rural status). Physicians' financial interests in prescribing ancillary services have contributed to the growth of imaging in a major way and have motivated legislations such as the Deficit reduction Act (DRA; 2005).[22,23] To examine the effect of the passage and implementation of the DRA, we classified years of diagnosis as 2000 to 2004 (pre-passage period); 2005 to 2006 (post-passage, pre-implementation period); and 2007 to 2009 (post-implementation years).

We measured health status by applying NCI's algorithm for calculation of Klabunde's modification of the Charlson Comorbidity Index (CCI) to Medicare carrier, outpatient, and inpatient claims during the year prior to the diagnosis of FL, excluding the index month.[24,25] Additionally, we assigned patients to a poor performance status group if any indicators of poor performance—including durable medical equipment claims for oxygen, wheelchairs or related supplies; and also claims for skilled nursing facilities, home health agencies, or hospices—were detected in the year prior to diagnosis.[26] Additional predictors of poor survival available in the data were presence of B-symptoms, nodality (extranodal primary site of involvement), and anemia.[27] In order to identify patients with a

recent history of anemia, we modified Klabunde's algorithm to search for claims with International Classification of Diseases, 9th revision (ICD-9) diagnosis codes for anemia (280.X, 281.X, 283.X, 284.8, 284.9, 285.2 and 285.9) in the year prior to diagnosis. Extranodal disease involvement was ascertained from the ICD-O-3 site recode variable provided by SEER.[28]

To examine the impact of management-setting characteristics, we assigned patients to facilities based on the most frequently occurring provider number (hospital ID) from Medicare hospital outpatient and inpatient claims with the primary diagnosis code for FL in a one year window centered on the diagnosis. We scanned the next three diagnosis codes if no claims bore the primary diagnosis code for FL in these files (approximately 3% of the population). In case of a tie, we selected the hospital with the earliest claim date for that patient. Subsequently, we used the NCI's Hospital File to classify these facilities as teaching hospitals or 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).

To characterize the supply of nuclear medicine specialists, we aggregated the county-level health workforce data from the 2005 Area Health Resources File [29] to the patients' Hospital Referral Region (HRR)-level. The Dartmouth Atlas has divided the United States into 306 HRRs on the basis of patterns of care for Medicare patients who were hospitalized for cardiovascular and neurosurgical care.[30] We assigned each patient to an HRR using their county of residence. Patients were categorized as residents of areas

with a low (lowest tertile), medium (middle tertile), or high (highest tertile) density of nuclear medicine specialists.

2.2.3 Statistical Analysis

In a univariate analysis, we compared the baseline characteristics of the patients who received one or more staging PET scans (PET group) with those of patients who did not receive any staging PET scans (no-PET group) using chi-square tests.

We examined the associations between patient characteristics and the receipt of PET-staging using multivariable logistic regression. The dependent variable was an indicator for the receipt of one or more staging PET scans. The independent variables of interest were divided into four categories: patient characteristics including demographic characteristics, census tract characteristics, geographic region, and year of diagnosis; lymphoma characteristics including FL grade and nodal or extra-nodal involvement; measures of baseline health status including CCI, poor performance status, presence of B-symptoms and anemia; and features of the management-setting including types of facilities planning management and local-area supply of nuclear medicine specialists. Huber-White robust standard errors were used to account for heteroskedasticity in the data. We used SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC) and Stata 13 statistical software (StataCorp LP, College Station, Texas) for all analyses.

2.3 Results

The final study sample consisted of 6,033 patients. The mean age at diagnosis was 76 years (standard deviation of 6.6 years). Approximately 77% of patients were under 80 years of age, 93% were Caucasian, and 56% were female. Approximately 41 percent of the

patients in this cohort underwent PET-staging (n = 2,490). Among patients in the no-PET group, 90% received initial staging CT scans during the period under study. Compared to the no-PET group, patients in the PET-group were significantly more likely to be: less than age 80; married; living in the Northeast; living in metropolitan areas; and from census tracts with greater education status (Table 2.1). FL patients undergoing PET-staging were also more likely to: be diagnosed with grade 3 FL; have extra-nodal involvement; have good performance status; and be evaluated at a teaching or NCTCG-member hospital. Patients in the PET-group were less likely to present with B-symptoms or a recent history of anemia. The utilization of PET-staging increased sharply during the study period, reaching nearly 60% of all patients diagnosed by 2006. Socio-demographic, local, and regional differences in PET-staging for FL diminished over time (Figure 2.2).

Patients with shorter expected survival were less likely to receive PET-staging (Table 2.2). The multivariable analysis showed that receipt of PET-staging was negatively associated with age 76 to 80 years (odds ratio [OR] 0.83; 95% confidence interval [CI] 0.71-0.97; reference group [ref.] 66-70 years), age over 80 years (OR 0.57; 95% CI 0.49-0.68, ref. 66-70 years), African-American race (OR 0.64; 95% CI 0.44-0.91; ref. Caucasian race), poor performance status (OR 0.54; 95% CI 0.46-0.64; ref. good performance status), presence of B-symptoms (OR 0.74; 95% CI 0.62-0.89; ref. B-symptoms absent), and history of anemia (OR 0.70; 95% CI 0.52-0.94; ref. no history of anemia). High CCI did not influence the use of PET-staging, but patients with grade 3 FL (OR 1.60; 95% CI 1.36-1.87; ref. grade 1 or 2 patients) more commonly received PET-staging.

Utilization of PET-staging continued to increase after the passage of DRA in 2005 (OR for the 2005-2006 period 3.94; 95% CI 3.41-4.56; ref. 2000-2004 period), however

year-to-year increases were small after the implementation of DRA in 2007 (OR 5.29 in 2007, 5.83 in 2008, and 6.07 in 2009; ref. 2000-2004 period).

Management-setting and local concentration of nuclear medicine specialists also significantly influenced the use of PET-staging. Patients who were evaluated at NCCTG-member hospitals were more likely to receive PET-staging (OR 1.25; 95% CI 1.09-1.42; ref. non-member). Compared with the lowest tertile of HRR-density of nuclear medicine specialists, patients in the highest tertile (OR 1.28; 95% CI 1.09-1.50) were more likely to receive PET-staging.

2.4 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 its approval for reimbursement and plateaued at 60% by 2007. The magnitude of this increase was unexpected, considering the lack of consensus around the role of PET in the initial management of FL at that time. This rapid increase notwithstanding, adoption of PET-staging varied across geographical regions, socio-economic strata, and residence in areas of greater nuclear-medicine density.

Regional-variation in the utilization of imaging technology has been reported previously.[31] Possible explanations include variation in the availability of PET equipment, patient education, patient preferences, and physician practice styles. Socio-demographic disparities in the use of PET-staging may be attributed to systematic differences in patient-level factors including baseline health status and education; provider perceptions and bias; and structural factors including access to care. Our results suggest that PET-staging is more

likely to be used when physicians believe that it will have an impact on survival outcomes—as evidenced by lower rates among patients with a poorer performance status, older patients, and patients who presented with B-symptoms. While our findings may reflect patterns of belief regarding the benefits of PET as a prognostic tool to stratify outcomes for subsets patients with FL, there were limited clinical data available at that time to justify this approach.

The slowdown in the diffusion of PET coincided with the implementation of the DRA in 2007. Prior to the DRA, Medicare reimbursed private office imaging at substantially higher rates than hospital outpatient imaging. By reducing payments for private office imaging, the DRA reduced profits for stand-alone imaging centers and incentives for physicians to install in-office imaging equipment. Earlier studies have reported similar slackening of trends in the use of CT and magnetic resonance imaging (MRI) attributable to the DRA.[32]

Grade 3 FL emerged as the most significant clinical predictor of the receipt of PET-staging. Grade 3 FL undergoes histological transformation in 5-10% of patients to a more aggressive subtype of NHL—diffuse large B-cell lymphoma (DLBCL)—which may require early intensified immunochemotherapy.[33,34] There is also an emerging paradigm that a subset of grade 3 FL patients (Grade 3B) belong to the DLBCL subtype.[35] Standardized uptake values (SUV) derived from PET imaging may be useful in distinguishing indolent from aggressive disease and in directing confirmatory biopsy in Grade 3 FL.[36] However, studies examining SUV-related uses of PET are quite recent and report different optimum SUV cutoff values.[37-39] The use of PET also was quite common in Grade 1 and 2 patients (62% in 2007-2009), only a small proportion of whom are

expected to benefit from immediate IFRT. Therefore, it is likely that PET was used in a large proportion of the study population not for selection of candidates for IFRT or in accordance with the prevailing state of knowledge about histological transformation but as a baseline investigation.

There are several important limitations to this study. First, we could not include FL-stage and initial management in regression analyses since these variables may be altered by the receipt of PET. While it is not possible to disentangle the complex relationships between these factors using observational data, our findings do suggest that the use of baseline PET scans may be quite common in FL. Second, we could not identify the characteristics of the providers ordering PET scans. Previous studies have found associations between provider characteristics such as training, age, practice setting, and specialty with the patterns of management of cancer patients.[40-43] These physician characteristics currently are not available in the SEER-Medicare dataset. Moreover, the management of FL is quite fragmented, and, unlike for surgically managed cancers, there is no single procedure code linking patients to the physicians planning their management. An additional limitation is that our results are generalizable only to fee-for-service Medicare beneficiaries. Finally, we could only detect PET paid for by Medicare. Although reimbursements by private insurers or out of pocket payments for PET may have occurred, the resulting misclassification is unlikely to be empirically important in the Medicare-eligible elderly population.

Nevertheless, an important contribution of the present study is the examination of the features of management setting and local healthcare markets on the use of PET-staging in FL. We assigned patients to facilities involved in their management using frequencies

of outpatient and inpatient claims for FL. We found that NCCTG-member hospitals were more common users of PET-staging during this period. Since advanced imaging is included in the protocol for initial work-up and follow-up in many clinical trials, such institutions are expected to be early adopters of PET-equipment. 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. Furthermore, some institutions associated with research networks alone may be smaller and more revenue-driven in the investments they make compared with larger, higher volume centers such as teaching hospitals. Similar findings on the influence of research networks and teaching status on diffusion of innovations have been reported earlier.[44] Another important factor influencing the use of PET-staging was the local concentration of nuclear medicine specialists. This is consistent with supply-induced demand for medical care. Technical reimbursements for PET—of which the major share goes to the interpreting physicians, most commonly nuclear medicine specialists—constitute a large proportion of total reimbursement for the procedure.[45] Thus, these specialists are likely to be concentrated in regions with greater availability of PET equipment or potential for referral arrangements.

Advanced imaging represents the fastest growing component of medical expenditures in the United States, increasing at double-digit rates in recent years.[46] 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.[23] The widespread use of PET-staging in FL, along with the socio-demographic, local and regional variations in its use underscore the importance of non-clinical factors in the utilization of new technology. In the clinical management of FL the

use of PET in the initial staging process should be driven by peer-review published evidence of clinical benefit derived from reducing the complications of therapy or additional diagnostic tests or improving quality of life or survival. The patterns of use of PET-staging described in this study motivate future research on the impact of PET-staging of FL on patient care and outcomes.

TABLE 2.1 Baseline characteristics of the cohort stratified by the receipt of PET-staging

	No-PET Group (n=3,543)	PET Group (n=2,490)	p value	Total (n=6,033
Patient Characteristics				
Age				
Mean (SD)	76.0 (6.8)	74.7 (6.2)		75.5 (6.6)
66-70 yr	899 (25.3)	749 (30.0)	<0.0001	1,648
71-75 yr	902 (25.5)	689 (27.7)		1,591
76-80 yr	797 (22.5)	567 (22.8)		1,364
> 80 yr	945 (26.7)	485 (19.5)		1,430
Race				
Caucasian	3,258 (92.0)	2,314 (92.9)	0.0480	5,572
African American	128 (3.6)	62 (2.5)		190 (3.2)
Others	157 (4.4)	114 (4.6)		271 (4.5)
Sex				
Male	1,492 (42.1)	1,085 (43.6)	0.2580	2,577
Female	2,051 (57.9)	1,405 (56.4)		3,456
Marital Status				
Married	1,966 (55.5)	1,501 (60.3)	0.0010	3,467
Others	1,353 (38.2)	854 (38.7)		2,207
Unknown	224 (6.3)	135 (5.4)		2359
Year of Diagnosis				
2000-2002	1,414 (39.9)	211 (8.5)	<0.0001	1,625
2003-2005	1,169 (33.0)	812 (32.6)		1,981
2006-2009	960 (27.1)	1,467 (58.9)		2427
Region				
Northeast	658 (18.6)	600 (24.1)	<0.0001	1,258
Midwest	597 (16.9)	251 (10.1)		848
West	1,392 (39.3)	946 (38.0)		2,338
South	896 (25.2)	693 (27.8)		1589
Residence				
Metropolitan	2,818 (79.5)	2,064 (82.9)	0.0230	4,882
Urban	244 (6.9)	144 (5.8)		388 (6.4)
Less Urban/Rural	481 (13.6)	282 (11.3)		763
% in Census Tract with Less Education than High School Diploma				
< 25	2,644 (74.6)	1,915 (76.9)	0.0423	4,559
≥25	899 (25.4)	575 (23.1)		1,474
% in Census Tract Living in Poverty				
< 5	1,133 (32.0)	865 (34.7)	0.0599	1,998
5-7	471 (13.3)	349 (14.0)		820
7-12	822 (23.2)	550 (22.1)		1,372
> 12	1,117 (31.5)	726 (29.2)		1,843
Lymphoma Characteristics				
Grade				
1	1,024 (28.9)	572 (22.9)	<0.0001	1,596
2	844 (23.8)	618 (24.8)		1,462
3	499 (14.1)	504 (20.2)		1,003

Not specified	1,176 (33.2)	796 (31.9)		1,972
Stage				
I/II	1,673 (47.2)	1,223 (49.1)	0.1945	2,896
III/IV	1,601 (45.2)	1,102 (44.3)		2,703
Unknown	269 (7.6)	1,65 (6.6)		434 (7.2)
Primary Site				
Nodal	2,978 (84.1)	2,034 (81.7)	0.0484	5,012
Extra-nodal	565 (16.0)	456 (18.3)		1,021
Measures of Baseline Health Status				
NCI Comorbidity Index				
0	2,200 (62.1)	1,549 (62.2)	0.7078	3,749
1	871 (24.6)	626 (25.1)		1,497
≥2	472 (13.3)	315 (12.7)		787
Performance Status				
Good	2,929 (82.7)	2,217 (89.0)	<0.0001	5,146
Poor	614 (17.3)	273 (11.0)		887
History of Anemia				
Present	185 (5.2)	78 (3.1)	<0.0001	263 (4.4)
Absent	3,358 (94.8)	2,412 (96.9)		5,770
B-Symptoms				
Present	441 (12.5)	258 (10.5)	<0.0001	701
Absent	1,666 (47.0)	1,417 (56.9)		3,083
Unrecorded	1,436 (40.5)	813 (32.7)		2,249
Features of Management Setting				
NCI Clinical Trials Cooperative Group Membership[§]				
No	1,257 (41.0)	966 (39.2)	0.1687	2,389
Yes	1,809 (59.0)	1,500 (60.8)		3,644
Teaching Hospital				
No	1,824 (51.5)	1,187 (47.7)	<0.0001	3,011
Yes	1,719 (48.5)	1,303 (52.3)		3,022
Local Density of Nuclear Medicine Specialists[#]				
1st tertile (lowest)	1,215 (34.3)	819 (32.9)	0.4673	2,034
2nd tertile	1,258 (35.5)	890 (35.7)		2,148
3rd tertile (highest)	1,070 (30.2)	781 (31.4)		1,851

§ 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

TABLE 2.2 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	0.90 [0.78-1.05]
76-80 yr	0.83* [0.71-0.97]
> 80 yr	0.57*** [0.49-0.68]
Race	
Caucasian	Reference
African American	0.64* [0.44-0.91]
Others	0.98 [0.74-1.32]
Sex	
Male	Reference
Female	1.07 [0.95-1.21]
Marital Status	
Others	Reference
Married	1.1 [0.97-1.26]
Unknown	0.89 [0.69-1.13]
Year of Diagnosis	
2000-2004	Reference
2005-2006	3.94*** [3.41,4.56]
2007	5.29*** [4.38,6.40]
2008	5.83*** [4.79,7.09]
2009	6.07*** [4.95,7.45]
Region	
Midwest	Reference
Northeast	2.35*** [1.93,2.87]
West	2.40*** [1.90,3.02]
South	1.66*** [1.36,2.02]
Residence	
Less Urban/Rural	Reference
Urban	1.06 [0.80,1.42]
Metropolitan	1.14 [0.94,1.39]
% in Census Tract with Less Education than High School Diploma	
≥25	Reference
<25	1.14 [0.96,1.37]
% in Census Tract Living in Poverty	
< 5	Reference
5-7	1.1 [0.92,1.32]
7-12	1.01 [0.86,1.19]
> 12	1.07 [0.88,1.30]
Lymphoma Characteristics	
Grade	
1 or 2	Reference
3	1.60*** [1.36,1.87]
Not specified	0.95 [0.84,1.09]
Primary Site	

Nodal	Reference
Extra-nodal	1.21* [1.04,1.41]
Measures of Baseline Health Status	
NCI Comorbidity Index	
0	Reference
1	1.15* [1.00,1.32]
>2	1.05 [0.88,1.26]
Performance Status	
Good	Reference
Poor	0.54*** [0.46,0.64]
History of Anemia	
Absent	Reference
Present	0.70* [0.52,0.94]
B-Symptoms	
Absent	Reference
Present	0.74** [0.62,0.89]
Unrecorded	0.89 [0.79,1.01]
Features of Management Setting	
Teaching Hospital[§]	
No	Reference
Yes	1.05 [0.93,1.20]
NCI Clinical Trials Cooperative Group Membership[§]	
No	Reference
Yes	1.25*** [1.09,1.42]
Local Density of Nuclear Medicine Specialists[#]	
1st tertile (lowest)	Reference
2ndtertile	1.05 [0.91,1.22]
3rd terttile (highest)	1.28** [1.09,1.50]

§ 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

FIGURE 2.1 Selection criteria for the study cohort

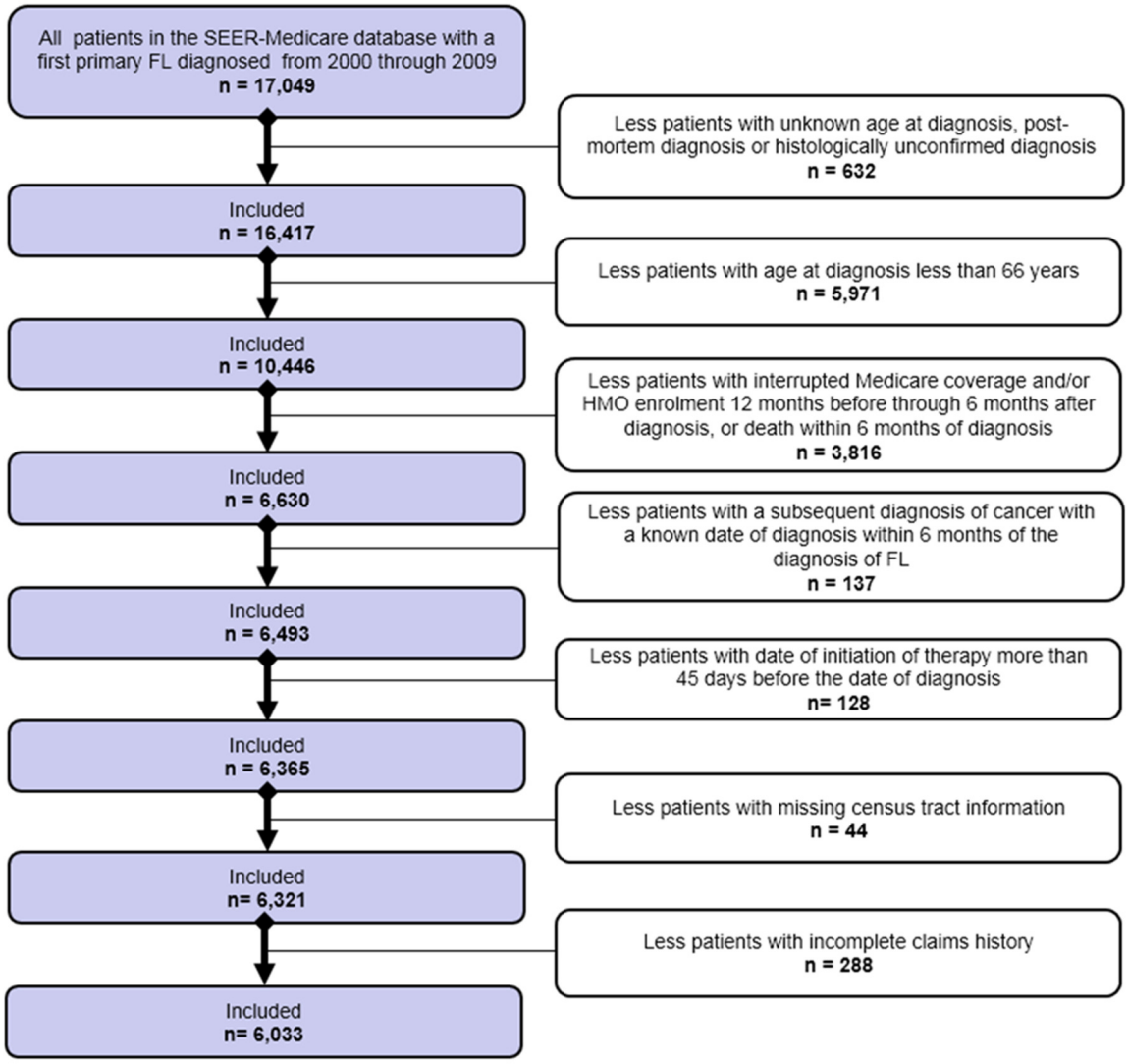
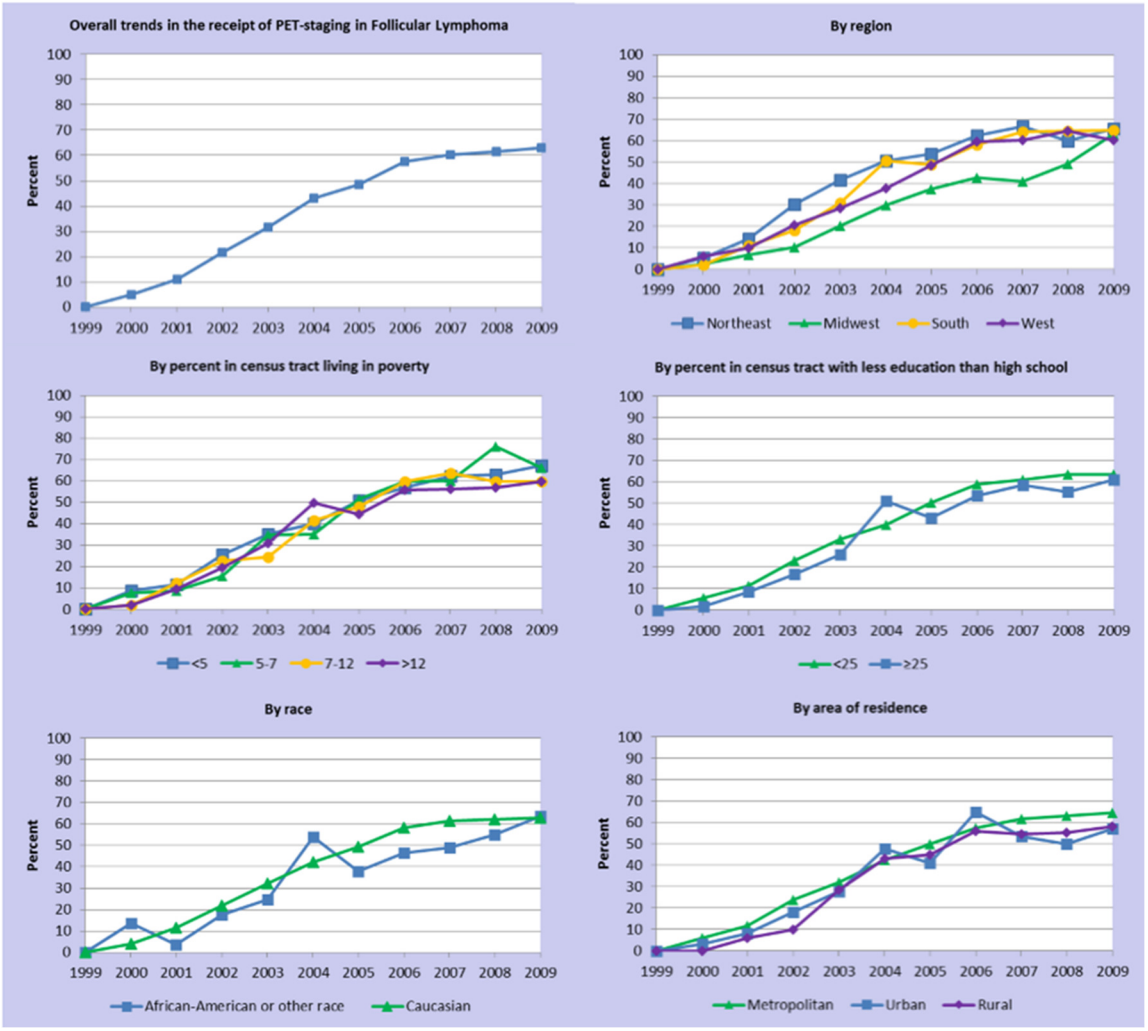


FIGURE 2.2 Proportions of patients receiving one or more PET-staging scans by years of diagnosis



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CHAPTER 3:
Variations in the Management of Follicular Lymphoma: the Role of Clinical Practice Guidelines in Shaping Management Decisions

3.1 Introduction

A body of literature links unexplained variation in cancer outcomes to variations in cancer care.[1-7] Adherence to professional guidelines and recommendations is emphasized to mitigate undesirable variations in care. However, studies linking treatments to outcomes in follicular lymphoma (FL) have not yet provided definitive evidence regarding optimal strategies for frontline therapy and authoritative guidelines are lacking. As a result, considerable variations in care and outcomes have been reported.[8-10]

Follicular lymphoma is an indolent, incurable subtype of non-Hodgkin lymphoma (NHL) that accounts for 15-30% of all NHL cases and is the second most common subtype of NHL in the United States.[8,11-13] Advances in research and technology have led to a rapid proliferation of treatment options for FL in recent years. A major milestone was the introduction of rituximab (R), which is now a standard part of treatment. Nevertheless, due to the heterogeneity of the disease and the difficulties in conducting systematic trials and comparative effectiveness studies, there is no consensus yet on the optimal management strategy in FL.[8]

The extent of the disease (stage) and the histological subtype (grade) are two important factors which determine management and prognosis in FL. Staging for FL is generally based on the Ann Arbor staging classification.[14] Involved-field radiotherapy (IFRT) is considered potentially curative in the minority of patients that present with stage I or limited stage II FL and is the National Comprehensive Cancer Network (NCCN)-preferred treatment for patients with stage I or limited stage II, grade 1-2 FL (Figure 3.1).[15-

[19] However, it is unclear whether clinically defined stages I and II really represent a localized disease.[20] Moreover, observation (wait and watch) has emerged a viable option for patients with stage I/II FL if no indications for immediate treatment are present.[21-23]

Most patients present with stage III/IV, asymptomatic disease for which clinical guidelines are less clear (Figure 3.1).[17] Common strategies for these patients include expectant observation (wait and watch; WW), and immunotherapy (rituximab) with or without multi-agent chemotherapy. Common R-chemo regimens include R-CHOP (R, cyclophosphamide, doxorubicin, vincristine, prednisolone); R-CVP (R, cyclophosphamide, vincristine, prednisolone); R-Flu (R and fludarabine); and R-Benda (R and bendamustine). Recent trials have also reported encouraging results from R monotherapy,[24,25] though the US Food and Drug Administration has yet to issue a label to R for use in this setting.[26]

Clinical presentation and behavior of FL also varies by the histological grade (Figure 3.1). Many different histological classification systems for FL have historically coexisted.[27-30] The WHO classification, which is the most commonly used currently, subdivides FL into 4 histological subtypes—1, 2, 3A, and 3B. As distinct from FL Grades 1 and 2, which display an indolent behavior, the status of FL grade 3 as an indolent or aggressive neoplasm is unresolved.[31,32] As grade 3B may belong to an aggressive subtype—diffuse large B cell lymphoma (DLBCL)—immediate aggressive treatment may be more appropriate than the watch and wait approach in these patients. The NCCN guidelines acknowledge the controversy about the status of grade 3 and mention that these patients are commonly managed as DLBCL, for which the treatment of choice is R-CHOP.[17]

Thus, clinical decisions in FL are made under substantial uncertainty relating to the classification of the disease; efficacy and effectiveness of candidate treatments in specific subpopulations; and goals of management. Clinical guidelines, such as those from the NCCN, have also not been able to provide clear guidance on which approach is better. Therefore, it is important to examine how management decisions in FL are influenced by a) medical, socioeconomic, and demographic characteristics of the patient; b) organizational characteristics of the treating facility; and c) availability of healthcare resources, such as the supply of oncologists and radiation oncologists, in the patient's residential area.

In the current study, we examine the patterns of care in a large population of FL patients. Our aims are: 1) to identify clinical and non-clinical factors that influence management approaches in FL; 2) to examine how clarity and the perceived validity or relevance of clinical guidelines affect clinical practice, given the ongoing emergence of evidence; and 3) to discuss how the observed patterns of care relate to gaps in the evidence base about the efficacy of candidate management approaches, alignment of physicians' financial incentives, and possible lapses in risk communication.

We focused on two subpopulations of FL patients that are on two extremes vis-à-vis the clarity in the NCCN guidelines—those with stage I/grade 1-2 FL and those with grade 3 FL. Although the NCCN guidelines recommend IFRT as the preferred treatment for stage I/limited stage II, grade 1-2 patients, recent studies have shown that other treatment approaches, including simply observation may have comparable or better results than IFRT alone. Many experts also believe that FL is most commonly a disseminated disease at diagnosis and that IFRT may confer benefit in rare cases only. On the other hand,

not only are patients with grade 3 FL at a higher risk of disease progression, the expertise for differentiating aggressive (3B) from indolent (3A) may not be readily available. Thus, risk-averse physicians may believe that lowering the threshold for aggressive chemotherapy in grade 3 patients may improve survival outcomes in the grade 3 population. Furthermore, physicians' financial incentives are better aligned with systemic treatments administered in-office than with observation or IFRT. Therefore, we hypothesized that physicians would have variability in use of IFRT for stage I/grade 1-2 patients, although this is the preferred approach in the NCCN guidelines. On the other hand, a large proportion of grade 3 patients would undergo immediate aggressive chemotherapy, even in the absence of specific guidelines recommendations that can be applied for grade 3 FL.

3.2 Materials and Methods

3.2.1 Data Sources and Study Population

We used the Surveillance, Epidemiology, and End Results (SEER) registry data linked to Medicare claims data. The SEER program is a National Cancer Institute (NCI)-sponsored epidemiologic surveillance system of population-based tumor registries that routinely seeks to collect demographic and clinical information on all incident cancer cases that occur in persons residing in SEER areas.[33] Medicare is the primary health insurer for 97% of the U.S. population aged 65 years and older. The linked data included all Medicare eligible persons in the SEER data from 1998 through 2009 and their claims for Medicare Part A (inpatient) and Part B (outpatient and physician) services through 2010.

We used the SEER registry data to identify patients who were at least 66 years old at the time of a histologically confirmed first primary diagnosis of FL. We identified FL diagnoses based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes 9695 (FL Grade 1), 9691 (FL Grade 2), 9698 (FL Grade 3), and 9690 (FL not otherwise specified).[34] We excluded patients who were diagnosed at autopsy or who died within 6 months of diagnosis; had interrupted Medicare Part A or B coverage or were enrolled in a Health Maintenance Organization (HMO) at least one year prior through 6 months after diagnosis; had another diagnosis of cancer within 6 months of being diagnosed with FL; had chemotherapy, immunotherapy, or radiotherapy claims preceding the date of diagnosis by more than 45 days (deemed as patients with erroneous dates of diagnosis); had missing census tract information; had no physician, hospital outpatient or inpatient claims with a primary diagnosis of FL in a 1 year window around the diagnosis; or for whom the management strategy could not be accurately ascertained due to missing chemotherapy agents (Figure 3.2).

3.2.2 Study Variables

We defined the primary variable of interest—initial management strategy—based on the claims for chemotherapy, immunotherapy, or radiotherapy occurring within six months of the date of diagnosis (Appendix Table 3.4). According to a prior report of the National LymphoCare Study (NLCS)—the largest prospective database in FL in the United States—approximately 82% of patients in the NLCS cohort received active treatment within three months of diagnosis.[8] However, since our patient population was considerably older than the NLCS cohort, we considered six months as a more reasonable choice to account for potential delays in management planning. Specific FL-directed treatment

strategies were identified by searching the Medicare inpatient, outpatient and carrier files for the relevant International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) Diagnosis; ICD-9-CM Procedural; Current Procedural Terminology (CPT); HCPCS; and revenue centers codes (Appendix Table 3.4) [35]. We categorized patients into the following groups based on the first treatment received: chemo, R-chemo, IFRT (alone or in combination with chemo and/or R), and R alone (R-mono). Those who did not receive any FL-directed treatment within the first six months of diagnosis were categorized as undergoing observation. Since SEER provides only the month and year of diagnosis, we assigned the 15th day of the month of diagnosis as the start date for follow-up.

The following patient characteristics were included from the SEER registry data (Patient Entitlement and Diagnosis Summary File): age, sex, race/ethnicity, region of residence at the time of diagnosis (Northeast, Midwest, South, or West), marital status, year of diagnosis, census tract characteristics of residence (education, poverty, and metropolitan/urban/rural status), FL grade (1, 2, 3, or unspecified), primary site of involvement (nodal or extranodal), and presence of B-symptoms (yes, no, or unrecorded) and stage. We defined initial staging scans as any PET scans received during the index month of diagnosis through six months after the diagnosis, and before the receipt of any treatment. Comorbidities were assessed by applying NCI's algorithm for calculation of Klabunde's modification of the Charlson Comorbidity Index (CCI) to Medicare carrier, outpatient, and inpatient claims during the year prior to the diagnosis of FL, excluding the index month.[36,37] In addition, we identified measures of service use from insurance claims that would be correlated with the key elements of the Eastern Cooperative Oncology Group

(ECOG) performance status metric.[38] We assigned patients to a poor performance status group if any indicators of poor performance—including durable medical equipment claims for oxygen, wheelchair or related supplies; and for services performed by skilled nursing facilities, home health agencies, and hospices—were detected in the year prior to diagnosis.[39]

To characterize the institutional setting where management was planned, patients were assigned to facilities based on the most frequently occurring provider identification number (hospital id) from Medicare inpatient and hospital outpatient claims bearing the primary diagnosis code for FL in a one-year window centered on the date of diagnosis. We scanned the next three diagnosis codes if no claims bore the primary diagnosis code for FL in these files (approximately 3% of the population). In case of a tie, we selected the hospital with the earliest claim date for that patient. Subsequently, we used the NCI's Hospital File provided with the SEER-Medicare data to classify these facilities as teaching hospitals or 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), and North Central Cancer Treatment Group (NCCTG).

To characterize the supply of hematologists/oncologists and radiation oncologists in the healthcare market where the patient resides, we linked the SEER-Medicare data with the publicly available 2006 Dartmouth Atlas data, aggregated to the Hospital Referral Region (HRR) level. The Dartmouth Atlas has divided the United States into 306 HRRs on the basis of patterns of care for Medicare patients who were hospitalized for cardiovascular and neurosurgical care.[40] We assigned each patient to an HRR using their

county of residence at diagnosis and classified patients into tertiles of density of hematologists/oncologists and radiation oncologists per 100,000 individuals—the first tertile representing lowest density and the third tertile representing highest density.

3.2.3 Statistical Analysis

Temporal trends in management were plotted by years of diagnosis. Descriptive statistics were tabulated in the two groups of interest: those with stage I and grade 1 or 2 FL, and those with grade 3 FL. Multinomial logistic regressions in the two groups were used to model management approaches (chemo, R-chemo, IFRT, R-mono, and observation) as a function of patient clinical and demographic factors, selected hospital characteristics, and variables indexing the concentration of cancer specialists in the patient's residential area. Observation was used as the reference category in all regressions. The following set of predictors were included: patient characteristics including demographic characteristics, census tract characteristics, geographic region, and year of diagnosis; lymphoma characteristics including FL grade, stage of grade 3 FL, receipt of PET-staging, and nodal or extra-nodal primary site; measures of baseline health status including CCI, performance status, presence of B-symptoms; and features of the management-setting including hospital teaching status, hospital NCTCG membership, and local-area supply of oncologists and radiation oncologists. We used SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC) and Stata 13 statistical software (StataCorp LP, College Station, Texas) for all analyses.

3.3 Results

The final study sample consisted of 1,075 patients in the stage I/grade1-2 group and 1,000 patients in the grade 3 group (Table 3.1). In the stage I/grade 1-2 group, the mean age at diagnosis was 76 years (standard deviation 6.7 years). Approximately 73% of patients in this group were under 80 years of age, 93% were Caucasian, and 60% were female. Approximately 28% of stage I/ grade 1-2 patients received IFRT, 10% received R-chemo, 10% received R alone, 8% received chemo alone, and 44 % received observation. Among those receiving R-chemo, 13% received R-CHOP, 15% received R-CVP, and 4% received R-Fludarabine-based regimens.

The mean age at diagnosis was 76 years in the grade 3 group (standard deviation 6.6 years). Approximately 75% of grade 3 patients were under 80 years of age, 91% were Caucasian, and 59% were female. Approximately 47% of patients in this group received R-chemo, 18% received chemo alone, 9% received R alone, 9% received IFRT, and 16 % received observation. Among those receiving R-chemo, 33% received R-CHOP, 9% received R-CVP, and 2% received R-Fludarabine-based regimens.

Temporal trends in management approaches are shown in Figure 3.3. The proportion of stage I/grade 1-2 patients receiving IFRT declined from 40% in 1998 to 20% in 2009. There was a progressive increase in the use of R-chemo in both subpopulations even in the absence of guideline recommendations. Approximately 20% of stage I/grade 1-2 and 70% of grade 3 patients received R-chemo in 2009.

Multinomial logistic regressions in the stage I population revealed that patients with shorter expected survival were less likely to receive IFRT or other cytotoxic treatments (Table 3.2). Compared to age 66-70 years, patients with age greater than 80 years were less

likely to receive IFRT (odds ratio [OR] 0.49; 95% confidence interval [CI] 0.31-0.77) , R-chemo (OR 0.40; CI 0.20-0.79), or Chemo alone (0.34; 0.16-0.70), and more likely to receive R-mono (OR 2.23; CI 1.02-4.86). Patients with a poor performance status (OR 0.54; CI 0.32-0.90; ref. good performance status), B-symptoms (OR 0.54; CI 0.32-0.90; reference [ref.] absence of B-symptoms), and African-American patients (OR 0.38; CI 0.17-0.85; ref. Caucasian race) less commonly received IFRT. Receipt of staging PET-scans was more commonly associated with IFRT (OR 2.11; CI 1.44-3.10; ref. no PET-staging) or R-chemo (OR 3.05; CI 1.83-5.08; ref no PET-staging). Characteristics of the management setting also significantly impacted IFRT use as patients managed at NCTCG member facilities (OR 1.35; CI 1.03-1.77; ref. NCTCG non-member), and those who resided in HRRs with the highest concentration of radiation oncologists (OR 1.64; CI 1.18-2.27; ref. 1st tertile of radiation oncologist density) were more likely to receive IFRT. Over the years, there was a progressive increase in R-chemo and a corresponding decline in chemo alone and IFRT use.

In the grade 3 group, age greater than 80 years was associated with less common use of R-chemo (OR 0.49; CI 0.27-0.90; ref. 66-70 years), but poor performance status or presence of B-symptoms were not significantly associated with treatment choice (Table 3.3). Stage of FL also influenced the likelihood of treatment. Patients with stage III or IV FL more commonly received R-chemo (OR 2.12; CI 1.38-3.28) or R-mono (OR 2.63; CI 1.47-4.72). Those who received PET-staging more commonly received R-chemo (OR 2.49; CI 1.55-4.02; ref. no PET staging). Temporal increases were observed in R-chemo and R-mono use, while the use of chemo alone declined over time.

3.4 Discussion

In the current study, we examine the patterns of care in a large population of FL patients to identify the clinical and non-clinical factors that influence management approaches in FL. We restrict our inquiry to two subpopulations of FL patients—those with stage I/grade 1-2 FL and those with grade 3 FL—with an aim to examine the role of clarity in guidelines and emerging scientific evidence on variations in treatment patterns in these patients.

The proportion of IFRT use in stage I / grade 1-2 patients in our study population (28%) agreed closely with the low proportion reported in the National LymphoCare Study (24%),[8] confirming that IFRT is not regarded as the standard approach in these patients. The declining use of IFRT in stage I patients is likely due to the perceived dated nature of the NCCN guidelines. The NCCN guidelines recommending IFRT for stage I and limited stage II FL are based on retrospective studies and clinical trials performed in the pre-rituximab era in the late '90s.[41-43] The prognosis for FL has greatly improved over the past decade with the advent of R-chemo. Retrospective studies performed over the last 2 decades do not show any survival advantage with immediate IFRT in limited stage patients.[21-23] These recent findings may have also reinforced the view that FL is mainly a disseminated disease as most patients relapse eventually. Physicians may believe that even in the rare event of an "actual" limited-stage FL, upfront or downstream use of R-chemo would produce durable responses similar to immediate IFRT.

Nevertheless, it is important to note that approximately 56% of the patients in the stage I/grade 1-2 group received upfront treatment as opposed to observation, with almost one fifth receiving R-chemo by 2009. The proportions of patients receiving R-chemo or R-

mono may be inappropriately high given the age profile of our analytic sample. In the absence of any compelling evidence of benefit with early initiation of systemic treatment in stage I patients, our results are suggestive of a conflict between the medical interests of the patient and the economic interests of the oncologist.

Perverse financial incentives have been intrinsic to the "buy and bill" reimbursement of cancer treatment agents in Medicare's fee-for-service program. Oncologists typically purchase chemotherapy and immunotherapy medications directly from distributors, administer them to patients, and then bill Medicare for the reimbursement of the drug costs and administration expenses. As newer, more expensive agents are introduced, drug-price margins surpass professional fees as the major source of a medical oncologist's income and the frequency of treatment increases. Concerns about inappropriate use of costly drugs led to the passage of the Medicare Modernization Act (MMA) in 2003. The Act was followed by changes in the Medicare fee-for-service payment system for drugs. However, there is evidence that medical oncologists responded to these changes by increasing treatment frequency and selectively prescribing agents that had a higher markup. For instance, Jacobson et al reported the following consequences of the enactment of MMA on treatment patterns in lung cancer: more patients had access to chemotherapy; the use of inexpensive generic drugs declined; and the use of costly drugs increased.[44] We cannot test using our data whether our observed treatment patterns were similarly motivated by monetary gains. Nevertheless, it is very likely that oncologists' financial benefits play an important role in treatment choice in FL, especially given the high cost and long infusion time of R.[45]

As expected, most grade 3 patients received upfront systemic treatment, with almost 70% receiving R-chemo in 2009. A major source of uncertainty regarding the management of FL concerns the lack of a uniform classification system for FL. Several publications have suggested that grade 3B FL may be biologically distinct from grades 1-3A and may be closely related to a more aggressive form of NHL—diffuse large B-cell lymphoma (DLBCL). The Revised European American Lymphoma (REAL) classification and the current World Health Organization (WHO) classification also make a distinction between FL grades 3A and 3B,[27,29] albeit the reproducibility of this distinction and its clinical and pathological relevance is still unclear. Retrospective evidence suggests that the clinical outcome of grade 3A is identical to grade 1-2 irrespective of upfront treatment with anthracyclines.[46] However, the fuzzy nature of classification of grade 3 FL, the difficulty in differentiating grade 3A from 3B disease, risk-averse attitudes of physicians and patients, and financial incentives associated with aggressive treatment may restrict watchful waiting in this group. The observed statistically insignificant effect of performance status on treatment choice in grade 3 patients also suggests that physicians may discount inconvenience and risks of chemotherapy in some of these patients.

The shift toward systemic treatments in FL may not be driven by financial incentives or risk-averse attitudes alone. Oncologists are trained as proactive interventionists and doing nothing may be psychologically and even morally difficult for them. Moreover, early detection and treatment has been shown to save lives in so many cancers that many patients may not be receptive to deferring of initial treatment. Thus, oncologists may find it challenging to accurately and effectively communicate risks and benefits of watchful waiting as a reasonable management option. Systemic treatments,

especially those with a favorable toxicity profile such as R-mono, may be prescribed by oncologists in some cases to avoid difficult conversations with patients or to reason through their own inner conflicts. Sometimes no explanation may be enough to ease a patient who is understandably worried about the diagnosis of cancer. These patients are likely to prefer upfront treatment even if the probability of benefit from treatment is small.

We acknowledge several limitations to this study. First, important prognostic factors and indicators of treatment initiation—such as organ compression, serum lactate dehydrogenase, and β2-microglobulin levels—are absent in the data. Information on the above factors will be required to estimate the extent of inappropriate treatment in FL. Second, neither SEER not Medicare identifies observation as a management approach. We defined observation as lack of any FL-directed treatment claims in the first six months following diagnosis. Delays in administration of treatment may have led to misclassification of some patients into the observation group. Third, we could not identify the characteristics of the providers prescribing treatments. Previous studies have found associations between provider characteristics such as training, age, practice setting, and specialty with the patterns of management of cancer patients.[47-50] These physician characteristics currently are not available in the SEER-Medicare dataset. Fourth, we used ICD-O-3 for classifying grade 1, 2, and 3 histology. Since SEER was using ICD-O-2 till 2001, some patients diagnosed in 1998-2000 may have been misclassified. Finally, our results are generalizable only to fee-for-service Medicare enrollees who resided in SEER registry areas and did not participate in managed care plans.

The above limitations notwithstanding, the current study is the first, large-scale, population-based retrospective analysis of patterns of care in FL and includes all common

management approaches. Our results provide important insights into the factors determining management of FL in the United States. In summary, we found that IFRT in stage I/grade 1-2 disease was not the standard approach despite NCCN recommending this use. Systemic treatment with R-chemo or R-mono in stage I/grade 1-2 patients was very common, even though observation is a reasonable approach in these patients. On the other hand, most grade 3 patients received upfront R-chemo even in the absence of clear recommendations in the NCCN guidelines.

In the rapidly evolving world of oncology, clinical guidelines are only one factor affecting treatment decisions and outcomes. Very often cancer treatment decisions fall in the discretionary realm and interventions with unclear benefits are adopted rapidly, especially in a favorable reimbursement environment. Efforts to improve quality of cancer care should focus not only on guideline concordance but also on alignment of payment systems with the desired outcomes for cancer patients and society.

TABLE 3.1 Baseline characteristics of the sample stratified by analytic group

	Stage I/ Grade 1-2	Grade3
Patient Characteristics		
Age		
Mean (SD)	76 (6.7)	75.5 (6.7)
66-70 yr	283 (26.3)	278 (27.8)
71-75 yr	272 (25.3)	256 (25.6)
76-80 yr	238 (22.1)	229 (22.9)
> 80 yr	282 (26.2)	237 (23.7)
Race		
Caucasian	1004 (93.4)	908 (90.8)
AA	34 (3.2)	33 (3.3)
Others	37 (3.4)	59 (5.9)
Sex		
Male	429 (39.9)	410 (41)
Female	646 (60.1)	590 (59)
Marital Status		
Married	626 (58.2)	569 (56.9)
Others	378 (35.2)	373 (37.3)
Unknown	71 (6.6)	58 (5.8)
% in Census Tract with Less Education than High School		
< 25	837 (77.9)	770 (77)
≥25	238 (22.1)	230 (23)
% in Census Tract Living in Poverty		
< 5	349 (32.5)	328 (32.8)
5-7	161 (15)	156 (15.6)
7-12	261 (24.3)	231 (23.1)
> 12	304 (28.3)	285 (28.5)
Residence		
Metropolitan	879 (81.8)	819 (81.9)
Urban	67 (6.2)	55 (5.5)
Less Urban/Rural	129 (12)	126 (12.6)
NCI Comorbidity Index		
0	681 (63.3)	643 (64.3)
1	281 (26.1)	221 (22.1)
≥2	113 (10.5)	136 (13.6)
Performance Status		
Good	943 (87.7)	869 (86.9)
Poor	132 (12.3)	131 (13.1)
Year of Diagnosis		
1998-2000	231 (21.5)	158 (15.8)
2001-2003	315 (29.3)	258 (25.8)
2004-2006	297 (27.6)	303 (30.3)
2007-2009	232 (21.6)	281 (28.1)
Lymphoma Characteristics		
Primary Site		
Nodal	797 (74.1)	857 (85.7)
Extra-nodal	278 (25.9)	143 (14.3)

B-Symptoms		
Present	504 (46.9)	61 (6.1)
Absent	25 (2.3)	499 (49.9)
Unrecorded	546 (50.8)	440 (44)
Features of Management Setting		
Region		
Northeast	196 (18.2)	202 (20.2)
Midwest	196 (18.2)	156 (15.6)
West	411 (38.2)	439 (43.9)
South	272 (25.3)	203 (20.3)
Teaching Hospital		
No	495 (46)	487 (48.7)
Yes	580 (54)	513 (51.3)
NCI Clinical Trials Cooperative Group Membership[§]		
No	419 (39)	418 (41.8)
Yes	656 (61)	582 (58.2)
Local Density of Oncologists/Hematologists[#]		
1st tertile (lowest)	383 (35.6)	336 (33.6)
2nd tertile	336 (31.3)	339 (33.9)
3rd tertile (Highest)	356 (33.1)	325 (32.5)
Local Density of Radiation Oncologists[#]		
1st tertile (Lowest)	359 (33.4)	336 (33.6)
2nd tertile	344 (32)	360 (36)
3rd tertilen (Highest)	372 (34.6)	304 (30.4)
Features of Management		
Staging PET-scan received		
Yes	717 (66.7)	517 (51.7)
No	358 (33.3)	483 (48.3)
Treatment Received		
Chemo (+/-IFRT)	86 (8)	180 (18)
R-Chemo (+/-IFRT)	111 (10.3)	473 (47.3)
IFRT (+/- R)	300 (27.9)	98 (9.8)
R Alone	102 (9.5)	93 (9.3)
Observation	476 (44.3)	156 (15.6)

§ Patients assigned to facilities based on the frequency of outpatient and inpatient claims bearing diagnosis codes of Follicular Lymphoma in the follow-up period

From the 2006 Dartmouth Atlas data

Abbreviations: PET, Positron Emission Tomography; SD, standard deviation; NCI, National Cancer Institute

TABLE 3.2 Results from multinomial logistic regression comparing management choice in stage I/grade 1 or 2 patients (n= 1,075)

	Chemo vs Obs	R-chemo vs Obs
Age		
71 – 75 vs 66 -70 yr	0.65 [0.34,1.22]	1.01 [0.57,1.81]
76 - 80 vs 66 -70 yr	0.73 [0.38,1.42]	0.74 [0.38,1.43]
> 80 vs 66 -70yr	0.34** [0.16,0.70]	0.40** [0.20,0.79]
Race		
AA vs Caucasian	0.51 [0.10,2.50]	0.73 [0.18,2.87]
Others vs Caucasian	2.96 [0.81,10.78]	2.68 [0.77,9.36]
Sex		
Female vs Male	0.96 [0.57,1.60]	1.05 [0.65,1.70]
Marital Status		
Married vs Single/Widowed	1.10 [0.63,1.93]	1.55 [0.90,2.69]
Unknown vs Single/Widowed	1.31 [0.53,3.22]	1.31 [0.47,3.60]
Years of Diagnosis		
2001-2003 vs 1998-2000	0.62 [0.33,1.15]	4.14* [1.34,12.77]
2004-2006 vs 1998-2000	0.30** [0.14,0.67]	4.07* [1.28,12.95]
2007-2009 vs 1998-2000	0.15*** [0.06,0.37]	4.91** [1.53,15.76]
Region of Residence		
Northeast vs Midwest	1.51 [0.69,3.31]	1.03 [0.48,2.19]
South vs Midwest	1.25 [0.46,3.43]	1.02 [0.42,2.47]
West vs Midwest	0.71 [0.31,1.65]	0.73 [0.35,1.52]
Type of Residence		
Metro vs Less Urban/Rural	1.28 [0.56,2.92]	0.72 [0.33,1.58]
Urban vs Less Urban/Rural	0.52 [0.14,1.93]	1.03 [0.37,2.84]
% Living in Poverty		
5% - 7% vs < 5%	1.34 [0.62,2.89]	1.17 [0.59,2.34]
7% - 12% vs < 5%	1.76 [0.86,3.61]	0.49 [0.23,1.03]
> 12% vs < 5%	2.69* [1.17,6.18]	0.84 [0.38,1.89]
Census Tract Education		
More vs Less Educated	1.25 [0.58,2.70]	0.57 [0.26,1.23]
Primary Site		
Extranodal vs Nodal	0.83 [0.46,1.48]	0.66 [0.38,1.14]
Comorbidity Index		
1 vs 0	0.95 [0.53,1.70]	0.78 [0.46,1.33]
≥ 2 vs 0	1.51 [0.69,3.29]	1.22 [0.57,2.57]
Performance Status		
Poor vs Good	0.55 [0.24,1.28]	0.54 [0.24,1.22]
B-symptoms		
Present vs Absent	2.45 [0.96,6.21]	1.20 [0.39,3.72]
Unrecorded vs Absent	1.48 [0.86,2.54]	1.02 [0.63,1.65]
Staging PET-scan		
Yes vs No	0.74 [0.36,1.55]	3.05*** [1.83,5.08]
NCCTG Membership		
Member vs Non-Member	0.64 [0.38,1.08]	1.02 [0.62,1.67]
Hospital Teaching Status		

Teaching vs Non-teaching	1.02 [0.60,1.76]	0.65 [0.40,1.07]
Oncologist Density Tertile		
2nd vs 1st	0.72 [0.37,1.41]	1.51 [0.81,2.82]
3rd vs 1st	0.86 [0.43,1.72]	1.33 [0.66,2.66]
Radiation Oncologist Density Tertile		
2nd vs 1st	1.49 [0.80,2.79]	0.90 [0.48,1.69]
3rd vs 1st	1.19 [0.58,2.46]	1.36 [0.71,2.59]

* p<0.05, ** p<0.01, *** p<0.001
Abbreviations: PET, Positron Emission Tomography; NCCTG, National Cancer Institute Clinical Trial Cooperative Group

TABLE 3.2 (Continued) Results from multinomial logistic regression comparing management choice in stage I/grade 1 or 2 patients (n= 1,075)

	R-mono vs Obs	**IFRT vs Obs**
Age		
71 – 75 vs 66 -70 yr	0.72 [0.36,1.42]	0.71 [0.46,1.08]
76 - 80 vs 66 -70 yr	1.06 [0.54,2.08]	1.17 [0.76,1.81]
> 80 vs 66 -70yr	2.23* [1.02, 4.86]	0.49** [0.31,0.77]
Race		
AA vs Caucasian	1.65 [0.61,4.42]	0.34* [0.12,0.98]
Others vs Caucasian	2.52 [0.70,9.03]	1.97 [0.79,4.94]
Sex		
Female vs Male	1.37 [0.84,2.24]	1.06 [0.76,1.48]
Marital Status		
Married vs Single/Widowed	1.01 [0.58,1.75]	1.4 [0.98,2.01]
Unknown vs Single/Widowed	1.80 [0.81,4.00]	1.03 [0.50,2.14]
Years of Diagnosis		
2001-2003 vs 1998-2000	1.78 [0.86,3.70]	0.69 [0.45,1.06]
2004-2006 vs 1998-2000	1.22 [0.57,2.60]	0.43*** [0.27,0.69]
2007-2009 vs 1998-2000	1.89 [0.86,4.16]	0.38*** [0.22,0.64]
Region of Residence		
Northeast vs Midwest	1.27 [0.57,2.84]	0.99 [0.61,1.62]
South vs Midwest	2.01 [0.86,4.69]	0.75 [0.40,1.41]
West vs Midwest	0.89 [0.39,2.04]	0.84 [0.52,1.35]
Type of Residence		
Metro vs Less Urban/Rural	1.65 [0.65,4.19]	0.95 [0.55,1.66]
Urban vs Less Urban/Rural	0.73 [0.18,2.95]	0.97 [0.45,2.08]
% Living in Poverty		
5% - 7% vs < 5%	1.36 [0.63,2.94]	1.03 [0.63,1.70]
7% - 12% vs < 5%	1.39 [0.72,2.68]	1.08 [0.71,1.66]
> 12% vs < 5%	0.94 [0.49,1.82]	1.41 [0.82,2.42]
Census Tract Education		
More vs Less Educated	1.16 [0.59,2.29]	0.79 [0.47,1.31]
Primary Site		
Extranodal vs Nodal	0.94 [0.56,1.57]	1.45* [1.03,2.04]

Comorbidity Index		
1 vs 0	0.78 [0.45,1.35]	0.91 [0.63,1.31]
≥ 2 vs 0	0.93 [0.40,2.13]	1.12 [0.66,1.90]
Performance Status		
Poor vs Good	0.95 [0.47,1.92]	0.54* [0.32,0.90]
B-symptoms		
Present vs Absent	2.03 [0.79,5.21]	0.54*** [0.39,0.77]
Unrecorded vs Absent	1.07 [0.66,1.73]	1.13 [0.54,2.36]
Staging PET-scan		
Yes vs No	1.49 [0.90,2.48]	2.11*** [1.44,3.10]
NCCTG Membership		
Member vs Non-Member	1.05 [0.64,1.74]	1.33*[1.02,1.68]
Hospital Teaching Status		
Teaching vs Non-teaching	1.04 [0.64,1.70]	1.08 [0.76,1.55]
Oncologist Density Tertile		
2nd vs 1st	1.64 [0.94,2.87]	1.14 [0.74,1.75]
3rd vs 1st	0.55 [0.27,1.12]	0.92 [0.58,1.47]
Radiation Oncologist Density Tertile		
2nd vs 1st	0.9 [0.50,1.63]	1.13 [0.74,1.72]
3rd vs 1st	1.22 [0.66,2.26]	1.90** [1.22,2.96]

* p<0.05, ** p<0.01, *** p<0.001

Abbreviations: PET, Positron Emission Tomography; NCCTG, National Cancer Institute Clinical Trial Cooperative Group

TABLE 3.3 Results from multinomial logistic regression comparing management choice in grade 3 FL (n= 1,000; results for IFRT vs observation not reported)

	Chemo vs Obs	R-chemo vs Obs	R-mono vs Obs
Age			
71 - 75 vs 66 -70 yr	0.62 [0.32-1.23]	1.01 [0.59-1.74]	0.66 [0.28-1.57]
76 - 80 vs 66 -70 yr	0.81 [0.40-1.65]	1.14 [0.63-2.07]	1.68 [0.75-3.75]
> 80 vs 66 -70yr	0.53 [0.26-1.10]	0.49* [0.27-0.90]	1.92 [0.90-4.12]
Race			
AA vs Caucasian	0.54 [0.18-1.69]	0.67 [0.17-2.65]	0.79 [0.18-3.47]
Other Race vs Caucasian	2.08 [0.71-6.08]	0.53 [0.23-1.20]	0.46 [0.13-1.68]
Sex			
Female vs Male	1.27 [0.74-2.19]	0.95 [0.62-1.47]	1.25 [0.70-2.24]
Marital Status			
Married vs Single/Widowed	1.01 [0.56-1.81]	0.73 [0.45-1.18]	1.15 [0.62-2.13]
Unknown vs Single/Widowed	0.39 [0.13-1.15]	0.61 [0.29-1.30]	0.45 [0.12-1.62]
Years of Diagnosis			
2001-2003 vs 1998-2000	0.20*** [0.10-0.38]	6.03*** [2.16-16.83]	1.4 [0.47-4.16]
2004-2006 vs 1998-2000	0.14*** [0.06-0.29]	10.10*** [3.44-29.63]	3.21* [1.09-9.47]
2007-2009 vs 1998-2000	0.05*** [0.02-0.13]	11.01*** [3.58-33.79]	3.23* [1.08-9.69]
% Living Under Poverty			
5% - 7% vs < 5	0.75 [0.32-1.77]	0.9 [0.49-1.65]	0.94 [0.40-2.18]
7% - 12% vs < 5%	1.65 [0.78-3.48]	1.33 [0.72-2.46]	1.44 [0.66-3.17]
> 12% vs < 5%	1.06 [0.45-2.48]	1.01 [0.47-2.17]	1.57 [0.62-3.99]
Census Tract Education			
More vs Less Educated	0.83 [0.40-1.74]	1.28 [0.64-2.55]	1.48 [0.61-3.62]
Type of Residence			
Metro vs Less Urban/Rural	1.22 [0.48-3.08]	0.96 [0.47-1.97]	1.12 [0.43-2.93]
Urban vs Less Urban/Rural	1.45 [0.38-5.58]	1.74 [0.58-5.19]	1.87 [0.43-8.01]
Region of Residence			
Northeast vs Midwest	0.7 [0.29-1.66]	0.53 [0.26-1.09]	0.75 [0.29-1.94]
South vs Midwest	0.48 [0.14-1.69]	0.73 [0.29-1.85]	0.83 [0.25-2.81]
West vs Midwest	0.53 [0.22-1.28]	0.47 [0.22-1.00]	0.62 [0.25-1.57]
Comorbidity Index			
Comorbidity Index 1 vs 0	0.92 [0.49-1.71]	0.98 [0.60-1.62]	0.54 [0.25-1.17]
Comorbidity Index ≥ 2 vs 0	0.7 [0.29-1.71]	1.04 [0.55-1.96]	1.71 [0.77-3.79]
Performance Status			
Poor vs Good	0.63 [0.30-1.30]	0.62 [0.34-1.12]	1.04 [0.49-2.22]
Stage			

III-IV vs I-II	1.57 [0.90-2.75]	2.12*** [1.38-3.28]	2.63** [1.47-4.72]
Unknown vs I-II	0.45 [0.14-1.47]	0.87 [0.37-2.01]	0.65 [0.19-2.22]
Primary Site			
Extranodal vs Nodal	0.64 [0.32-1.28]	0.86 [0.48-1.54]	0.66 [0.28-1.57]
B-symptoms			
Present vs Absent	1.29 [0.54-3.03]	1.98 [1.00-3.89]	1.55 [0.65-3.68]
Unrecorded vs Absent	0.95 [0.54-1.66]	1.25 [0.78-1.99]	1.32 [0.71-2.43]
PET-staging Received			
Yes vs No	0.61 [0.32-1.18]	2.49*** [1.55-4.02]	1.15 [0.62-2.13]
NCTCG Membership			
Yes vs No	1.03 [0.60-1.77]	1.63* [1.03-2.58]	1.93* [1.02-3.66]
Teaching Hospital			
Yes vs No	1.02 [0.59-1.76]	1.26 [0.80-1.99]	0.99 [0.55-1.77]
Oncologist Density Tertile			
2nd vs 1st	1.52 [0.76-3.06]	1.22 [0.69-2.15]	0.85 [0.40-1.78]
3rd vs 1st	0.74 [0.35-1.60]	0.66 [0.36-1.21]	0.57 [0.26-1.24]

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Abbreviations: PET, Positron Emission Tomography; NCCTG, National Cancer Institute Clinical Trial Cooperative Group

APPENDIX TABLE 3.4 ICD-9-CM and CPT/HCPCS codes used to identify management strategy and PET-staging

Treatment	Codes
Chemotherapy/Immunotherapy	ICD-9-CM diagnosis: V58.1, V66.2, V67.2 ICD-9-CM procedure: 99.25 Revenue center: 0331, 0332, 0335 CPT/HCPCS: 964xx, 965XX, A9542, A9543, A9522, A9523, A9533, A9534, A9544, A9545, C1080 -C1083, G3001, G0355, G0359, J8530, J8562 J9000-J9999, Q0083- Q0085, S0172
Radiotherapy	ICD-9-CM procedure: 92.21-92.29 Revenue center: 0330, 0333, 0339 CPT/HCPCS: 7740X, 7741X, 7775X-7777X, 7779X, 7743X-7749X, 7727X-7730X, 7739X, 77420-77425, 77520-77525, 77427-77429, 77011, 77014, 76950, 77261-77269, G0173, G0251, G0256, G0261, G0334, G0340
PET	CPT/HCPCS: 78608-78816, G0125, G0126, G0163-G0165, and G0210-G0235

Abbreviations: ICD-9-CM: International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Classification System; PET: Positron Emission Tomography

FIGURE 3.1 Current National Comprehensive Cancer Network Clinical Practice Guidelines for management of follicular lymphoma

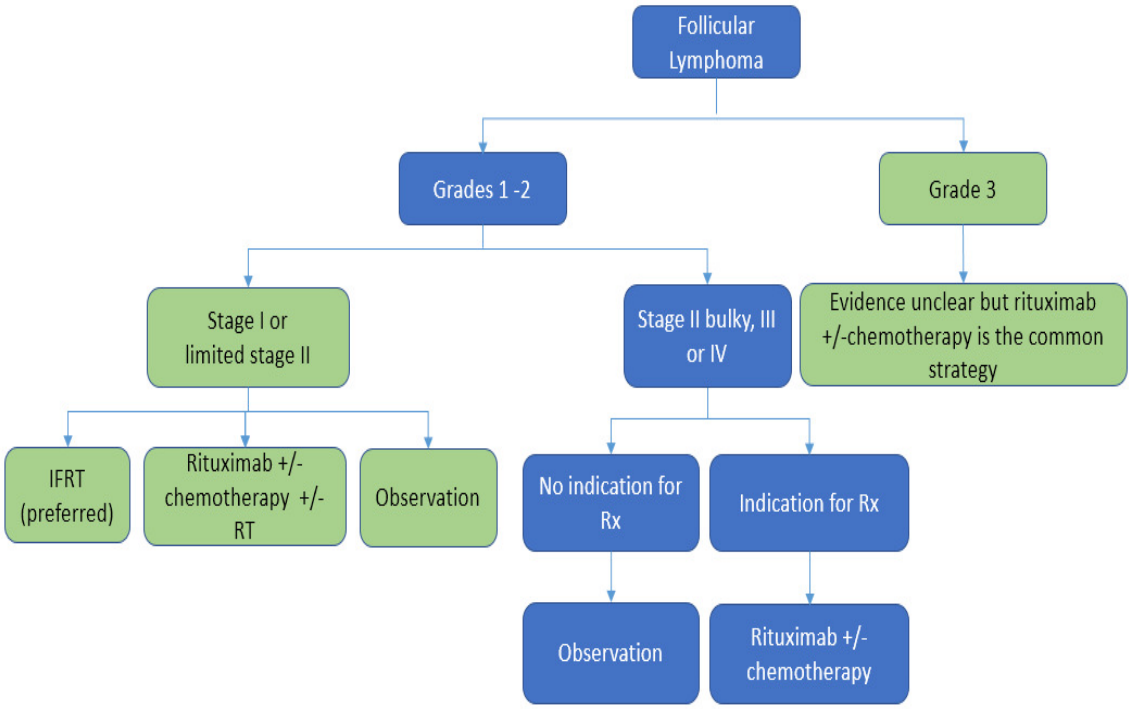


FIGURE 3.2 Selection criteria for the study cohort

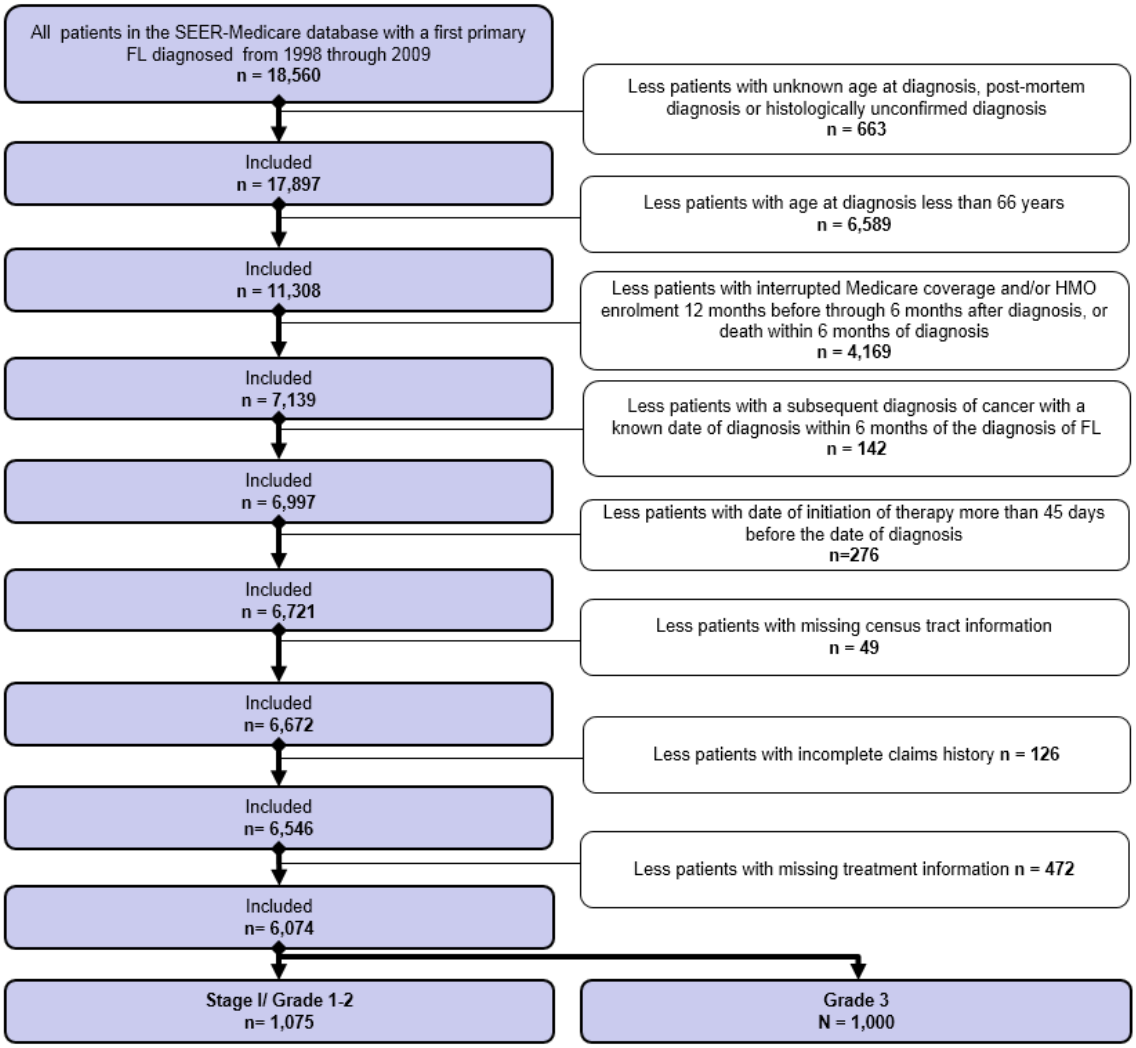
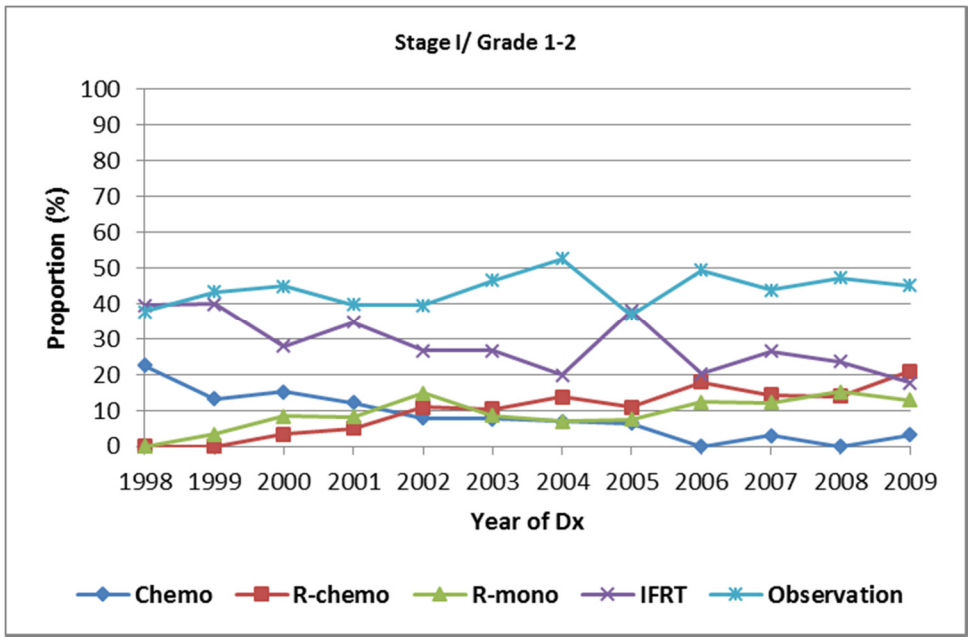
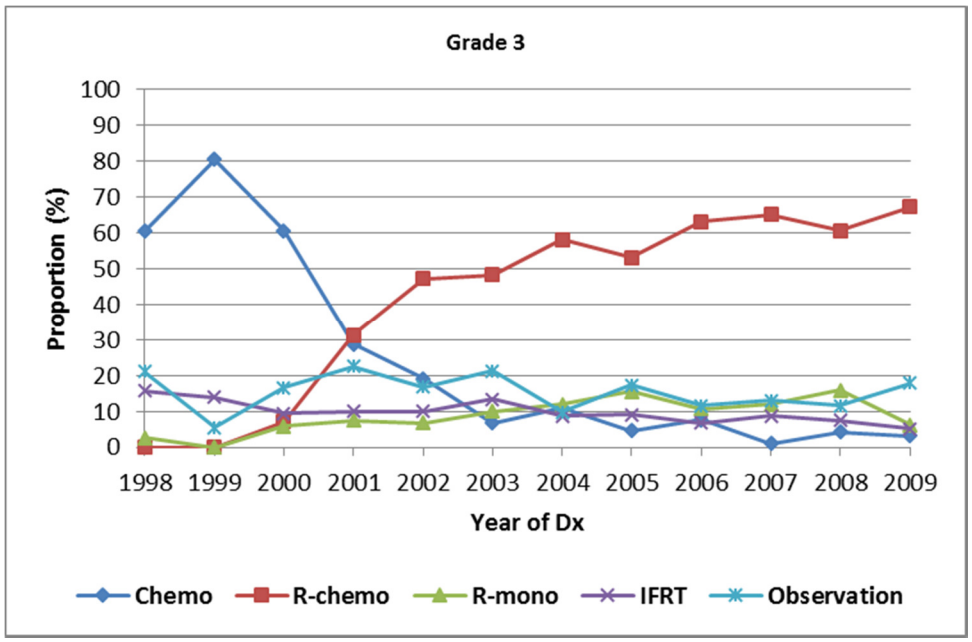


FIGURE 3.3 Time trends in management choice in stage I/ grade 1-2 FL and grade 3 FL patients





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CHAPTER 4:
Survival Outcomes in Follicular Lymphoma and the Role of Positron Emission Tomography (PET)-Staging

4.1 Introduction

With an estimated incidence of 70,800 in the United States (U.S.) in 2014, Non-Hodgkin lymphoma (NHL) is the seventh most common cancer among males and the sixth most common cancer among females.[1] Follicular lymphoma (FL) is the second most common subtype of NHL in the United States, constituting more than 70% of all indolent NHL histologies. [2-4] Recent advances in treatment options for FL have led to substantial improvements in survival. Among these, the combination of rituximab plus chemotherapy (R-chemo) is the most important therapeutic innovation that has led to major gains in response rates and survival outcomes.[5-8] Expectant observation or rituximab alone (R-mono) are viable options for asymptomatic patients and a minority of stage I and limited stage II patients may benefit from involved field radiation therapy.

Follicular lymphoma typically follows a long clinical course. Most FL patients present with widespread disease at diagnosis, are asymptomatic, and generally considered incurable. Specific characteristics of the disease including grade, stage, tumor-burden, presence of symptoms, patient health status, and age play important roles in deciding management strategy. Disease extension (FL-stage) is acknowledged as an important prognostic factor for patients with FL and plays a major role in management decisions.[9,10]

Conventional staging of FL involves computerized tomography (CT) imaging of the chest, abdomen and pelvis. A more sensitive imaging technique, [^{18}F] Fluoro-2 deoxyglucose (FDG)-positron emission tomography (PET), was approved for reimbursement by Medicare in 1998. Unlike older imaging techniques such as CT and

magnetic resonance imaging (MRI) scans that rely on the size of lesions, the fundamental basis for PET is increased cellular activity of malignant cells as indicated by increased FDG uptake. Therefore, PET offers greater sensitivity and negative predictive value than conventional CT in FDG-avid malignancies such as FL.

For a long period after its approval, clinical guidelines regarding PET were ambiguous and it was unclear whether PET-staging in FL substantially affected management decisions or survival outcomes. For instance, the International Harmonization Project, initiated to develop recommendations that were consistent across study groups, did not include pretreatment PET scans for FL in its 2007 recommendations.[11] The National Comprehensive Cancer Network (NCCN) guidelines also did not provide advice on the use of PET-staging for FL.[12] However, several recent studies have demonstrated the potential of PET-staging to modify therapeutic decisions in a proportion of FL patients[13-15] and clinical opinion has been shifting in favor of the use of PET for staging and pretreatment evaluation in FL.[16] Accordingly, in June 2011, in a workshop held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, it was decided that PET-CT should be recommended for routine staging of FDG-avid lymphomas (including FL) as the gold-standard.[17]

A rigorous diagnostic workup of FL, involving PET-staging, may influence initial management strategy and, ultimately, survival outcomes through complex mechanisms. We have described the possible impact of the interplay between initial management approaches, PET-staging, and structural and organizational characteristics of healthcare on survival in a conceptual model (Figure 4.1).

There are several ways through which PET-staging may influence initial management approach in FL. Positron emission tomography has been found useful for an accurate identification of stage I and limited stage II FL patients as candidates for immediate involved-field radiation therapy (IFRT) that might be curative in a minority of patients. An accurate assignment of FL stage may also alter the prognostic evaluation of some patients at diagnosis,[14] thereby inducing not only a change in the initial management from a conservative (R-mono or observation) to an aggressive approach (R-chemo), but also possibly modifying the intensity or sequencing of treatment. Another advantage of PET over conventional staging concerns a timely identification of histologic transformation (HT) of FL. Histologic transformation is a dramatic event often requiring prompt initiation of intensified systemic therapy. Estimates of incidence of HT in FL vary from 10 to 70 percent.[18-23] Several studies have demonstrated that the standardized uptake value (SUV), a relative measure of FDG uptake derived from PET, may be useful in identifying HT.[24,25] When HT is suspected, PET also may assist in guiding a confirmatory biopsy.[26]

Alternatively, the anticipated initial management approach may also influence the prescription of PET-staging. Positron emission tomography has a distinct advantage over CT in assessing response to treatment.[27-29] To this effect, accurate initial staging may improve the adequacy of post-treatment response assessment and downstream management strategy.[30] Thus, if active treatment is expected to begin soon after diagnosis, a physician may order a pre-treatment PET-scan to improve the adequacy of treatment response evaluation. The initial management approach or PET-staging may in turn be

impacted by several clinical and non-clinical factors that may also influence survival independently.

Given the above conceptual model, we expect PET-staging to have a potential positive impact on survival, mainly through its effect on the assignment of initial treatment, but also by being associated with better execution of treatment and assessment of treatment response. In the current study, we examine a large population of FL patients to assess: 1) whether PET-staging has a significant impact on the choice of R-chemo versus other treatments, after accounting for various observed and un-observed factors that may determine initial management and/or PET-staging; and 2) if there is an apparent effect of PET-staging on survival outcomes.

4.2 Materials and Methods

4.2.1 Data Sources and Study Population

We identified FL patients from the Surveillance, Epidemiology, and End Results (SEER) registry data linked to Medicare claims data. 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 cancer cases that occur in persons residing in SEER areas.[31] Medicare is the primary health insurer for 97% of the U.S. population aged 65 years and older. The linked data included all Medicare eligible persons in the SEER data from 2000 through 2009 and their claims for Medicare Part A (inpatient) and Part B (outpatient and physician) services through 2011.

We used the SEER registry data to identify patients who were at least 66 years old at the time of a histologically confirmed first primary diagnosis of FL. We identified FL diagnoses based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes 9695 (FL Grade 1), 9691 (FL Grade 2), 9698 (FL Grade 3), and 9690 (FL not otherwise specified).[32] We sequentially excluded patients: who were diagnosed at autopsy or who died within 6 months of diagnosis; who had interrupted Medicare Part A or B coverage or were enrolled in a Health Maintenance Organization (HMO) at least one year prior through 6 months after diagnosis; who had another diagnosis of cancer within 6 months of being diagnosed with FL; who had chemotherapy, immunotherapy, or radiotherapy claims preceding the date of diagnosis by more than 45 days (deemed as patients with erroneous dates of diagnosis); who had missing census tract information; who had no physician, hospital outpatient or inpatient claims with a primary diagnosis of FL in a 1 year window around the diagnosis; or for whom the management strategy could not be accurately ascertained due to missing chemotherapy agents (Figure 4.2).

4.2.2 Study Variables

The primary outcome of interest was all-cause survival (time from diagnosis to death from any cause). The date of death is reported to the Centers for Medicare and Medicaid Services by the Social Security Administration and is complete through December 31, 2011. Since SEER provides only the month and year of diagnosis, we assigned the 15th day of the month of diagnosis as the start date for observation.

The primary variables of interest were the receipt of PET-staging and the initial management approach. Follicular lymphoma-directed treatment strategies were identified

by searching the Medicare inpatient, outpatient and carrier files for the relevant International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) Diagnosis; ICD-9-CM Procedural; Current Procedural Terminology (CPT); HCPCS; and revenue centers codes (Appendix Table 4.7).[33] Although IFRT may be used with a curative intent in a small proportion of patients diagnosed with limited stage disease, a recent retrospective study has reported that the use of IFRT in stage I/II patients is not common in the United States and chemotherapy or R-chemo are the commonest approaches.[3] The addition of rituximab to chemotherapy (R-chemo) has been demonstrated to produce higher response rates and a clear improvement in overall survival. Therefore, we categorized patients into two groups based on the management approach during the first six months of diagnosis: those who received R-chemo (R-chemo +/- IFRT); and those who received other management approaches (others), including chemo (chemotherapy +/- IFRT), IFRT (alone or in combination with rituximab), R-mono (rituximab alone), and expectant observation.

Patients were classified into PET and no-PET groups on the basis of receipt of PET-staging which was defined as any PET scan performed during the index month of follow-up through six months after the start date of follow-up, and before the receipt of any treatment. We identified claims for PET scans in the Medicare carrier and outpatient claims files as those with the following comprehensive list of Healthcare Common Procedure Coding System (HCPCS) codes: 78608-78816, G0125, G0126, G0163-G0165, and G0210-G0235.

As indicated in our conceptual model, a number of clinical or non-clinical factors that are not observed in the data may influence the use of R-chemo or PET-staging. Important factors among these are anticipated downstream treatment strategies, elements

of prognostic assessment at diagnosis and access to healthcare resources. We also hypothesize (and find confirmation in analyses below) that PET-staging and R-chemo may not be discrete, independent decisions, but rather may be jointly determined. In response, we created four packages of initial management approaches as follows: PET-staging and R-chemo (PET + R-chemo), no PET-staging and R-chemo (no PET + R-chemo), PET-staging and others (PET + others); and no PET-staging and others (no PET + others).

The following patient characteristics were included from the SEER registry data: age, sex, race/ethnicity, region of residence (Northeast, Midwest, South, or West), marital status, year of diagnosis (categorized into 4 groups as 2000-2002, 2003-2005, and 2006-2009), census tract characteristics of residence (education, poverty, and metropolitan/urban/rural status), FL stage (I/II, III/IV, or unknown), FL grade (1, 2, 3, or unspecified), and presence of B-symptoms (yes, no, or unrecorded). Comorbidities were assessed by applying NCI's algorithm for calculation of Klabunde's modification of the Charlson Comorbidity Index (CCI) to Medicare carrier, outpatient, and inpatient claims during the year prior to the diagnosis of FL, excluding the index month.[34,35] We searched for claims with the ICD-9-CM diagnosis codes 280.X, 281.X, 283.X, 284.8, 284.9, 285.2, and 285.9 in the year prior to the diagnosis to identify a recent history of anemia. Additionally, we assigned patients to a poor performance status group if any indicators of poor performance—including durable medical equipment claims for oxygen, wheelchair or related supplies; and for services performed by skilled nursing facilities, home health agencies, and hospices—were detected in the year prior to diagnosis. This measure of performance is a proxy for the Eastern Cooperative Oncology Group (ECOG) performance

status metric and has been shown to be a strong predictor of cancer treatment and prognosis.[36-38]

As described in Chapters 2 and 3, characteristics of the management-setting may significantly impact receipt of PET-staging and initial management. Patients were assigned to facilities based on the most frequently occurring provider identification number (hospital id) from Medicare inpatient and hospital outpatient claims bearing the primary diagnosis code for FL in a one year window centered on the date of diagnosis. We scanned the next three diagnosis codes if no claims bore the primary diagnosis code for FL in these files (approximately 3% of the population). In case of a tie, we selected the hospital with the earliest claim date for that patient. Subsequently, we used the Hospital File provided with the SEER-Medicare data to classify these facilities 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).

Greater concentration of nuclear-medicine specialists per-capita was associated with increased use of PET-staging in Chapter 2. Conceptually, the supply of nuclear medicine specialists may also serve as a proxy for the availability of other infrastructural and healthcare resources in the healthcare market where a patient resided as of the time of diagnosis. To characterize the supply of nuclear medicine specialists, we aggregated the county-level health workforce data from the 2005 Area Health Resources File [39] to the patients' Hospital Referral Region (HRR)-level. The Dartmouth Atlas has divided the United States into 306 HRRs on the basis of patterns of care for Medicare patients who

were hospitalized for cardiovascular and neurosurgical care.[40] We assigned each patient to an HRR using their county of residence. Patients were categorized as residents of areas with a low (lowest tertile), medium (middle tertile), or high (highest tertile) density of nuclear medicine specialists.

4.2.3 Statistical Analysis

Our conceptual model provides the methodological underpinnings of our analytic approach to describing the impact of PET-staging on initial management and survival outcomes in FL. In order to draw causal inference about the effect of a variable of interest on an outcome, the variable is required to be exogenous—that is, a variable which is not related to any of the other variables in the system, unobserved and observed. In observational studies relying on secondary data, it is common for important factors that may influence both outcomes and variables of interest (particularly interventions) to be unobserved or imperfectly measured. In the regression context, the effects of these unobserved factors are absorbed by the residual (error) terms and hence, the estimated coefficients of the variables of interest are biased. Such omitted variable bias is the most common illustration of what economists refer to as endogeneity—that is, correlation between an explanatory variable and the error term.

In our conceptual model, we have identified possible sources of endogeneity between a) PET-staging and initial treatment in relation to the choice to administer R-chemo, and b) PET-staging or initial treatment and survival outcomes. For instance, healthier patients may be more likely to be staged with PET and treated with R-chemo, and those who are expected to be treated with R-chemo may be more likely to receive PET-staging as a baseline investigation to facilitate post-treatment evaluation.

As a first step of our analysis, we tested whether PET-staging is endogenous in the context of the decision to administer R-chemo. While this is an important analysis on its own, any evidence of endogeneity between PET-staging and R-chemo would also justify a decision to not consider PET-staging and treatment as statistically independent entities in a survival analysis. Our chosen response to such endogenity is to define mutually exclusive and exhaustive PET-treatment "management packages," then analyze the impact of these packages on survival. Our subsequent analyses are aimed at comparing survival outcomes between different management packages while statistically controlling for potential selection bias due to observed and unobserved confounders. There are two alternative approaches to dealing with selection bias in observational data—propensity score-based methods and instrumental variable analysis. We adopt each in turn to investigate robustness of overall findings to alternative approaches.

Descriptive Analysis:

In a univariate analysis, we compared the baseline characteristics of patients who received one or more staging PET scans (PET group) with those of patients who did not receive any staging PET scans (no-PET group) using chi-square tests. Kaplan-Meier analyses and log-rank tests were used to compare the survival distribution in PET versus no-PET and in the R-chemo versus others groups.

Instrumental Variable-Based Approach to Assess the Effect of PET-staging on R-chemo Use:

In the economics literature, instrumental variables (IV) methods are commonly used to reduce the impact of endogeneity of variables in the regression model predicting the outcome of interest. These methods rely on finding an exogenous variable (instrument)

that is highly correlated with the endogenous variable of interest, but uncorrelated with the outcome of interest (except through its correlation with the variable of interest). In such a case, the variation in the value of the instrument may be utilized to account for the variation in the omitted variables and reduce potential bias in the variables of interest. Two-stage residual inclusion (2SRI) is a type of IV methodology that is used in the context of non-linear outcomes, such as survival when analyzed within the Cox proportional hazards model.[41] The first stage equation is run to predict the potentially endogenous variable of interest as a function of the instrument and the exogenous covariates from the outcome equation of interest. The potentially endogenous variable of interest, the residuals from the first stage, and all exogenous covariates from the first stage are then used to predict the outcome in the second stage.

The application of 2SRI is becoming common in the healthcare outcomes research literature. We used this method, first, to assess the effect of PET-staging on the selection of R-chemo as the initial therapeutic choice, using local area (HRR) proclivity for the use of PET-staging as the instrument for PET-staging. The instrument was constructed based on the two-step method similar to that employed by Hadley et al.[42-44] In the first step, we calculated the predicted probability of receiving PET-staging using multivariable logistic regression models controlling for patient-level covariates. We then calculated the difference between the actual proportion of patients receiving PET-staging and the average predicted probability of receiving PET-staging in each HRR. This measure served as our IV for PET-staging. Thus HRRs with a negative value for the IV had fewer patients than predicted who received PET-staging while HRRs with a positive value had more patients than predicted to receive PET-staging. We excluded HRRs with less than 15 patients to

obtain reliable estimates of actual proportions and average predicted probabilities (total 86 patients).

In the first stage of the 2SRI approach, a multivariable logistic regression was run to predict PET-staging as a function of a patient-level covariates and the instrument. Adjustments were made for the following characteristics: age, sex, race/ethnicity, region of residence, marital status, year of diagnosis, census tract characteristics of residence, FL stage, FL grade, presence of B-symptoms, CCI, recent history of anemia, performance status, concentration of nuclear medicine specialists, and NCTCG membership status of the facilities where management was planned. In this first stage regression, the IV was strongly associated with receipt of PET-staging (partial F-statistics 155.5) and was assumed not to be causally related to R-chemo. The first stage residuals, the indicator for variable for PET-staging, and all other covariates hypothesized to be associated with R-chemo were then entered in the second stage logistic regression to predict the receipt of R-chemo.

Survival Analyses Using Multivariable Proportional Hazards Regressions:

We modeled all-cause survival using multivariable Cox proportional hazards (CPH) regression. The four categories of management packages were the independent variables of interest. Adjustments were made for the following characteristics: age, sex, race/ethnicity, region of residence, marital status, year of diagnosis, census tract characteristics of residence, FL stage, FL grade, presence of B-symptoms, CCI, recent history of anemia, performance status, concentration of nuclear medicine specialists, and NCTCG membership status of the facilities where management was planned. This initial base-case model was naïve to the potential selection bias due to observed and observed

confounders, and was meant to serve as a comparator for subsequent models that attempted to accounted possible selection bias.

Propensity Score-Based Survival Analyses:

Propensity score-based CPH model relied on weighting each individual observation in the base CPH model by the inverse of the predicted probability of receiving the management package that the patient actually received, given the patient's covariates. Inverse probability of treatment weights were calculated using multinomial logistic regression, where the dependent variable was the management package (PET + R-chemo, no PET + R-chemo, PET + others, or no PET + others). Adjustments were made for the same set of covariates as in the base CPH model. This method is intended to minimize the potential bias due to selection of R-chemo based on observable covariates. Direct adjusted survival curves were constructed to visually inspect the average predicted survival function in each management package.

Instrumental Variable-Based Survival Analyses:

Although PS-based methods account for selection bias introduced by observed covariates, they do not address the potential bias due to selection on unobserved factors. Adjusting for selection on unobserved factors is germane to survival analyses in this study because several potential predictors of R-chemo, PET-staging, and survival are either unobserved or measured indirectly. Instrumental variable-based methods seek to account for both observed and unobserved factors that potentially influence selection into the intervention of interest, thus potentially providing more reliable causal inference than PS-based approaches. The 2SRI approach described above is used to account for endogenous

variables in Cox proportional hazards regressions, although we rarely encounter in the IV literature a treatment variable that has multiple levels.

Our approach to 2SRI model estimation is a direct extension of the method for binary endogenous variables and is based on the procedures implemented by Zimmer.[45] In our approach, the first stage was a multinomial regression predicting the package of management approach as a function of an instrument and the exogenous predictors of survival in the survival equation. A set of four residuals for each patient were calculated, each as the difference between the coded value of the management package (1 for the management package actually received and 0 for all others) and the predicted probability of receiving that management package. These residuals were entered into the second stage Cox proportional hazards model, in addition to the management bundles and other covariates hypothesized to be associated with survival.

Successful application of IV-based methods hinges on the statistical strength and validity of the instruments. After careful consideration, we used NCTCG membership of the treating facility and local area proclivity to receive PET-staging as instruments for the management packages. Our chosen instruments are proxies for high-resource settings and meet an essential criterion for instruments in an IV analysis inasmuch as they are jointly statistically strong predictors of the management packages in the first stage regression. The second major assumption in our IV analysis is that the instruments are not significantly associated with survival, except through their effect on the choice of management package. This latter assumption may not be tested statistically, but is plausible since neither NCTCG membership of the treating facility or local area proclivity to receive PET-staging is likely to be correlated with the most important, although imperfectly observed, predictors of

survival: patient's baseline health status and indicators of lymphoma prognosis. (That said, we acknowledge the possibility that patients in higher resource settings may be systematically different on potential predictors of survival that are unobserved in the data. For instance, NCTCG-member facilities may administer more effective chemotherapy regimens, doses, and schedules than non-member facilities; patients treated at NCTCG providers may be sicker; and patients living in areas with high proclivity of PET-staging may be more effectively managed for FL and other comorbidities than patients from low proclivity areas. Hence, this choice of instruments is based on the untestable assumption that if systematic differences in on unobserved predictors of survival existed between those who were treated in high versus low resource settings, such differences did not significantly influence survival in the FL population.)

Another variable which is strongly correlated with management packages is the year of diagnosis of FL. However, we chose to control for year of diagnosis and not to use it as an instrument because patients diagnosed in the later years could be followed for shorter durations and thus were less likely to die during the study period. We constructed direct-adjusted survival curves from the second stage CPH regression.

4.3 Results

A total of 5,664 patients satisfied our inclusion criteria (Figure 4.2). Characteristics of the population are described in Table 4.1. The mean age at diagnosis was 76 years (standard deviation of 6.6 years). Approximately 76% of patients were under 80 years of age, 93% were Caucasian, and 58% were female. Approximately 42% of the patients in this cohort underwent PET-staging (n = 2,404). Compared to the no-PET group, patients

in the PET group were more likely to be treated with R-chemo. Patients in the PET-group were significantly more likely to be: less than age 80; married; living in the Northeast and in metropolitan areas. FL patients undergoing PET-staging were also more likely to: be diagnosed with grade 3 FL; have extra-nodal primary site of involvement; and have good performance status. Patients in the PET-group were less likely to present with B-symptoms or a recent history of anemia.

Of all patients, 2,610 died during the follow-up. Median duration of follow up was 4.64 years. Unadjusted Kaplan-Meier survival curves in Figure 4.3 suggest that those in the PET+ R-chemo group had increased overall survival. The most pronounced separation was between no PET + others (lowest curve) and the rest.

In the model used to test endogeneity between PET-staging and R-chemo, the instrumental variable was found to be highly correlated with PET-staging (partial F-statistic from the first stage equation was 132.94). In the second stage equation (Table 4.2), while the residual from the first stage was close to being significant at the 5% level (p=0.058), PET-staging did not affect R-chemo use (odds ratio 0.73; p=0.4448), controlling for all other covariates.

In the base multivariable CPH model (Table 4.3), compared to patients in the no-PET-staging + others group, patients who received any other management package experienced better survival (no PET + R-chemo hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.69-0.89; PET + others HR 0.71, CI 0.64-0.80; and PET + R-chemo HR 0.62, CI 0.53-0.72). However, the differences between the above management bundles were not statistically significant. In addition, survival was negatively related to age, stage III/IV FL, recent history of anemia, B-symptoms, higher comorbidity index, and poorer performance

status. Female sex, marriage, higher census tract education, and NCTCG membership status were associated with better survival.

In the propensity score adjusted analysis (Table 4.4), bundles including PET or R-chemo were associated with better survival outcomes than the no PET-staging + others group: no PET + R-chemo HR 0.80, CI 0.72-0.90; PET + others HR 0.69, CI 0.63-0.76; and PET + R-chemo HR 0.62, CI 0.57-0.69. Direct adjusted survival curves from the above models suggested most superior survival in the PET + R-chemo group (Figure 4.4). Further analyses (not shown here) to examine the degree to which application of the propensity-score weights led to a good balance of covariate values across treatment arms showed that only age at diagnosis and year of diagnosis remained unbalanced.

In the 2SRI models, bundles with PET or R-chemo had superior survival outcomes compared to the no PET + others group, but the HR differences between these bundles were not significant (Table 4.5). Interestingly, the management package estimates from the 2SRI models differed considerably from the base model: no PET + R-chemo HR 0.23, CI 0.08-0.71; PET + others HR 0.15, CI 0.06-0.36; and PET + R-chemo HR 0.13, CI 0.02-0.86. The direct adjusted curve for the no PET + others group was prominently lower than the rest of the bundles in this model (Figure 4.5). The residual for PET + others was significant at the 5% level ($p = 0.0004$), whereas the residuals for PET+R-chemo and no PET + R-chemo were significant at the 10% level ($p = 0.0834$ and 0.0632 respectively). The incremental likelihood ratio chi square for the instruments in the first stage multinomial regression was 158.12 ($p<0.0001$), suggesting they were statistically "strong" by conventional criteria (results from the first stage multinomial regression are displayed in Appendix Table 4.8).

4.4 Discussion

We conducted this retrospective study, performed in a large nationally representative population with FL, with an aim to examine the relationship between R-chemo use and PET-staging, and possible implications of the PET-R-chemo interface on survival. Our maintained hypothesis was that PET-staging impacts survival mainly through its effect on the selection of R-chemo as the initial treatment, but also by being associated with better execution of initial treatment and assessment of treatment response.

An important finding of our inquiry is that the relationship between the decision to do PET-stage, the choice of treatment, and patient survival is a complex one. Specifically, we found evidence suggesting an endogenous relationship between PET-staging and R-chemo use. A possible source of the endogenous relationship between PET-staging and R-chemo is a bi-directional association between these two variables; i.e. while PET-staging may influence use of R-chemo in some patients, it is also possible that many patients receive PET-staging because treatment with R-chemo is anticipated. In this scenario, the motivation behind a staging PET-scan may be to acquire accurate information about the extension of the disease at baseline. Information from the baseline PET-scan may be deemed useful in assessing the response to initial treatment and in developing an appropriate downstream management strategy. In either case, PET and R-chemo jointly exercise their effect on survival.

Analysis of survival outcomes of staging or diagnostic modalities is complicated if both the modality of interest and the subsequent treatment are potentially endogenous. In the present study, a direct examination of survival outcomes of PET-staging using

multivariable equations, which treat R-chemo as exogenous, may yield biased results. A recent analysis of survival outcomes of endoscopic ultrasound (EUS) in pancreatic cancer employs the 2SRI approach to address endogeneity in EUS.[46] The treatments enter the second stage equation as predictors of survival and are excluded from the first stage equation, making a tacit assumption that treatments are exogenous. An inquiry into survival outcomes of PET-staging that ignores R-chemo is also problematic because R-chemo conceptually is the primary driver of survival. Therefore, we employed an analytic strategy to indirectly assess the effect of PET-staging on survival by comparing survival estimates in patients receiving management packages that involved PET-staging versus in those receiving packages that did not use PET-staging.

In all analyses, packages with PET and/or R-chemo were associated with better survival as compared to the no PET + others group. There was also a gradient in the HRs, although statistically insignificant, such that the PET + R-chemo group had the lowest HRs, followed by PET + others and then by no PET + others. If PET improves survival mainly through appropriate assignment of patients for R-chemo and their post-treatment evaluation, then we would expect patients in the PET+R-chemo group to have significantly superior survival experience than patients in the no PET+R-chemo group. However, significant survival differences were not observed between PET + R-chemo, no PET + R-chemo, or PET + others groups, indicating that PET-staging may not work to improve survival only in the hypothesized manner. Another unexpected finding was significantly better survival in the PET + others group compared to the no PET + others group. This difference may be partly attributable to better response evaluation in the PET + others group but may also result from systematic differences in observed and unobserved

characteristics between the two groups which remained influential even after propensity weighting and 2SRI. For instance, more patients in the PET + others group may have been managed in high-resource settings, and received R-chemo more commonly downstream, both as initial treatment or after relapse.

Our propensity score-weighted models attempted to adjust for significant, bias-inducing unbalances observed confounders. Results from the propensity score-weighted analyses were closely similar to the base model, suggesting weak selection on observed confounders. However, hazard ratios from the IV-based models, seeking to control for unobserved confounding, were substantially lower than other models. The residuals from the first stage regression were statistically significantly greater than one (two at the 10% level and one at the 5% level), indicating strong evidence of selection for PET or R-chemo based on unobserved confounders. The second stage results apply mainly to the marginal patients, i.e. those who received management packages with PET or R-chemo (or both) primarily because they were managed in a high-resource setting, such as NCTCG hospitals or areas with high proclivity of PET-staging, and not because of poor prognostic indicators. Given the results from the second stage, it is possible that, in general, those who received PET-staging or R-chemo also more commonly presented with indicators of poor prognosis not observed in the data. The IV analysis serves to adjust for the impact of this "unadjusted" poor prognosis by yielding (adjusted) HRs that are considerably lower than the regular or propensity-score weighted CPH models.

Nevertheless, the very substantial improvement in predicted survival is extraordinary and needs to be discussed in the context of statistical validity of our IV approach. The IV estimator may be susceptible to imprecision and bias if the sample size

is small, and to bias even if the sample size is large and one of the underlying assumptions is only slightly violated.[47] Although our IVs are strongly correlated with the management packages, the assumption that they are not associated with survival (independent of their effect on R-chemo or PET use) is untestable and may not be the case. Another debate about the 2SRI approach concerns the nature and functional form of the residuals to be included in the second stage regression.[48] Although results from models with functions of the residuals (such as squares or cubes of residuals) were considerably different, we chose the simple, first-order residuals because there are no clear recommendations yet on the optimal functional form of the residuals. IV-based methods for multilevel endogenous variables are still in the developmental stage.

Although lymphoma accounts for only 4% of cancers diagnosed annually in the United States, its diagnosis, staging, and management requires frequent imaging such that lymphoma may account for more than approximately 50% of the PET scans performed at a referral institution.[49] However, notwithstanding the recent changes in clinical recommendations and the widespread use of PET-staging in FL even before these changes came into effect,[50] it has been unclear whether PET-staging alters management decisions in a considerable proportion of FL patients, subsequently leading to improvement in survival outcomes.

To our knowledge, this is the first retrospective study examining survival outcomes of PET-staging in a large cohort of FL patients. We draw important conclusions about the PET-treatment interface, including a possible endogenous relationship between PET-staging and R-chemo use. The structure and accompanying analyses depart from the current analyses of survival outcomes of staging tests in that we deal with endogeneity not

only in PET-staging or initial treatment but also in a multi-step process involving both PET-staging and initial treatment.

We found that patients who received PET-staging or R-chemo (or both) had longer survival than those who received neither, with the PET + R-chemo group having the most superior outcomes. However, no significant difference in survival was observed between those who received PET-staging followed by R-chemo and those who did not receive PET-staging but received R-chemo.

An immediate limitation of these data is the limited sample sizes of management bundles. Although we observed consistent trends in survival differences among 3 management packages, we did not have sufficient statistical power to distinguish among these packages. Our attempts at minimizing omitted variable bias in management approaches were also fraught with analytic challenges. Our study highlights the limitations of using observational data to examine outcomes of staging or diagnostic tests. Further investigation is warranted into the role of PET-staging in the initial management and survival experience in FL, preferably based on data from randomized controlled clinical trials in patients treated with first-line R-chemo regimens. However, randomizing patients to PET-staging or conventional staging arms is logistically and ethically challenging.

TABLE 4.1 Baseline characteristics of the cohort stratified by receipt of PET-staging

	No-PET Group	PET Group (n=2,404)	p value	Total (n=5,664)
Patient Characteristics				
Age				
Mean (SD)	76.0 (6.8)	74.7 (6.2)		75.5 (6.6)
66-70 yr	835 (25.6)	726 (30.2)	<0.0001	1,561 (27.6)
71-75 yr	820 (25.2)	661 (27.5)		1,481 (26.2)
76-80 yr	731 (22.4)	549 (22.8)		1,280 (22.6)
> 80 yr	874 (26.8)	468 (19.5)		1,342 (23.7)
Race				
Caucasian	3,023 (92.7)	2,236 (93.0)	0.1405	5,259 (92.9)
African American	109 (3.3)	61 (2.5)		170 (3.0)
Others	128 (4.9)	107 (4.5)		235 (4.2)
Sex				
Male	1,357 (41.6)	1,045 (43.5)	0.2580	2,402 (42.4)
Female	1,903 (58.4)	1,359 (56.5)		3,262 (57.6)
Marital Status				
Married	1,817 (55.7)	1,455 (60.5)	0.0013	3,272 (57.8)
Others	1,233 (37.8)	818 (34.0)		2,051 (36.2)
Unknown	210 (6.4)	131 (5.5)		341 (6.0)
Year of Diagnosis				
2000-2002	1,314 (40.3)	205 (8.5)	<0.0001	1,519 (26.8)
2003-2005	1,065 (32.7)	787 (32.7)		1,852 (32.7)
2006-2009	881 (27.0)	1,412 (58.7)		2,293 (40.5)
Region				
Northeast	596 (18.3)	576 (24.0)	<0.0001	1,172 (20.7)
Midwest	559 (17.2)	242 (10.1)		801 (14.1)
West	1,281 (39.3)	914 (38.0)		2,195 (38.8)
South	824 (25.3)	672 (28.0)		1,496 (26.4)
Residence				
Metropolitan	2,590 (79.5)	1,993 (82.9)	0.0045	4,583 (80.9)
Urban	232 (7.1)	138 (5.7)		370 (6.5)
Less Urban/Rural	438 (13.4)	273 (11.4)		711 (12.6)
% in Census Tract with Less Education than High School Diploma				
< 25	2,457 (75.4)	1,859 (77.3)	0.0867	4,316 (76.2)
≥25	803 (24.6)	545 (22.7)		1,348 (23.8)
% in Census Tract Living in Poverty				
< 5	1,056 (32.4)	838 (34.9)	0.1285	1,894 (33.4)
5-7	441 (13.5)	341 (14.2)		782 (13.8)
7-12	758 (23.3)	536 (22.3)		1,294 (22.9)
> 12	1,005 (30.8)	689 (28.7)		1,694 (29.9)
Lymphoma Characteristics				
Grade				
1 or 2	1,744 (53.5)	1,163 (48.4)	<0.0001	2,907 (51.3)
3	444 (13.6)	482 (20.1)		926 (16.4)
Not specified	1,072 (32.9)	759 (31.6)		1,831 (32.3)

Stage				
I/II	1,673 (47.2)	1,223 (49.1)	0.1945	2,793 (49.3)
III/IV	1,601 (45.2)	1,102 (44.3)		2,446 (43.2)
Unknown	269 (7.6)	1,65 (6.6)		425 (7.5)
Primary Site				
Nodal	2,728 (83.7)	1,958 (81.5)	0.0279	4,686 (82.7)
Extra-nodal	532 (16.3)	446 (18.6)		978 (17.3)
Measures of Baseline Health Status				
NCI Comorbidity Index				
0	2,033 (62.4)	1,501 (62.4)	0.5369	3,534 (62.4)
1	795 (24.4)	606 (25.2)		1,401 (24.7)
≥2	432 (13.3)	297 (12.4)		729 (12.9)
Performance Status				
Good	2,750 (84.4)	2,153 (89.6)	<0.0001	4,903 (86.6)
Poor	510 (15.7)	251 (10.4)		761 (13.4)
History of Anemia				
Present	154 (4.7)	76 (3.2)	<0.0032	230 (4.1)
Absent	3,106 (95.3)	2,328 (96.8)		5,434 (95.9)
B-Symptoms				
Present	364 (11.2)	243 (10.1)	<0.0001	607 (10.7)
Absent	1,545 (47.4)	1,374 (57.2)		2,919 (51.5)
Unrecorded	1,351 (41.4)	787 (32.7)		2,138 (37.8)
Features of Management Setting				
NCI Clinical Trials Cooperative Group Membership[§]				
No	1,309 (40.2)	941 (39.1)	0.4425	2,250 (39.7)
Yes	1,951 (59.9)	1,463 (60.9)		3,414 (60.3)
Local Density of Nuclear Medicine Specialists[#]				
1st tertile (lowest)	1,133 (34.8)	799 (33.2)	0.3109	1,932 (34.1)
2nd tertile	1,156 (35.5)	847 (35.2)		2,003 (35.4)
3rd tertile (highest)	971 (29.8)	758 (31.5)		1,729 (30.5)
Management Strategy				
Chemo (+/- IFRT)	463 (14.2)	121 (5.0)	<0.0001	584 (10.3)
R-Chemo (+/- IFRT)	742 (22.8)	955 (39.7)		1,697 (30.0)
IFRT (+/- R)	392 (12.0)	312 (13.0)		704 (12.4)
R Alone	480 (14.7)	373 (15.5)		853 (15.1)
Observation	1,183 (36.3)	643 (26.8)		1,826 (32.2)

§ 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

IFRT, Involved Field Radiotherapy; Chemo, chemotherapy; R-Chemo, rituximab + chemotherapy

TABLE 4.2 Results from the 2nd-stage multinomial logistic regression predicting receipt of R-chemo

Variable	OR (95% CI)	P value
PET-staging Received **vs** Not Received	0.73 (0.33 - 1.63)	0.4448
Residual from the First Stage Regression	2.19 (0.97 - 4.92)	0.0584
71 - 75 **vs** 66 -70 yr	0.90 (0.76 - 1.06)	0.2040
76 - 80 **vs** 66 -70 yr	0.82 (0.69 - 0.97)	0.0248
> 80 **vs** 66 -70yr	0.40 (0.32 - 0.49)	<.0001
AA **vs** Caucasian	0.69 (0.46 - 1.03)	0.0699
Other Race **vs** Caucasian	1.26 (0.92 - 1.72)	0.1540
Female **vs** Male	0.91 (0.79 - 1.03)	0.1451
Married **vs** Single/Widowed	1.05 (0.91 - 1.22)	0.4985
Unknown Marital Status **vs** Single/Widowed	0.78 (0.58 - 1.05)	0.1046
Dx in 2003-2005 **vs** 2000-2002	3.09 (2.28 - 4.19)	<.0001
Dx in 2006-2009 **vs** 2000-2002	4.61 (2.96 - 7.17)	<.0001
Northeast **vs** Midwest	1.05 (0.8 - 1.37)	0.7244
South **vs** Midwest	1.17 (0.89 - 1.55)	0.2673
West **vs** Midwest	1.01 (0.81 - 1.27)	0.9171
Metropolitan **vs** Less Urban/Rural	0.93 (0.75 - 1.16)	0.5294
Urban **vs** Less Urban/Rural	0.93 (0.69 - 1.26)	0.6401
5% - 7% **vs** < 5% Living in Poverty	1.02 (0.83 - 1.25)	0.8555
7% - 12% **vs** < 5% Living in Poverty	0.90 (0.75 - 1.08)	0.2571
> 12% **vs** < 5% Living in Poverty	1.13 (0.91 - 1.39)	0.2759
More Educated **vs** Less Educated	1.09 (0.89 - 1.33)	0.4153
Stage 3/4 **vs** 1/2	1.74 (1.53 - 1.99)	<.0001
Stage Unknown **vs** 1/2	1.00 (0.77 - 1.32)	0.9742
Grade 3 **vs** Grade 1-2	4.04 (3.33 - 4.91)	<.0001
Grade Not Specified **vs** Grade 1-2	1.38 (1.19 - 1.59)	<.0001
Extranodal **vs** Nodal primary site	0.68 (0.56 - 0.82)	<.0001
B-symptoms Present **vs** Absent	1.83 (1.50 - 2.24)	<.0001
B-symptoms Unrecorded **vs** Absent	1.06 (0.92 - 1.23)	0.4186
Comorbidity Index 1 **vs** 0	0.78 (0.67 - 0.91)	0.0016
Comorbidity Index ≥ 2 **vs** 0	0.82 (0.67 – 1.00)	0.0484
Poor **vs** Good Performance Status	0.70 (0.56 - 0.88)	0.0022
History of Anemia **vs** no History	1.01 (0.73 - 1.40)	0.9635
NCICTG Member **vs** Non-Member	1.01 (0.87 - 1.16)	0.9219
2nd **vs** 1st Nuclear Medicine Specialist Density Tertile	0.90 (0.76 - 1.05)	0.1891
3rd **vs** 1st Nuclear Medicine Specialist Density Tertile	0.84 (0.7 - 1.01)	0.0642

Abbreviations: PET, positron emission tomography; NCCTG, National Cancer Institute Clinical Trials Cooperative Group

TABLE 4.3 Associations between patient and disease characteristics and risk of death from the base CPH models (propensity scores or 2SRI not applied)

Variable	Overall Survival	P value
	HR (95% CI)	
Management Approach		
No PET + R-chemo **vs** No PET + Others	0.78 (0.69 -0.89)	0.0002
PET + Others **vs** No PET + Others	0.71 (0.64 -0.80)	<0.0001
PET + R-chemo **vs** No PET + Others	0.62 (0.53 -0.72)	<0.0001
Age		
71 - 75 **vs** 66 -70 yr	1.45 (1.27 -1.64)	<0.0001
76 - 80 **vs** 66 -70 yr	1.89 (1.66 -2.14)	<0.0003
> 80 **vs** 66 -70yr	3.37 (2.98 -3.81)	<0.0004
Race		
African American **vs** Caucasian	1.05 (0.83 -1.31)	0.6965
Other Race **vs** Caucasian	0.89 (0.71 -1.10)	0.2792
Sex		
Female **vs** Male	0.68 (0.62 -0.74)	<0.0001
Marital Status		
Married **vs** Single/Widowed	0.79 (0.72 -0.87)	<0.0002
Marital-status Unknown **vs** Single/Widowed	0.92 (0.77 -1.10)	0.3849
Year of Diagnosis		
Dx in 2003 - 2005 **vs** 2000 - 2002	0.95 (0.85 -1.05)	0.2785
Dx in 2006 -2009 **vs** 2000 - 2002	0.86 (0.76 -0.98)	0.0206
Region of Residence		
Northeast **vs** Midwest	1 (0.87 -1.14)	0.9789
South **vs** Midwest	1.15 (0.98 -1.35)	0.0777
West **vs** Midwest	1.01 (0.88 -1.15)	0.8876
Type of Residence		
Metropolitan **vs** Less Urban/Rural	1.02 (0.89 -1.16)	0.8259
Urban **vs** Less Urban/Rural	1.02 (0.84 -1.23)	0.8679
Census Tract Poverty		
5% - 7% **vs** < 5% Living in Poverty	1.03 (0.9 -1.17)	0.6899
7% - 12% **vs** < 5% Living in Poverty	1 (0.89 -1.13)	0.9825
> 12% **vs** < 5% Living in Poverty	1 (0.87 -1.15)	0.9618
Census Tract Education		
More Educated **vs** Less Educated	0.81 (0.72 -0.91)	0.0006
FL Stage		
Stage 3/4 **vs** Stage1/2	1.36 (1.24 -1.48)	<0.0001
Stage Unknown **vs** Stage 1/2	1 (0.85 -1.18)	0.9931
FL Grade		
Grade 3 **vs** 1 or 2	1.1 (0.97 -1.24)	0.1230
Grade Not Specified **vs** 1 or 2	1.13 (1.03 -1.24)	0.0078

Primary Site		
Extarnodal **vs** Nodal Primary Site	0.81 (0.72 -0.90)	0.0003
B-symptoms		
Present **vs** Absent	1.24 (1.09 -1.41)	0.0014
Unrecorded **vs** Absent	1.05 (0.96 -1.15)	0.3012
Comorbidity Status		
Comorbidity Index 1 **vs** 0	1.28 (1.16 -1.41)	<0.0001
Comorbidity Index ≥ 2 **vs** 0	1.86 (1.66 -2.09)	<0.0002
Performance Status		
Poor **vs** Good	1.66 (1.49 -1.84)	<0.0003
History of Anemia		
Yes **vs** No	1.29 (1.08 -1.53)	0.0041
Membership of NCI Clinical Trial Cooperative Group		
Member **vs** Non-Member	0.85 (0.78 -0.93)	0.0005
Local Density of Nuclear Medicine Specialists		
2nd **vs** 1st NM Specialist Density Tertile	1.06 (0.96 -1.18)	0.2608
3rd **vs** 1st NM Specialist Density Tertile	0.96 (0.86 -1.08)	0.4995

Abbreviations: FL, Follicular lymphoma; PET, positron emission tomography; NCI, National Cancer Institute

TABLE 4.4 Associations between patient and disease characteristics and risk of death, weighted by inverse probabilities of management approaches

Variable	Overall Survival	P value
	HR (95% CI)	
Management Approach		
No PET + R-chemo **vs** No PET + Others	0.80 (0.72 - 0.90)	0.00014
PET + Others **vs** No PET + Others	0.69 (0.63 - 0.76)	<0.0001
PET + R-chemo **vs** No PET + Others	0.62 (0.57 - 0.69)	<0.0001
Age		
71 - 75 **vs** 66 -70 yr	1.51 (1.35 - 1.69)	<0.0001
76 - 80 **vs** 66 -70 yr	2.01 (1.8 - 2.25)	<0.0001
> 80 **vs** 66 -70yr	3.39 (3.05 - 3.78)	<0.0001
Race		
African American **vs** Caucasian	0.91 (0.74 - 1.12)	0.3846
Other Race **vs** Caucasian	1.01 (0.85 - 1.20)	0.90021
Sex		
Female **vs** Male	0.61 (0.56 - 0.66)	<0.0001
Marital Status		
Married **vs** Single/Widowed	0.76 (0.7 - 0.82)	<0.0001
Marital-status Unknown **vs** Single/Widowed	0.87 (0.74 - 1.02)	0.09603
Year of Diagnosis		
Dx in 2003 - 2005 **vs** 2000 - 2002	0.97 (0.89 - 1.06)	0.50507
Dx in 2006 -2009 **vs** 2000 - 2002	0.89 (0.8 - 0.98)	0.01973
Region of Residence		
Northeast **vs** Midwest	1.08 (0.95 - 1.22)	0.23891
South **vs** Midwest	1.26 (1.09 - 1.45)	0.00144
West **vs** Midwest	1.06 (0.94 - 1.20)	0.34934
Type of Residence		
Metropolitan **vs** Less Urban/Rural	0.94 (0.83 - 1.06)	0.28729
Urban **vs** Less Urban/Rural	0.94 (0.8 - 1.12)	0.49817
Census Tract Poverty		
5% - 7% **vs** < 5% Living in Poverty	0.97 (0.86 - 1.09)	0.57761
7% - 12% **vs** < 5% Living in Poverty	1.12 (1.01 - 1.24)	0.02727
> 12% vs < 5% Living in Poverty	1.07 (0.95 - 1.2)	0.26764
Census Tract Education		
More Educated **vs** Less Educated	0.85 (0.76 - 0.94)	0.00142
FL Stage		
Stage 3/4 **vs** Stage1/2	1.55 (1.44 - 1.67)	<0.0001
Stage Unknown **vs** Stage 1/2	1.04 (0.89 - 1.21)	0.62556
FL Grade		
Grade 3 **vs** 1 or 2	1.17 (1.06 - 1.29)	0.00149
Grade Not Specified **vs** 1 or 2	1.19 (1.1 - 1.28)	0.00002

Primary Site		
Extarnodal **vs** Nodal Primary Site	0.89 (0.81 - 0.98)	0.02176
B-symptoms		
Present **vs** Absent	1.35 (1.21 - 1.51)	<0.0001
Unrecorded **vs** Absent	1.00 (0.92 - 1.08)	0.9178
Comorbidity Status		
Comorbidity Index 1 **vs** 0	1.30 (1.2 - 1.42)	<0.0001
Comorbidity Index ≥ 2 **vs** 0	1.87 (1.7 - 2.07)	<0.0001
Performance Status		
Poor **vs** Good	1.68 (1.53 -1.84)	<0.0001
History of Anemia		
Yes **vs** No	1.22 (1.04 - 1.42)	0.01204
Membership of NCI Clinical Trial Cooperative Group		
Member **vs** Non-Member	0.85 (0.79 - 0.92)	0.00003
Local Density of Nuclear Medicine Specialists		
2nd **vs** 1st NM Specialist Density Tertile	1.08 (0.98 - 1.23)	0.2497
3rd **vs** 1st NM Specialist Density Tertile	1.04 (0.94 - 1.15)	0.4376

Abbreviations: FL, Follicular lymphoma; PET, positron emission tomography; NCI, National Cancer Institute

TABLE 4.5 Associations between patient characteristics and risk of death from the second stage of 2SRI-based CPH models

Variable	Overall Survival	P value
	HR (95% CI)	
Management Approach		
No PET + R-chemo **vs** No PET + Others	0.14 (0.02 - 0.87)	0.0338
PET + Others **vs** No PET + Others	0.15 (0.07 - 0.36)	<.0001
PET + R-chemo **vs** No PET + Others	0.24 (0.08 - 0.71)	0.0099
Residuals from the First Stage Regression		
No PET + R-chemo **vs** No PET + Others	5.71 (0.89 -36.44)	0.0655
PET + Others **vs** No PET + Others	4.65 (1.97 - 10.98)	0.0005
PET + R-chemo **vs** No PET + Others	2.64 (0.87 - 8.07)	0.0876
Age		
71 - 75 **vs** 66 -70 yr	1.45 (1.27 - 1.65)	<.0001
76 - 80 **vs** 66 -70 yr	1.79 (1.56 - 2.05)	<.0001
> 80 **vs** 66 -70yr	2.84 (2.3 - 3.53)	<.0001
Race		
African American **vs** Caucasian	1.04 (0.82 - 1.31)	0.7713
Other Race **vs** Caucasian	0.95 (0.76 - 1.20)	0.6676
Sex		
Female **vs** Male	0.68 (0.62 - 0.74)	<.0001
Marital Status		
Married **vs** Single/Widowed	0.80 (0.72 - 0.87)	<.0001
Marital-status Unknown **vs** Single/Widowed	0.85 (0.7 - 1.04)	0.1082
Year of Diagnosis		
Dx in 2003 - 2005 **vs** 2000 - 2002	1.50 (1.08 - 2.07)	0.0155
Dx in 2006 -2009 **vs** 2000 - 2002	1.60 (1.06 - 2.41)	0.0254
Region of Residence		
Northeast **vs** Midwest	1.13 (0.97 - 1.33)	0.1217
South **vs** Midwest	1.31 (1.1 - 1.56)	0.0023
West **vs** Midwest	1.08 (0.93 - 1.24)	0.3109
Type of Residence		
Metropolitan **vs** Less Urban/Rural	0.99 (0.86 - 1.14)	0.8798
Urban **vs** Less Urban/Rural	1.03 (0.84 - 1.25)	0.7932
Census Tract Poverty		
5% - 7% **vs** < 5% Living in Poverty	1.04 (0.91 - 1.19)	0.5218
7% - 12% **vs** < 5% Living in Poverty	1.04 (0.92 - 1.17)	0.5573
> 12% **vs** < 5% Living in Poverty	1.08 (0.94 - 1.25)	0.2906
Census Tract Education		
More Educated **vs** Less Educated	0.85 (0.74 - 0.96)	0.0103
FL Stage		

Stage 3/4 **vs** Stage1/2	1.43 (1.24 - 1.64)	<.0001
Stage Unknown **vs** Stage 1/2	1.02 (0.86 - 1.20)	0.8216
FL Grade		
Grade 3 **vs** 1 or 2	1.32 (0.99 - 1.75)	0.0594
Grade Not Specified **vs** 1 or 2	1.17 (1.05 - 1.31)	0.0038
Primary Site		
Extarnodal **vs** Nodal Primary Site	0.79 (0.68 - 0.91)	0.0012
B-symptoms		
Present **vs** Absent	1.31 (1.07 - 1.61)	0.0094
Unrecorded **vs** Absent	1.05 (0.95 - 1.15)	0.3326
Comorbidity Status		
Comorbidity Index 1 **vs** 0	1.24 (1.11 - 1.39)	0.0001
Comorbidity Index ≥ 2 **vs** 0	1.80 (1.58 - 2.04)	<.0001
Performance Status		
Poor **vs** Good	1.50 (1.31 - 1.72)	<.0001
History of Anemia		
Yes **vs** No	1.18 (0.99 - 1.42)	0.0641
Local Density of Nuclear Medicine Specialists		
2nd **vs** 1st NM Specialist Density Tertile	1.02 (0.91 - 1.14)	0.7135
3rd **vs** 1st NM Specialist Density Tertile	0.97 (0.86 - 1.10)	0.6662

Abbreviations: FL, Follicular lymphoma; PET, positron emission tomography; NCI, National Cancer Institute

TABLE 4.6 Adjusted Cox proportional hazards models comparing survival of management approaches by analytic method

	Overall Survival HR (95% CI)	**p value**
Base Multivariable CPH Models		
No PET + R-chemo vs No PET + Others	0.78 (0.69 - 0.89)	0.0002
PET + Others vs No PET + Others	0.71 (0.64 - 0.80)	<0.0001
PET + R-chemo vs No PET + Others	0.62 (0.53 - 0.72)	<0.0001
Propensity score weighted CPH Models		
No PET + R-chemo vs No PET + Others	0.80 (0.72 - 0.90)	0.0001
PET + Others vs No PET + Others	0.69 (0.63 - 0.76)	<0.0001
PET + R-chemo vs No PET + Others	0.62 (0.57 - 0.69)	<0.0001
Instrumental variable (2SRI) CPH Models		
No PET + R-chemo vs No PET + Others	0.24 (0.08 -0.71)	0.0099
PET + Others vs No PET + Others	0.15 (0.07 -0.36)	<.0001
PET + R-chemo vs No PET + Others	0.14 (0.02 -0.87)	0.0338

Abbreviations: PET, positron emission tomography

APPENDIX TABLE 4.7 ICD-9-CM and CPT/HCPCS codes used to identify management strategy and PET-staging

Treatment	Codes
Chemotherapy/Immunotherapy	ICD-9-CM diagnosis: V58.1, V66.2, V67.2 ICD-9-CM procedure: 99.25 Revenue center: 0331, 0332, 0335 CPT/HCPCS: 964xx, 965XX, A9542, A9543, A9522, A9523, A9533, A9534, A9544, A9545, C1080 -C1083, G3001, G0355, G0359, J8530, J8562 J9000-J9999, Q0083- Q0085, S0172
Radiotherapy	ICD-9-CM procedure: 92.21-92.29 Revenue center: 0330, 0333, 0339 CPT/HCPCS: 7740X, 7741X, 7775X-7777X, 7779X, 7743X-7749X, 7727X-7730X, 7739X, 77420-77425, 77520-77525, 77427-77429, 77011, 77014, 76950, 77261-77269, G0173, G0251, G0256, G0261, G0334, G0340
PET	CPT/HCPCS: 78608-78816, G0125, G0126, G0163-G0165, and G0210-G0235

Abbreviations: ICD-9-CM: International Statistical Classification of Diseases and Related Health Problems, 9th revision, clinical modification; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Classification System; PET: Positron Emission Tomography

APPENDIX TABLE 4.8 Results from the first stage multinomial regression in the 2SRI survival model (no PET + others is the reference category)

	No PET + R-chemo	PET + Others
Instrument 1: NCTCG Membership		
Yes vs No	1.08 [0.89-1.30]	1.48*** [1.26-1.73]
Instrument 2: Local Area (HRR) Proclivity for PET-staging (Continuous Variable)		
	0.21* [0.05-0.84]	223.41*** [69.88-714.26]
Age		
71 - 75 vs 66 -70 yr	0.96 [0.77-1.21]	0.92 [0.76-1.13]
76 - 80 vs 66 -70 yr	0.8 [0.63-1.03]	0.87 [0.71-1.07]
> 80 vs 66 -70yr	0.49*** [0.38-0.63]	0.62*** [0.51-0.77]
Race		
AA vs Caucasian	1.03 [0.64-1.65]	0.87 [0.57-1.33]
Other Race vs Caucasian	1.38 [0.88-2.15]	1.15 [0.79-1.69]
Sex		
Female vs Male	0.88 [0.73-1.07]	1.06 [0.91-1.24]
Marital Status		
Married vs Single/Widowed	0.93 [0.76-1.14]	1.05 [0.90-1.24]
Unknown vs Single/Widowed	0.65* [0.43-0.98]	0.86 [0.63-1.18]
Years of Diagnosis		
2003-2005 vs 2000-2002	2.73*** [2.19-3.39]	5.39*** [4.37-6.65]
2006-2009 vs 2000-2002	2.83*** [2.24-3.56]	11.52*** [9.30-14.26]
% Living Under Poverty		
5% - 7% vs < 5	0.99 [0.75-1.32]	1.07 [0.85-1.35]
7% - 12% vs < 5%	0.94 [0.73-1.22]	1.16 [0.95-1.42]
> 12% vs < 5%	1.27 [0.95-1.69]	1.15 [0.90-1.47]
Census Tract Education		
More vs Less Educated	1.14 [0.88-1.49]	1.23 [0.98-1.54]
Type of Residence		
Metro vs Less Urban/Rural	0.90 [0.68-1.20]	0.94 [0.73-1.21]
Urban vs Less Urban/Rural	1.02 [0.69-1.51]	1.01 [0.71-1.44]
Region of Residence		
Northeast vs Midwest	0.84 [0.63-1.12]	2.68*** [2.08-3.44]
South vs Midwest	1 [0.73-1.38]	2.49*** [1.86-3.34]
West vs Midwest	0.82 [0.63-1.06]	1.69*** [1.33-2.16]
Comorbidity Index		
Comorbidity Index 1 vs 0	0.74** [0.60-0.92]	1.06 [0.89-1.25]
Comorbidity Index ≥ 2 vs 0	0.8 [0.60-1.05]	0.91 [0.73-1.13]

Performance Status		
Poor vs Good	0.80 [0.61-1.05]	0.59*** [0.47-0.73]
Stage		
III-IV vs I-II	1.64*** [1.36-1.97]	0.88 [0.75-1.02]
Unknown vs I-II	1.10 [0.77-1.59]	0.88 [0.66-1.17]
Grade		
3 vs 1 or 2	2.63*** [2.05-3.37]	1.19 [0.94-1.50]
Not Specified vs 1 or 2	1.35** [1.11-1.64]	0.93 [0.79-1.08]
Primary Site		
Extranodal vs Nodal	0.56*** [0.42-0.74]	1.17 [0.97-1.41]
B-symptoms		
Present vs Absent	1.92*** [1.47-2.49]	0.75* [0.58-0.98]
Unrecorded vs Absent	1.08 [0.88-1.31]	0.91 [0.77-1.06]
Primary Site		
Extranodal vs Nodal	1.02 [0.59-1.76]	1.26 [0.80-1.99]
Recent Anemia		
Yes vs No	0.83 [0.54-1.28]	0.72 [0.48-1.07]
Local (HRR) Nuclear-Medicine Density Tertile		
2nd vs 1st	0.83 [0.67-1.04]	1.03 [0.86-1.25]
3rd vs 1st	0.86 [0.68-1.10]	1.47*** [1.20-1.80]
* p<0.05, ** p<0.01, *** p<0.001		
Abbreviations: AA, African American; NCTCG, National Cancer Institute Clinical Trial Cooperative Group; PET, positron emission tomography; HRR, Hospital Referral Region;		

APPENDIX TABLE 4.8 (CONTINUED) Results from the first stage multinomial regression in the IV-2SRI survival model (no PET + others is the reference category)

	PET + R-chemo
Instrument 1: NCTCG Membership	
Yes vs No	1.28** [1.06-1.54]
Instrument 2: Local Area (HRR) Proclivity for PET-staging (Continuous Variable)	
	211.76*** [51.42-872.14]
Age	
71 - 75 vs 66 -70 yr	0.80 [0.64-1.00]
76 - 80 vs 66 -70 yr	0.75* [0.59-0.95]
> 80 vs 66 -70yr	0.24*** [0.18-0.32]
Race	
AA vs Caucasian	0.38** [0.20-0.72]

Other Race vs Caucasian	1.30 [0.83-2.04]
Sex	
Female vs Male	0.96 [0.80-1.15]
Marital Status	
Married vs Single/Widowed	1.21 [0.99-1.47]
Unknown vs Single/Widowed	0.84 [0.56-1.24]
Years of Diagnosis	
2003-2005 vs 2000-2002	10.54*** [7.52-14.79]
2006-2009 vs 2000-2002	34.73*** [24.76-48.71]
% Living Under Poverty	
5% - 7% vs < 5	1.11 [0.85-1.45]
7% - 12% vs < 5%	0.97 [0.76-1.24]
> 12% vs < 5%	1.13 [0.84-1.53]
Census Tract Education	
More vs Less Educated	1.19 [0.90-1.58]
Type of Residence	
Metro vs Less Urban/Rural	0.91 [0.67-1.24]
Urban vs Less Urban/Rural	0.86 [0.56-1.34]
Region of Residence	
Northeast vs Midwest	2.65*** [1.94-3.61]
South vs Midwest	2.68*** [1.89-3.82]
West vs Midwest	1.84*** [1.36-2.49]
Comorbidity Index	
Comorbidity Index 1 vs 0	0.84 [0.68-1.04]
Comorbidity Index ≥ 2 vs 0	0.78 [0.59-1.03]
Performance Status	
Poor vs Good	0.44*** [0.32-0.59]
Stage	
III-IV vs I-II	1.65*** [1.36-1.99]
Unknown vs I-II	0.83 [0.57-1.22]
Grade	
3 vs 1 or 2	6.01*** [4.72-7.65]
Not Specified vs 1 or 2	1.32** [1.08-1.61]
Primary Site	
Extranodal vs Nodal	0.88 [0.69-1.12]
B-symptoms	
Present vs Absent	1.40* [1.06-1.86]
Unrecorded vs Absent	0.98 [0.80-1.19]

Primary Site	
Extranodal vs Nodal	0.99 [0.55-1.77]
Recent Anemia	
Yes vs No	1.00 [0.64-1.54]
Local (HRR) Nuclear-Medicine Density Tertile	
2nd vs 1st	0.99 [0.79-1.24]
3rd vs 1st	1.08 [0.84-1.39]

* p<0.05, ** p<0.01, *** p<0.001

Abbreviations: PET, Positron Emission Tomography; NCCTG, National Cancer Institute Clinical Trial Cooperative Group

FIGURE 4.1 Conceptual model

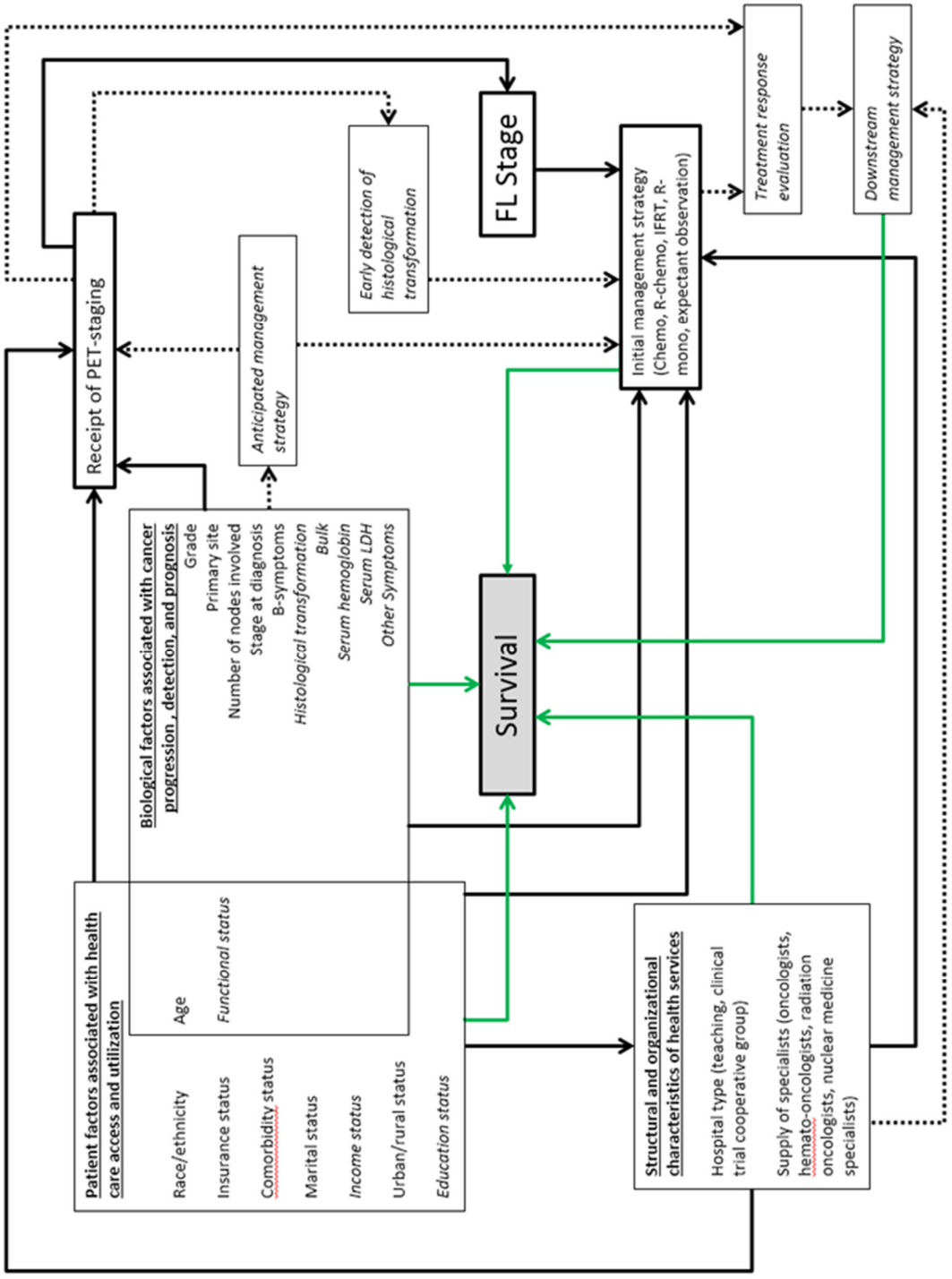


FIGURE 4.2 Selection criteria for the study cohort

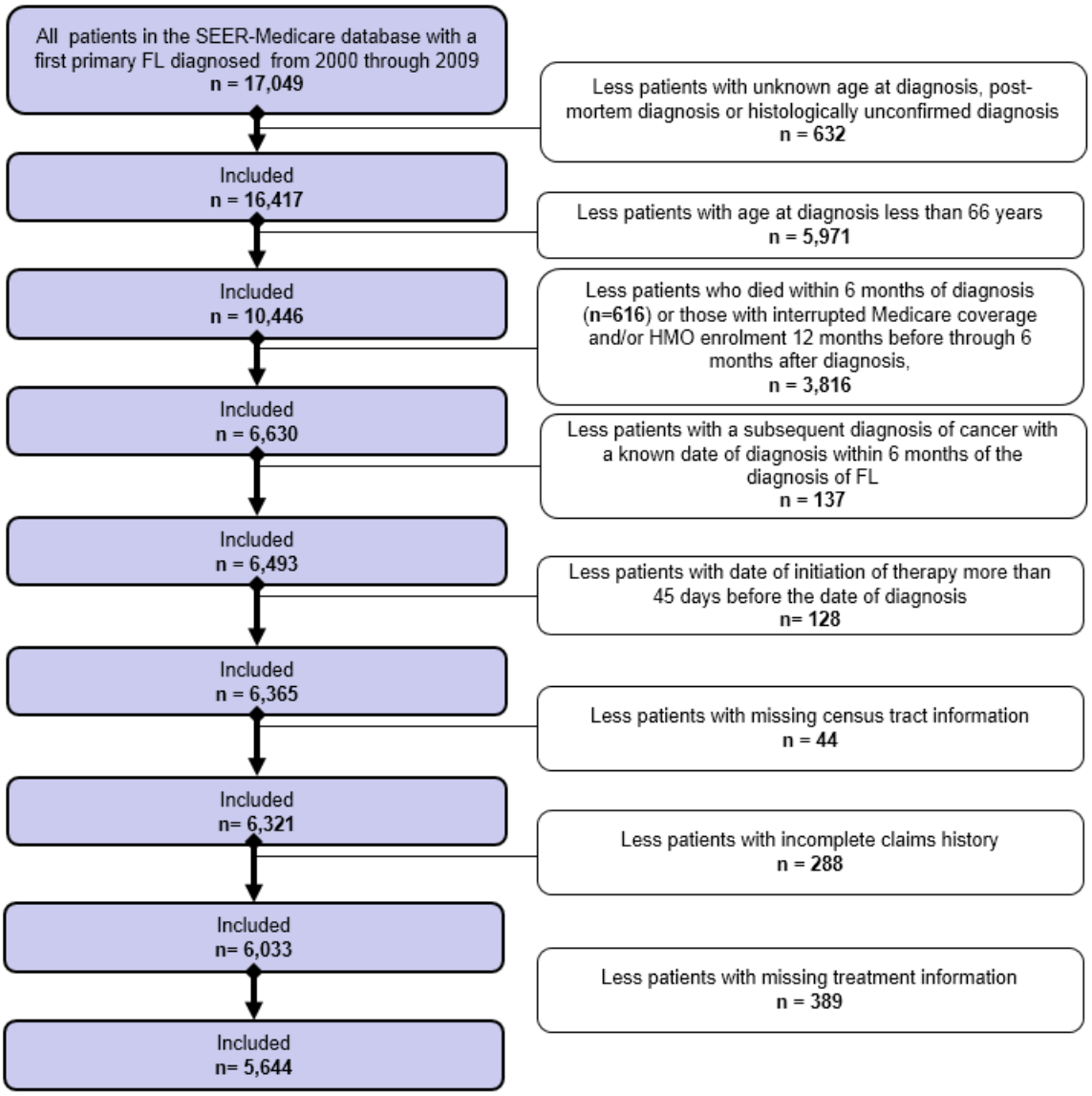


FIGURE 4.3 Unadjusted Kaplan-Meier survival curves by packages of management approaches

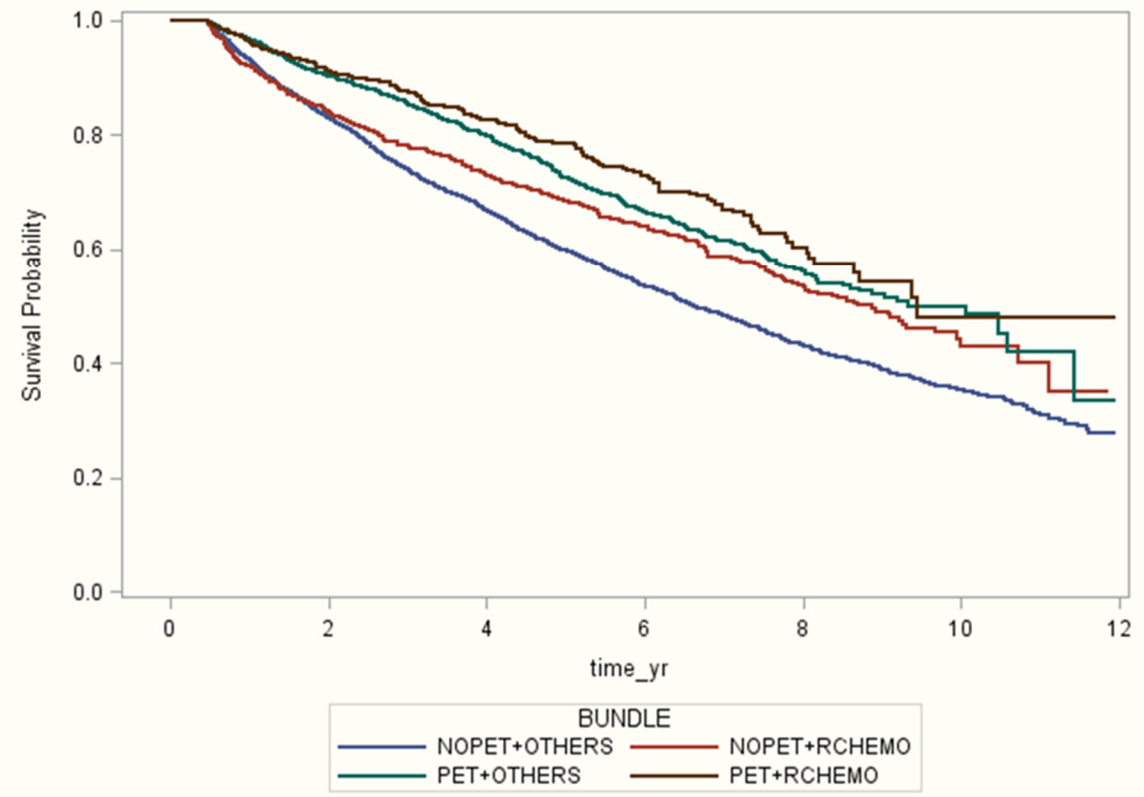


FIGURE 4.4 Direct-adjusted survival functions from propensity score-weighted multivariable Cox proportional hazards models

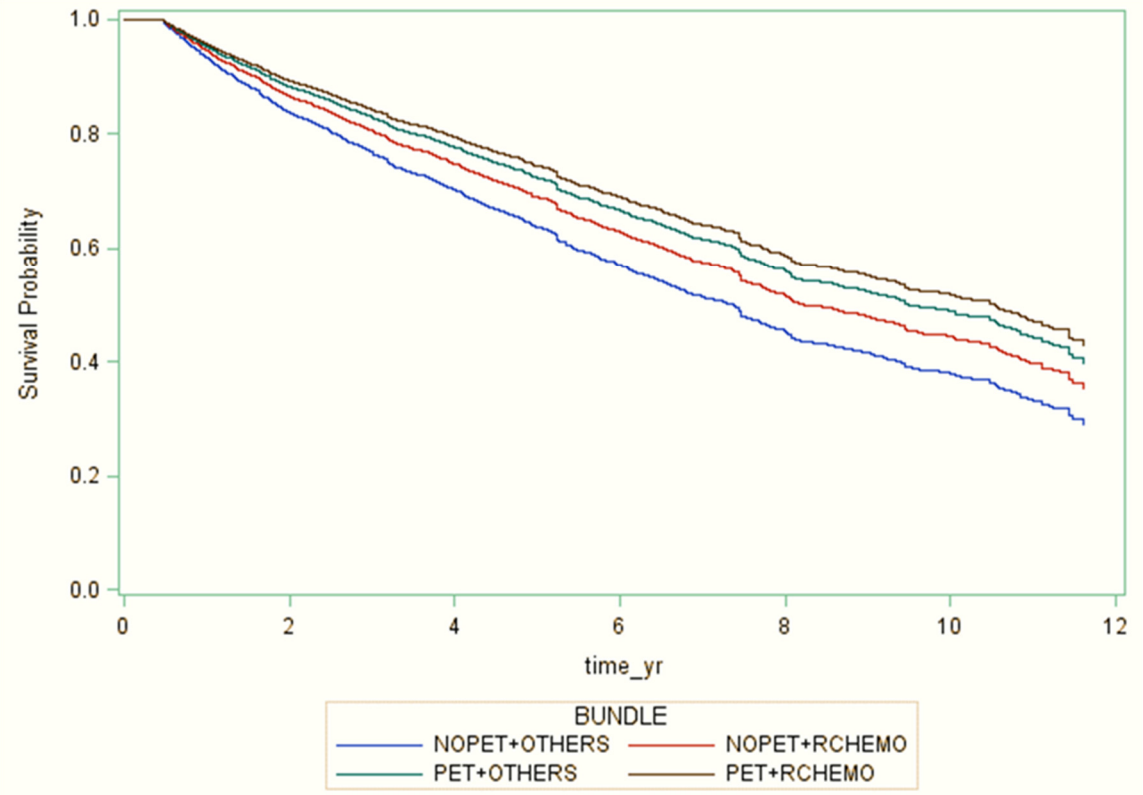
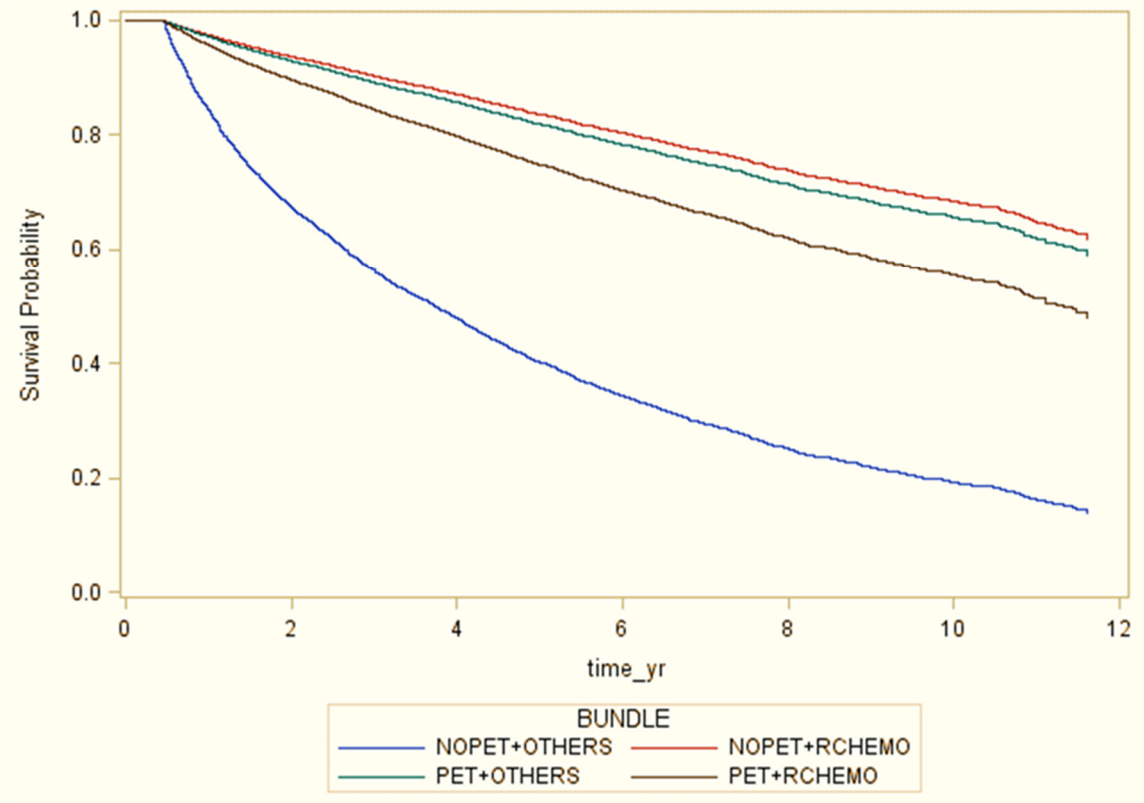


FIGURE 4.5 Direct-adjusted survivor functions from the 2SRI multivariable Cox proportional hazards models



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