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Very Low Utility of Surveillance Imaging in Early-Stage Classic Hodgkin Lymphoma Treated With a Combination of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine and Radiation Therapy

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Abstract

BACKGROUND—This study evaluated the need for surveillance imaging in early-stage classic Hodgkin lymphoma (cHL) after planned combined-modality therapy (CMT).

METHODS—Primary early-stage cHL patients who underwent CMT were included. Positron emission tomography (PET)/computed tomography (CT), CT, or both were performed at the initial staging, during or after chemotherapy, and for at least 2 years during follow-up. Imaging studies and medical records were reviewed to determine if and when relapse had occurred. Radiation doses and costs were also calculated from follow-up imaging.

RESULTS—The study included 78 patients with a median follow-up of 46 months; 85% of the patients had stage II disease (32% with bulky disease). Four of 77 interim PET scans were positive; none of these patients relapsed during follow-up, which ranged from 24 to 80 months. After a total of 466 follow-up imaging studies (91% with CT and 9% with PET/CT), no cHL relapse was detected. Eleven abnormal findings were noted on surveillance imaging: 9 were false-positives, and 2 were second primary malignancies. The average cumulative dose per patient from follow-up imaging was 107 mSv, which translated into an estimated lifetime excess cancer risk of 0.5%; the estimated total costs were $296,817 according to Medicare reimbursements.

CONCLUSIONS—Surveillance imaging with either CT or PET/CT can be omitted safely for early-stage cHL treated with a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine and radiation therapy because the risk of relapse is extremely low. This observation also applies to patients with bulky disease. The elimination of surveillance imaging will also reduce healthcare expenses and cumulative radiation doses in these predominantly young patients.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosure.

Keywords

combined-modality therapy; early stage; Hodgkin lymphoma; positron emission tomography (PET) scan; surveillance imaging

INTRODUCTION

Roughly 43% of newly diagnosed Hodgkin lymphoma (HL) patients are younger than 35 years of age. With current treatment regimens, the 5-year overall survival exceeds 90% in early-stage HL and 75% to 90% in advanced-stage HL.[1,2] Limiting long-term treatment-related toxicities[3,4] is an important goal in the management of these predominantly younger patients. Several risk-adapted treatment strategies, such as altering the intensity and duration of chemotherapy,[5] limiting the radiation field and dose,[6] and omitting radiation therapy completely,[7] are, therefore, under investigation.

Combined-modality therapy (CMT) is considered by most to be the standard treatment for early-stage classic Hodgkin lymphoma (cHL).[8,9] CMT includes 2 to 6 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and involved-field radiotherapy or involved-site radiotherapy.[10] Alternatively, some patients are treated with ABVD alone. After completion of the planned therapy, patients are followed for at least 5 years. Recommendations for follow-up imaging include chest X-ray/chest computed tomography (CT) and abdomen/pelvis CT every 6 to 12 months for the first 2 years. [^{18}F]fludeoxyglucose ([^{18}F]FDG) positron emission tomography (PET)/CT has an established role in the staging and response assessment of HL and is sometimes employed during follow-up. Moreover, interim PET after a few cycles of therapy is being studied to derive prognostic information and possibly alter planned therapy.[11–13]

Approximately 10% of early-stage HL patients and 20% to 30% of advanced-stage patients relapse after a complete response to first-line therapy, with the greatest risk in the first 2 years.[14] Excellent disease-free survival can be achieved in more than one-half of relapsed patients,[15,16] and many new treatment strategies based on molecular targets are being investigated.[17] Imaging is often used in an attempt to detect early relapse, and it is inferred that early disease detection enables early treatment, which leads to better patient outcomes. However, surveillance imaging in asymptomatic patients after the successful treatment of HL is controversial. Neither National Comprehensive Cancer Network nor European guidelines recommend the use of PET/CT for surveillance imaging.[8,9] Chest X-rays and CT scans are recommended, although most HL relapses are detected on the basis of clinical suspicion or patient-reported symptoms rather than imaging.[18–24] The increasing use of medical imaging has also led to concerns about the potential long-term biologic effects of ionizing radiation, particularly in young patients with early-stage cHL who have a high probability of long-term survival.[1,25,26] On the basis of our prior work,[27] we investigated the utility of any surveillance imaging in patients with early-stage cHL treated with CMT who achieved a complete metabolic response according to either interim or postchemotherapy PET/CT.

MATERIALS AND METHODS

Patient Selection

Our institutional review board approved this retrospective study; informed consent was not required. We searched the institutional database with DAVInCI (a Memorial Sloan Kettering Cancer Center Web-based application that enables data queries to be independently run) to identify HL patients treated with CMT between January 2000 and December 2012. We initially identified a total of 218 patients with cHL, and 78 of these patients were eligible for analysis with the following inclusion criteria: 1) biopsy-proven early-stage (IA to IIB) cHL of any subtype with or without bulky disease, 2) an age >18 years, 3) completion of planned ABVD and radiation therapy, 4) interim/postchemotherapy PET/CT to document the treatment response, and 5) at least 24 months of follow-up (or until proven relapse if earlier).

One hundred forty of these 218 patients were excluded (Fig. 1). The medical records of the remaining 78 eligible patients were reviewed. All patients were staged according to the Cotswolds modification of the Ann Arbor staging system.[28] Bulky disease was defined as a single nodal mass measuring greater than 10 cm or a mediastinal mass greater than or equal to one-third of the maximum transverse thoracic diameter on a standard posteroanterior chest radiograph at the level of the T5-T6 intervertebral disc.

Treatment Plan

All patients were treated with ABVD and then involved-field or extended-field radiotherapy. The number of ABVD cycles administered was based on risk factors and institutional guidelines. Sixty-eight patients received involved-field radiotherapy and 10 patients received extended-field radiotherapy with the following doses: 36 Gy in 20 patients, 30 Gy in 49 patients and 20 Gy in 9 patients.

Imaging Studies

Imaging studies included PET/CT and dedicated CT scans performed either at our institution or outside facilities that followed standard protocols as described previously.[27] PET/CT scans were obtained from the base of the skull to the upper thighs (low-dose CT performed with 120 kV and 80 mA; 12–15 mCi of [^{18}F]FDG). Dedicated CT imaging included the chest, abdomen, and pelvis in most cases and neck imaging as required after the administration of oral and intravenous contrast material. CT was performed with dose-reduction protocols with 120 kV and adjusted milliamperes (range, 120–380 mA). Staff physicians who were unaware of patient outcomes reviewed all PET/CT and CT scans (PET/CT Volume Viewer 2, AW suite, version 2.0; GE Healthcare). Interim/postchemotherapy PET/CT scans were reviewed to assign scores with a 5-point scale,[29] with a score ≤3 considered to be negative.

Analysis of the Radiation Dose and Costs Associated With Surveillance Imaging

Average cumulative doses for each imaging modality, estimated from a representative cohort of patients imaged at our institution, were as follows: CT of the chest, abdomen, and pelvis, 23.2 mSv (range, 6–34.4 mSv); CT of the neck, 3.1 mSv (range, 1.4–4.9 mSv); CT of the chest, 6.7 mSv (range, 2.2–11.3 mSv); and fludeoxyglucose (FDG) PET/CT, 14.1 mSv

(range, 11–17.6 mSv). The lifetime excess cancer risk from the cumulative dose was calculated for each patient on the basis of a lifetime excess cancer risk of 5% for the general population from 1 Sv (National Council on Radiation Protection and Measurements report 115).[30] Costs for imaging studies were estimated with established US Medicare reimbursement rates for CT and PET/CT scans.

RESULTS

Patient Characteristics

Seventy-eight patients with a median age of 43 years were included in the final analysis (Table 1); 48 of the 78 patients (61.5%) were younger than 45 years of age. The major histologic subtype was nodular sclerosis (n = 62 or 79%). Fifty of the 78 patients were staged as IIA (64%), 25 patients had bulky disease (32%), and 5 patients (6.4%) had involvement of extranodal sites (chest wall, thyroid gland, lung, rib, and nasopharynx).

Imaging Studies (Fig. 2)

Baseline imaging—Seventy-seven patients had baseline PET/CT scans. One patient was pregnant at the time of diagnosis and hence had only a chest X-ray at the baseline. One patient had no detectable FDG-avid disease on the baseline scan because the single site of submandibular disease had been excised.

Imaging during and at the end of treatment—Seventy-seven patients underwent interim PET/CT to assess the treatment response either during chemotherapy (n = 34) or after chemotherapy (n = 43) before the initiation of radiation therapy. Interim scans were performed at the discretion of referring physicians after 2 to 4 ABVD cycles or after the completion of all ABVD cycles. One patient with stage IA disease confined to the submandibular region did not have any other FDG-avid disease at the baseline; therefore, follow-up PET/CT was not considered necessary. Twenty-two of the 77 patients had PET/CT both during and after the completion of chemotherapy.

Seventy-three of the 77 patients achieved a complete metabolic response, and 4 remained PET-positive (a score of 4 or 5). Scans obtained after the completion of radiotherapy showed a complete response in 2 of the latter 4 patients and inflammation in 1 patient. The fourth patient did not undergo PET/CT after radiotherapy, but follow-up CT scans showed resolution of all adenopathy. None of these 4 patients relapsed during follow-up, which ranged from 24 to 80 months.

Twenty patients had PET/CT scans after the completion of planned CMT. Three scans were suspicious for refractory lymphoma but on further workup were found to be false-positives: a new FDG-avid lung nodule (wedge resection was negative for lymphoma), mild FDG-avid foci in the bone marrow (negative for lymphoma on subsequent magnetic resonance imaging), and reactive pelvic nodes. Notably, these 3 patients had experienced a complete metabolic response according to interim PET/CT scans, and none have since relapsed.

Follow-up imaging—During a median follow-up of 46 months (range, 24–126 months), a total of 466 scans were performed in the 78 patients. The first posttreatment scan was

usually performed 6 to 8 weeks after the completion of therapy. Further follow-up scans were obtained as ordered by referring physicians. The majority of these scans were CT scans: 355 CT scans of the chest, abdomen, and pelvis (76.2%); 25 CT scans of the neck (5.4%); and 44 CT scans of the chest (9.4%). In addition, 42 patients underwent PET/CT (9%). No relapses occurred in the entire cohort. However, 1 patient was diagnosed with a new abdominal T-cell lymphoma 53 months after the achievement of a complete response to therapy for stage IA supradiaphragmatic cHL; this was diagnosed on the basis of new clinical symptoms, which led to imaging and biopsy. This patient later died from progressive T-cell lymphoma.

Three of the 78 patients were diagnosed with a second primary malignancy by either imaging (n = 2) or clinical presentation (n = 1; Table 2). Notably, 6 patients had false-positive imaging findings requiring further supplementary imaging or biopsy/surgery. There were 3 false-positive findings on PET/CT scans: asymmetric tonsillar uptake leading to tonsillectomy, a new left lung nodule leading to biopsy, and a new supraclavicular node requiring biopsy. There were also 3 false-positive findings on CT: a lung nodule leading to segmentectomy, a new breast nodule requiring biopsy, and a liver lesion that proved benign on subsequent magnetic resonance imaging and remained stable upon follow-up.

Bulky disease—Twenty-five of 78 patients (32%) had bulky disease. Twenty-four of 25 interim PET/CT scans performed during or after chemotherapy (before radiotherapy) were negative; 1 scan was positive, but follow-up dedicated CT scans showed complete resolution. No relapses were identified in this category.

Analysis of follow-up imaging radiation dose and costs—Among the 466 scans performed for surveillance imaging, dedicated CT scans (particularly those covering the entire chest, abdomen, and pelvis) contributed most of the cumulative dose. Most patients (83%) had 8 scans or fewer (25 patients had 1–4 scans; 40 patients had 5–8 scans; 12 patients had 9–12 scans; and 1 patient had 13 scans). The average cumulative dose per patient was 107 mSv, which translated into a lifetime excess cancer risk of 0.5%.[30] One of the 78 patients had a total of 13 scans at 114 months' follow-up. This was associated with an average cumulative dose of 259 mSv, which translated into a lifetime excess cancer risk of 1.3%. Thus, although the radiation dose received from medical surveillance imaging was substantial, the overall excess risk of radiation-induced malignancy compared to general population was judged to be low.

According to Medicare reimbursements, 466 surveillance studies performed in 78 patients incurred costs of $296,817. On average, the cost per patient in the current study was $3805. It should be noted that the real costs, if we assume a representative mix of third-party payers in the Metro New York area, are likely to be higher. Moreover, the aforementioned figures do not include additional costs associated with supplementary imaging and invasive procedures (ie, biopsy and surgery) caused by false-positive imaging findings.

DISCUSSION

We investigated the need for surveillance imaging in patients with early-stage cHL who were treated with CMT and had a complete metabolic response on PET/CT. No relapse of cHL was detected at a median follow-up of 46 months. Therefore, the current follow-up algorithm for early-stage cHL should be modified: routine imaging (either CT or PET/CT) for the early detection of relapse does not appear necessary or justified in these patients. This conclusion also applies to early-stage cHL with bulky disease.

Surveillance imaging is done with the expectation of improving survival by identifying and treating relapses early before they present clinically. However, several studies have shown no survival benefit in patients with asymptomatic relapse detected on imaging.[20,21,23,31,32] Notably, the studies included heterogeneous subsets of patients with HL and non-Hodgkin lymphoma[19,20] or patients with both early-and advanced-stage HL who were treated with various modalities and drug regimens.[20,32–34] We believe that the role of surveillance imaging should be addressed in homogeneous subsets of patients to derive meaningful clinical conclusions (Table 3). Our patient population is similar to the cohort studied by Patel et al,[22] who performed surveillance imaging in 78 patients with supradiaphragmatic early-stage cHL treated with CMT (ABVD, 86%; mechlorethamine, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine, 5%; and Stanford V, 9%). After a total of 2440 imaging studies, including 1636 CT scans, only 9 relapses were observed, and only 3 were detected by imaging. This study included 28 patients with bulky disease, in whom relapse rates were similarly low. We did not observe any relapses among the 32% of patients with bulky disease after a minimum follow-up of 2 years. Potential reasons for differences in patient outcomes between these 2 studies may include the early identification of refractory cHL and changes in treatment rather than the continuation of planned CMT, the exclusion of CD20-positive cHL from the analysis,[37] differences in radiation techniques (including field design), and the long record of successful radiotherapy for HL at our institution. Nevertheless, relapse rates are very low in both studies and do not justify extensive follow-up imaging studies.

The current study builds on prior work from our institution[27] showing that surveillance imaging is not required in patients with early-stage, nonbulky cHL who have been treated with 6 cycles of ABVD alone and have had a complete metabolic response on PET/CT. Our 2 studies were confined to patients with CD20-negative early-stage cHL and a complete metabolic response on interim or post-ABVD PET. This is in contrast to the 10% to 15% relapse rates reported in prior studies (Table 3),[22,32–35] which did not perform end-of-treatment PET in all patients[32] or included patients with positive end-of-treatment PET.[34,35] Notably, because residual FDG avidity at the completion of first-line therapy is associated with a higher risk of relapse,[38] the utility of surveillance imaging should be studied separately for patients with positive end-of-treatment PET/CT. Relapse rates are also higher in symptomatic patients, but the diagnostic yield of imaging is relatively low even in this group of patients. For instance, Mocikova et al[34] performed a total of 155 follow-up PET/CT scans in 67 patients who were PET-negative at the end of first-line therapy. Although the fraction of true-positive scans was higher among symptomatic patients (5 of 27 positive

scans or 18.5%) versus asymptomatic patients (1 of 27 positive scans), false-positive findings were quite common.

Interim PET after 2 to 4 cycles of chemotherapy is a predictor of treatment response and a prognostic marker of outcomes in patients with HL.[38] In the current study, 4 PET/CT scans performed during chemotherapy were positive. Nevertheless, all patients achieved a complete response at the end of CMT, and no relapses occurred. This is in keeping with the recognized high negative predictive value but somewhat lower positive predictive value of interim PET/CT. In particular, the outcome for patients with positive interim but negative end-of-treatment PET/CT who underwent radiation therapy as part of CMT was similar to the outcome for patients with negative interim PET/CT.[39] Moreover, the predictive and prognostic value of PET/CT depends on the pretest probability (a priori chance for a cure). In one recent study, cure was achieved in 75% of patients with early-stage, nonbulky disease and in 20% to 40% of patients with bulky disease who were treated with ABVD or CMT despite positive interim PET/CT.[40]

Another reason not to perform surveillance imaging is the occurrence of false-positive findings, which often lead to further imaging or invasive procedures; these are associated with patient anxiety, risks, and additional costs.[21,41] We encountered false-positive findings on surveillance imaging in 9 patients (11.5%). Previous studies reported positive predictive values for surveillance imaging in HL of 23% to 54% with PET/CT[31,35,36] and 28% with CT.[31]

In the current study, CT scans accounted for 91% of the surveillance imaging. The average cumulative dose per patient was 107 mSv (lifetime excess cancer risk of 0.5%), and the maximum was 259 mSv (lifetime excess cancer risk of 1.3%). The cancer risk estimates are comparable to those in a previous retrospective study, in which the mean increase in the cancer risk was estimated at 0.4% and, even with the highest cumulative dose of 209 mSv, was estimated at 1.2%.[42] Although the dose from imaging studies is considerably lower than that from radiotherapy administered during CMT, efforts at dose reduction should be made for malignancies in patients with long-term survival and especially in younger populations. This topic is of increasing concern among patients and radiologists alike.[25] Routine surveillance imaging in early-stage cHL does not appear meaningful or necessary. However, when pretest probability and clinical suspicion for relapse are strong, it would appear most meaningful to employ PET/CT (rather than CT only) as the single test with the highest expected utility.

Our study has some limitations. Patients were selected because this analysis was confined to early-stage cHL treated with CMT using ABVD. On the other hand, we consider this degree of selectivity a strength because the need for follow-up imaging is directly determined by tumor biology and treatment efficacy. As noted, it is difficult to interpret some previously published studies that included patients with a variety of stages, with or without bulky disease, and a variety of treatment regimens. The median follow-up for patients in this study is still relatively short, but most relapses of cHL are expected to occur within the 2-year time frame that constitutes our minimum follow-up.

Secondary solid malignancies appear to be more common in long-term cHL survivors; however, these usually occur with a latency of greater than 5 to 10 years.[4] Screening procedures to detect secondary malignancies in HL survivors are not fully settled but may include mammograms or breast magnetic resonance imaging screening beginning 7 years after at-risk upper torso radiotherapy before the age of 30 years, thyroid US monitoring beginning 10 years after at-risk radiotherapy to the neck or upper mediastinum, and lung cancer screening CT in prior smokers. Large prospective cohort studies with extended follow-up will be required to refine the best follow-up imaging strategy for this question.

In conclusion, routine surveillance imaging with CT or PET/CT can be omitted safely in early-stage cHL patients successfully treated with CMT because the risk of relapse is extremely low. This observation also applies to patients with bulky disease. The elimination of routine imaging will result in a lower cumulative radiation dose in these predominantly younger patients and may also help to reduce health care expenses.

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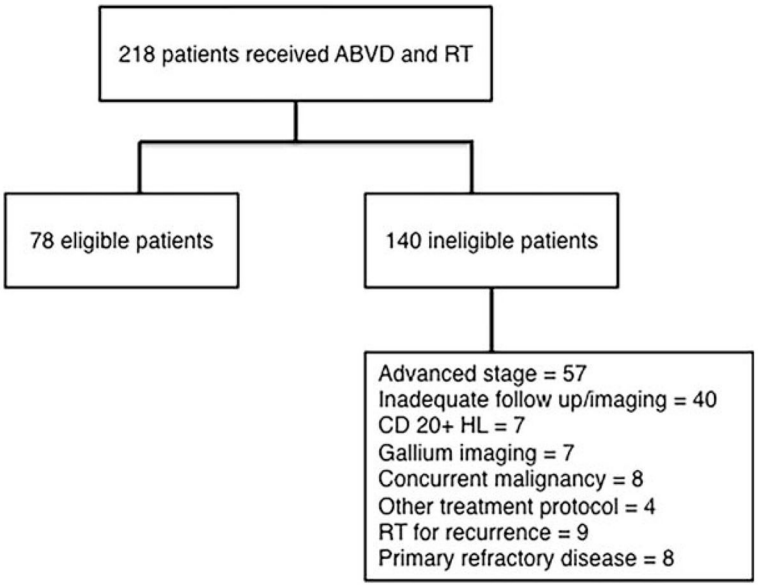

Figure 1.

Identification of eligible patients. ABVD indicates doxorubicin, bleomycin, vinblastine, and dacarbazine; HL, Hodgkin lymphoma; RT, radiation therapy.

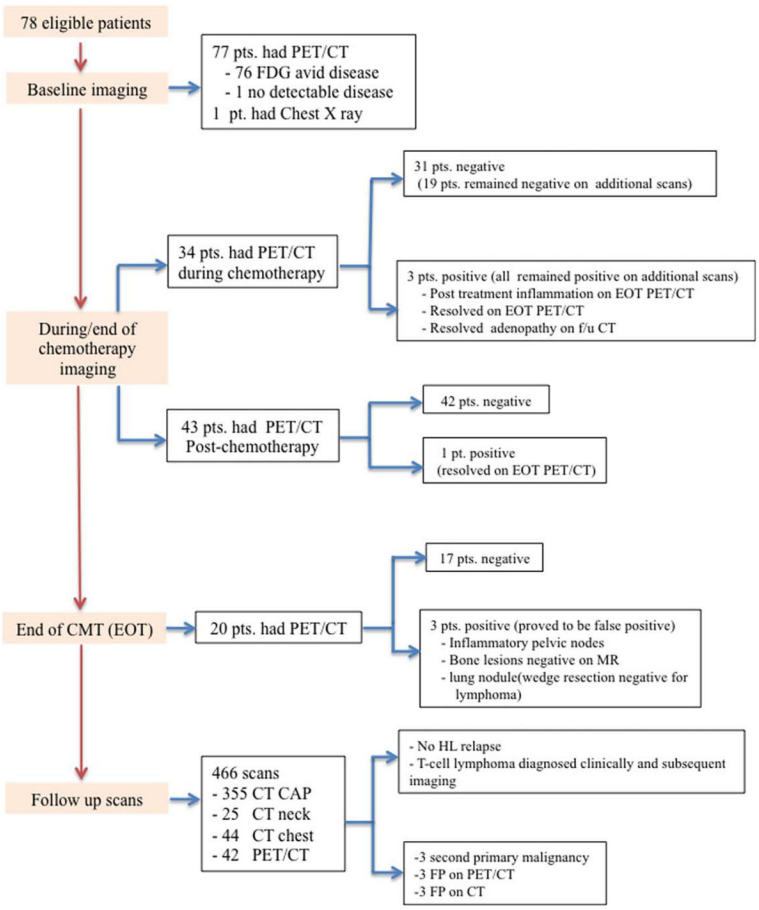

Figure 2.

Details of PET/CT and follow-up imaging. CAP indicates chest, abdomen, and pelvis; CMT, combined-modality therapy; CT, computed tomography; EOT, end of treatment; FDG, fludeoxyglucose; FP, false-positive; HL, Hodgkin lymphoma; MR, magnetic resonance; PET, positron emission tomography; pt, patient.

TABLE 1

Patient Characteristics

Characteristic	Total Patients
Sex, n (%)	
Male	35 (45)
Female	43 (55)
Age, y	
Median	43
Range	22–86
Stage, n (%)	
IA	12 (15)
IB	—
IIA	50 (64)
IIB	16 (21)
Histology, n (%)	
Nodular sclerosing	62 (79)
Mixed cellularity	6 (8)
Lymphocyte-rich	3 (4)
Not specified	7 (9)
>3 lymphoid regions, n (%)	
Yes	57 (73)
No	21 (27)
Extranodal site involvement, n (%)	
Yes	5 (6.4)
No	73 (93.6)
B symptoms, n (%)	
Yes	16 (21)
No	62 (79)
Bulky, n (%)	
Yes	25 (32)
No	53 (68)
Erythrocyte sedimentation rate (mm/h), n (%)	
≥50	27 (35)
<50	39 (50)
Unknown	12 (15)

TABLE 2

Second Primary Malignancies Detected on Surveillance Imaging

cHL Stage at Presentation	Radiation Field	Interval From CMT to Diagnosis (mo)	Second Primary Malignancy		Treatment	Outcome
			Type	Stage		
IIXB	Mini-mantle	24	Clear cell renal cell carcinoma	I	Partial nephrectomy	Disease-free
IIA	Mini-mantle	4	Thyroid cancer	III	Surgery and radioactive iodine	Disease-free
IA	IFRT: right axilla	52	T-cell lymphoma: abdomen	IIBS	Chemotherapy	Death
IAX	IFRT: neck/upper mediastinum	96	Gastroesophageal junction adenocarcinoma	IIIA	Chemotherapy	Recurrence therapy

Abbreviations: CMT, combined-modality therapy; IFRT, involved-field radiotherapy.

TABLE 3

Surveillance Imaging in Lymphoma Patients

			HL		Therapy Protocol			Relapse Rate		
Study (Year)	**Patients**	**NHL**	**Early Stage**	**Advanced Stage**	**Chemotherapy**	**RT**	**CMT**	**Total**	**Imaging Follow-Up Group**	**Clinical Follow-Up Group**
Pingali et al[23] (2014)	241	0	117	124	124	—	117	11	6/174	5/67
El-Galaly et al[19] (2014)	258	215	25	18	159	9	90	258	62	196
Patel et al[22] (2013)	78	—	78	—	—	—	78	9	3	6
Hartridge-Lambert et al[27] (2013)	47	—	47	—	47	—	—	2	1	1
Goldschmidt et al.[20] (2011)	125	83	21	21	—	—	—	125	47	78
Lee et al[31] (2010)	192	—	92	100	110	—	82	12	5	7
PET/CT										
Dann et al[32] (2014)	368	—	134	234	200	—	138	36	28/305	8/63
El-Galaly et al[35] (2012)	161	—	50%	50%	77	5	79	22	10/211	12/88
Mocikova et al[34] (2010)	113	—	59	54	47	1	65	14	6/155	5/27
Petrausch et al.[33] (2010)	134		80	54	—	—	—	42	10/83	32/81
Zinzani et al.[43] (2009)	421	261	160		—	—	—		274	105
Crocchiolo et al[36] (2009)	27	—	13	14	27	—	9	7	7	—
CT										
Dryver et al[18] (2003)	107	—	91	16	18	55	34	22	6	16

Abbreviations: CMT, combined-modality therapy; CT, computed tomography; HL, Hodgkin lymphoma; PET, positron emission tomography; RT, radiation therapy.

Numbers of patients are shown unless otherwise indicated.