American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Follow-up of Hodgkin's Lymphoma**

Variant 1: **Adolescent/young adult, male or female, now without signs or symptoms, IIA supradiaphragmatic HD, treated with combined chemo-XRT.**

Radiologic Procedure	Rating	Comments
History and physical examination every 2-4 months for 2 years, then every 6 months for 3 years, then yearly for life	9	
X-ray chest 2-3 times per year for 5 years, then yearly	8	Unless chest CT performed.
CT chest abdomen and pelvis every 6 months for 2 years, then yearly for 3 years	8	
FDG-PET whole body	No Consensus	See summary of literature review.
Screening exercise tolerance test and echocardiogram only if symptomatic	9	
Screening exercise tolerance test and echocardiogram periodic	8	Depending on mediastinal irradiation, Adriamycin dose, and other risk factors.
X-ray mammography annual, beginning 8-10 years after treatment or by age 40	9	For females only.
CT chest for lung cancer screening annual, beginning 5 years after treatment	1	
CT chest for lung cancer screening annual, beginning 5 years after treatment only if smoker	No Consensus	Studies are ongoing.
Laboratory Tests		
CBC 1-2 times per year	8	
Chemistry panel 1-2 times per year	8	
Thyroid panel 1-2 times per year	8	
ESR 1-2 times per year	8	
Lipid profile periodic	7	
Patient Education and Counseling		
Increased long-term risk of second malignancy (especially breast cancer risk) and cardiac disease	9	
Monthly self-breast examination	9	
Regular exercise	9	
Healthy diet	9	
Smoking cessation if current smoker	9	

Rating Scale: **1=Least appropriate, 9=Most appropriate**

Clinical Condition: **Follow-up of Hodgkin's Lymphoma**

Variant 2: **Adolescent/young adult, male or female, now without signs or symptoms, IIA subdiaphragmatic HD, treated with combined chemo-XRT.**

Radiologic Procedure	Rating	Comments
History and physical examination every 2-4 months for 2 years, then every 6 months for 3 years, then yearly for life	9	
X-ray chest once a year	8	At least once per year, unless chest CT performed.
CT chest abdomen and pelvis once a year times 5 years	8	
FDG-PET whole body	No Consensus	See summary of literature review.
Screening exercise tolerance test and echocardiogram only if symptomatic	9	
Screening exercise tolerance test and echocardiogram periodic	8	Depending on mediastinal irradiation, Adriamycin dose, and other risk factors.
CT chest for lung cancer screening annual, beginning 5 years after treatment if received alkylating agent chemotherapy	1	
CT chest for lung cancer screening annual, beginning 5 years after treatment only if smoker	No Consensus	Studies are ongoing.
Laboratory Tests		
CBC 1-2 times per year	8	
Chemistry panel 1-2 times per year	8	
ESR 1-2 times per year	8	
Patient Education and Counseling		
Increased long-term risk of second malignancy	9	
Regular exercise	9	
Healthy diet	9	
Smoking cessation if current smoker	9	

Rating Scale: **1=Least appropriate, 9=Most appropriate**

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Summary of Literature Review

Routine follow-up evaluation of patients after treatment for Hodgkin's lymphoma serves several functions. Detection of relapse is the most important in the first 5 years after treatment. For long-term survivors, the focus should be on detection of second neoplasms monitoring for other late effects of therapy, and patient education.

Detection of Relapse

Hodgkin's lymphoma remains the main cause of patient death during the first 10 to 15 years of follow-up [1-3]. Routine follow-up studies are used to detect relapse early so that salvage therapy can be instituted quickly.

The majority of relapses occur within the first 5 years of treatment [1-4]. As part of follow-up to detect recurrences, in addition to interim history (Hx) and physical examination (PE), radiographic tests that have been advocated include chest X-ray (CXR), abdominal radiograph (KUB), computed tomography (CT), gallium scan, and more recently, positron emission tomography (PET) scan. Blood work commonly performed includes complete blood count (CBC), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), serum copper, and chemistry panel (CHEM).

Interim history appears to be the most valuable follow-up tool in detecting relapse of Hodgkin's lymphoma. In their review of early-stage Hodgkin's lymphoma patients treated at Stanford, Torrey et al [3] found that 55% (59 of 107) of the detected relapses were discovered on the basis of the history, with the most commonly reported symptom being a new lump, followed by constitutional symptoms (fever, night sweats, weight loss) and pain. In a series from Christie Hospital in Manchester, England, Radford et al [2] found that 81% (30 of 37) of relapses were diagnosed in patients who reported symptoms, with the most common symptoms being a new lump, followed by cough, night sweats, and weight loss. Dryver et al [4] from Canada found that 45% (10 of 22) of relapses stemmed from patient concerns and 18% (4 of 22) from physician concerns. Physical examination also plays an important role. In the Stanford series, 14% (15 of 107) of the relapses were detected by PE. In the Manchester series, 5% (2 of 37) of relapses were detected by physical examination. Chest x-ray is also useful in detecting recurrence of Hodgkin's lymphoma. In the Stanford series, 23% (24 of 107) of relapses were detected by CXR. In the Manchester series, 5% (2 of 37) of relapses were detected by CXR. In the series from Canada, 18% (4 of 22) of relapses were detected by CXR.

In the last 10 to 15 years, CT scan is routinely included in the follow-up of Hodgkin's lymphoma patients. In the series from Canada, 9% (2 of 22) of relapses were detected by CT scans. Nuclear imaging studies are also increasingly performed as part of follow-up. A number of studies reviewed the role of gallium scan and PET scan in predicting preclinical relapses. Salloum et al [5] reviewed 101 patients who had been treated for Hodgkin's lymphoma and underwent gallium scans post-therapy. The positive predictive value (PPV) for relapse was 100% (although only four patients had positive gallium scans post-treatment), and the negative predictive value was 83.5%. In another series by Bogart et al [6] on 60 patients, 10 of 46 patients with a negative re-staging gallium scan subsequently relapsed (NPV=78%). In the remaining 14 patients with a positive re-staging gallium scan, 11 underwent further therapy and remained disease-free, and three died of progressive disease. In a study by Mikosch et al [7], 93 lymphoma patients (44 HD, 49 NHL) underwent PET scan as well as CT and ultrasound post therapy. Among the 44 Hodgkin's lymphoma patients (total of 59 scans), the sensitivity, specificity, PPV, and NPV of PET scan were 100%, 82%, 81%, and 100%, respectively, while for CT/ultrasound they were 83%, 23%, 43%, and 67%, respectively. A study from Germany also compared PET with conventional imaging methods in 81 patients treated for Hodgkin's lymphoma [8], showing a sensitivity and specificity of 95% and 89%, respectively, for PET scan in predicting relapses, while the sensitivity and specificity of conventional imaging methods were 95% and 39%, respectively. The superior specificity of PET scan compared with conventional imaging methods in these studies reflects the ability of PET scan to detect active disease in abnormal residual masses on CT post treatment. It should be noted that most of the literature to date has focused on the ability of post therapy nuclear imaging in predicting relapses, which may have implications on selecting patients for further therapy. However, no data are available on how

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frequently nuclear imaging studies, compared with other follow-up methods, pick up recurrences over the course of follow-up care.

Limited data are available on the role of routine blood work in detecting relapses. In the Stanford series, only one relapse was detected by an elevated ESR. CBC, CHEM, and serum copper did not detect any relapse [3]. In the series from Canada [4], abnormal laboratory findings picked up the same number of relapses as CT scans (2 of 22, 9%) though at a lower cost.

Detection of Second Malignancies

Numerous studies have demonstrated that patients who survive Hodgkin's lymphoma are at increased risk for second neoplasms. Solid tumors comprise the majority of cases of second malignancies, with the most common ones being breast cancer and lung cancer [9-13].

Breast cancers after Hodgkin's lymphoma typically occur after a long latency of 10 to 15 years. Available data suggest that they are similar to primary breast cancers in their histologic characteristics, although synchronous or metachronous cases are more frequently seen [14-16]. Young age at irradiation (under 30-35) has been consistently shown to be a major risk factor [11-13]. More recent data showed that the risk increases with increasing prior radiation dose to the breast tissue [17,18]. Women who underwent premature menopause from either chemotherapy or pelvic irradiation appeared to be at decreased risk, suggesting an effect of the hormonal milieu on the radiogenic breast cancer [17,18].

Mammography has been shown to be an effective tool for screening even among these young women. In a study by Yahalom et al [16], 81% of 37 women with breast cancer after Hodgkin's lymphoma had mammographic abnormalities of a mass and/or microcalcifications. Diller et al [19] prospectively evaluated the utility of mammogram in 90 female survivors of Hodgkin's lymphoma. During the study period, 10 women developed 12 breast cancers, all of which were evident on mammogram. The high frequency of mammographically detected abnormalities supports the value of mammographic screening in these patients. In a study on breast cancer after Hodgkin's lymphoma by Wolden et al [15], the authors found that the proportion of patients with early-stage breast cancer was higher in cases that were diagnosed after 1990, which may be due to the more frequent use of mammography screening in the more recent era. The role of breast magnetic resonance imaging has been studied in other high-risk population [20], but it remains unproven in female survivors of Hodgkin's lymphoma. The effectiveness of tamoxifen as chemoprevention has been demonstrated in other high-risk patients [21], but whether the data is applicable to women who survived Hodgkin's lymphoma is unclear.

Lung cancer is another well-documented second malignancy after Hodgkin's lymphoma. In addition to radiation therapy, prior chemotherapy exposure (alkylating agents in particular) significantly increases the lung cancer risk in a dose-dependent manner [12,22,23]. Several studies showed that tobacco use further adds to the risk of lung cancer after Hodgkin's lymphoma [22-24]. In a case-control study by Travis et al [23], those who been treated with radiation therapy and alkylating agents had a seven-fold increased risk of lung cancer after Hodgkin's lymphoma compared with survivors who did not have more than 5 Gy of radiation exposure and had never been exposed to alkylating agents. However, among those with the treatment exposures as well as tobacco exposure, there was a 49-fold increased risk, suggesting a multiplicative interaction between tobacco use and the alkylating agents and/or radiation.

Unlike breast cancer, the prognosis of lung cancer after Hodgkin's lymphoma is poor, with a median survival of only about a year [25]. Given the significantly increased risk of lung cancer after Hodgkin's lymphoma especially among smokers, and the associated poor prognosis, the question has been raised whether these patients may benefit from chest CT screening. The role of low-dose chest CT as screening is currently being studied in a prospective randomized trial in another high-risk group [26], but survivors of Hodgkin's lymphoma are not included in the study.

Detection of Nonmalignant Late Effects of Treatment

A number of studies have shown that patients who have been cured of the Hodgkin's lymphoma are at significantly increased risk of death from cardiac disease compared with the normal population [25,27-29].

A wide spectrum of radiation-induced cardiovascular disease has been identified in asymptomatic survivors of Hodgkin's lymphoma, including pericardial disease, coronary artery disease, cardiomyopathy, valvular disease, arrhythmia, and autonomic dysfunction [30-34].

The major contributor to the excess risk of cardiac mortality after Hodgkin's lymphoma is coronary artery disease, accounting for two-thirds of all cases of fatal cardiac events in survivors of Hodgkin's lymphoma. The main risk factor is mediastinal irradiation, and a dose-response relationship has been shown [31,32,34]. The presence of other traditional cardiac risk factors further increases the risk of cardiovascular disease after Hodgkin's lymphoma [31,34]. There may be a role for screening for and treatment of modifiable cardiac risk factors, and also cardiac screening tests for subclinical coronary artery disease in survivors of Hodgkin's lymphoma. Whether they can reduce the cardiac mortality in these patients remain unproven at this time.

The role of cardiac screening for other cardiac structural abnormalities was addressed in a prospective study from Stanford University, in which 294 asymptomatic patients treated with mediastinal irradiation for Hodgkin's lymphoma underwent electrocardiography and echocardiography screening [33]. The prevalence of valvular abnormality increased significantly with increasing follow-up time. Furthermore, the abnormality was rarely picked up on auscultation, with a diastolic murmur detected in only 6.3% of the patients who were found to have valvular disease on echocardiogram.

These findings support the value of screening echocardiogram in identifying patients who may benefit from endocarditis prophylaxis. In addition to valvular disease, the patients were also found to be significantly more likely than expected to have depressed left ventricular fractional shortening, regional wall motion abnormality, decreased left ventricular mass, and pericardial thickening, all of which also increased with increasing time from initial irradiation. The high prevalence of asymptomatic cardiac structural abnormalities requiring interventions noted with increasing follow-up time led to the authors' conclusion that screening echocardiography may be beneficial, particularly in those who have survived 10 years following mediastinal irradiation.

Irradiation to the upper mediastinum and low neck can result in thyroid abnormalities. An analysis of patients treated for Hodgkin's lymphoma at Stanford demonstrated that the 20-year actuarial risk of thyroid abnormality was 50% [35], with 90% of the cases being hypothyroidism. Fifty-seven percent of patients with primary hypothyroidism had subclinical disease detected by an elevated serum TSH level with a normal FT4 level. The greatest risk of hypothyroidism occurred during the first 5 years after treatment, but new cases continued to emerge beyond 20 years after Hodgkin's lymphoma. In a study by Sklar et al among pediatric Hodgkin's lymphoma survivors [36], risk factors for the development of hypothyroidism included increasing radiation dose, older age at diagnosis, and female gender.

Other late effects of Hodgkin's lymphoma treatment include pulmonary dysfunction, infertility, immunosuppression, fatigue, psychological distress, and social maladaptation [37-43]. Awareness of the potential consequences of treatment is necessary for physicians conducting patient follow-up to detect problems at the earliest possible time.

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