Complete Summary

GUIDELINE TITLE

Follow-up of Hodgkin´s disease.

BIBLIOGRAPHIC SOURCE(S)

Ng AK, Constine LS, Deming RL, Wolkov HB, Hoppe RT, Abrams RA, Mendenhall NP, Morris DE, Yahalom J, Chauvenet A, Hudson MM, Winter JN, Mauch PM, Expert Panel on Radiation Oncology-Hodgkin's Disease Work Group. Follow-up of Hodgkin's Disease. [online publication]. Reston (VA): American College of Radiology (ACR); 2005. 6 p. [43 references]

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previous version: Deming RL, Constine LS, Elman AJ, Hoppe RT, Mauch PM, Dosoretz DE, Pistenmaa DA, Prosnitz LR, Wolkov HB, Yahalom J, Chauvenet A, Connors JM, Glick JH, Leibel S. Follow-up of Hodgkin's disease. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1269-79.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Hodgkin's disease

- Complications of Hodgkin's disease

GUIDELINE CATEGORY

Evaluation
Management
Prevention

CLINICAL SPECIALTY

Oncology
Radiation Oncology
Radiology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide appropriate recommendations for the follow-up evaluation of patients after treatment for Hodgkin's disease

TARGET POPULATION

Patients (adolescent/young adult) with Hodgkin's disease who have completed their treatment and response assessment

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Management/Prevention

1. Interim history and physical exam
2. Radiographic tests
    - Chest x-ray (CXR)
    - Chest, abdomen, pelvic computed tomography (CT)
    - Positron emission tomography (PET)
    - Mammogram
3. Exercise tolerance test and echocardiogram
4. Laboratory tests
    - Complete blood count (CBC)
    - Erythrocyte sedimentation rate (ESR)
    - Chemistry panel (CHEM)
    - Thyroid panel
    - Lipid profile
5. Patient education and counseling

MAJOR OUTCOMES CONSIDERED

Utility of radiologic examination in the follow-up evaluation of Hodgkin's disease

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

The total number of source documents identified as the result of the literature search is not known.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table

and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Routine Follow-up Evaluation for Hodgkin's Disease after Completion of Treatment and Response Assessment

Variant 1: Adolescent/young adult, male or female, now without signs or symptoms, IIA supradiaphragmatic Hodgkin's Disease (HD), treated with combined chemo-radiation therapy (XRT).

Radiologic Exam Procedure	Appropriateness Rating	Comments

Radiologic Exam Procedure	Appropriateness Rating	Comments
History and Physical Examination Q2-4 months times 2 years. Then Q6 months times 3 years; then yearly for life	9	
CXR CXR 2-3 times per year times 5 years, then yearly	8	Unless chest computed tomography (CT) performed
Chest/Abdomen/Pelvic CT Q6 months times 2 years. Then yearly times 3 years	8	
PET	No Consensus	See summary of literature review
Screening Exercise Tolerance Test and Echocardiogram If symptomatic	9	
Periodic	8	Depending on mediastinal irradiation, adriamycin dose, and other risk factors
Mammogram Annual, beginning 8-10 years after treatment or by age 40	9	For females only
Chest CT for Lung Cancer Screening Annual, beginning 5 years after treatment	1	
Annual, beginning 5 years after treatment only if smoker	No Consensus	Studies are ongoing
Laboratory Tests CBC 1-2 times per year	8	

Radiologic Exam Procedure	Appropriateness Rating	Comments
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 periodically	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	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

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

Radiologic Exam Procedure	Appropriateness Rating	Comments
History and Physical Examination Q2-4 months times 2 years. Then Q6 months times 3 years then yearly for life	9	
CXR	8	At least once per year, unless chest

Radiologic Exam Procedure	Appropriateness Rating	Comments
CXR once a year		CT performed
Chest/Abdomen/Pelvic CT Once a year times 5 years	8	
PET	No Consensus	See summary of literature review
Screening Exercise Tolerance Test & Echocardiogram If symptomatic	9	
Periodic	8	Depending on mediastinal irradiation, adriamycin dose, and other risk factors.
Chest CT for Lung Cancer Screening Annual, beginning 5 years after treatment if received alkylating agent chemotherapy	1	
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	

Radiologic Exam Procedure	Appropriateness Rating	Comments
Smoking cessation if current smoker	9	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Routine follow-up evaluation of patients after treatment for Hodgkin's disease 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 disease remains the main cause of patient death during the first 10 to 15 years of follow-up. 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. 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, position 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 disease. In their review of early-stage Hodgkin's disease patients treated at Stanford, a study 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, a study 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. One study 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 disease. 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 disease 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. One study reviewed 101 patients who had been treated for Hodgkin's disease 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 on 60 patients, 10 of 46 patients with a negative re-staging gallium scan subsequently relapsed (negative predictive value [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 another study, 93 lymphoma patients (44 Hodgkin's disease [HD], 49 non-Hodgkin's lymphoma [NHL]) underwent PET scan as well as CT and ultrasound post therapy. Among the 44 Hodgkin's disease 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 disease, 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 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. In the series from Canada, 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 disease 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.

Breast cancers after Hodgkin's disease 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. Young age at irradiation (under 30 to 35) has been consistently shown to be a major risk factor. More recent data showed that the risk increases with increasing prior radiation dose to the breast tissue. 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. Mammography has been shown to be an effective tool for screening even among these young women. In one study , 81% of 37 women with breast cancer after Hodgkin's disease had mammographic abnormalities of a mass and/or microcalcifications. Another study prospectively evaluated the utility of mammogram in 90 female survivors of Hodgkin's disease. 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 disease, 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 populations, but it remains unproven in female survivors of Hodgkin's disease. The effectiveness of tamoxifen as chemoprevention has been demonstrated in other high-risk patients, but whether the data is applicable to women who survived Hodgkin's disease is unclear.

Lung cancer is another well-documented second malignancy after Hodgkin's disease. In addition to radiation therapy, prior chemotherapy exposure (alkylating agents in particular) significantly increases the lung cancer risk in a dose-dependent manner. Several studies showed that tobacco use further adds to the risk of lung cancer after Hodgkin's disease. In a case-control study, those who been treated with radiation therapy and alkylating agents had a seven-fold increased risk of lung cancer after Hodgkin's disease 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 disease is poor, with a median survival of only about a year. Given the significantly increased risk of lung cancer after Hodgkin's disease 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, but survivors of Hodgkin's disease 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 disease are at significantly increased risk of death from cardiac disease compared with the normal population.

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

The major contributor to the excess risk of cardiac mortality after Hodgkin's disease is coronary artery disease, accounting for two-thirds of all cases of fatal cardiac events in survivors of Hodgkin's disease. The main risk factor is

mediastinal irradiation, and a dose-response relationship has been shown. The presence of other traditional cardiac risk factors further increases the risk of cardiovascular disease after Hodgkin's disease. 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 disease. 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 disease underwent electrocardiography and echocardiography screening. 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 disease at Stanford demonstrated that the 20-year actuarial risk of thyroid abnormality was 50%, 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 disease. In a study among pediatric Hodgkin's disease survivors, risk factors for the development of hypothyroidism included increasing radiation dose, older age at diagnosis, and female gender.

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

Abbreviations

- CBC, complete blood count
- CT, computed tomography
- CXR, chest x-ray
- ESR, erythrocyte sedimentation rate
- PET, positron emission tomography
- Q, every

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate radiologic imaging procedures for follow-up evaluation of patients with Hodgkin's disease

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Ng AK, Constine LS, Deming RL, Wolkov HB, Hoppe RT, Abrams RA, Mendenhall NP, Morris DE, Yahalom J, Chauvenet A, Hudson MM, Winter JN, Mauch PM, Expert Panel on Radiation Oncology-Hodgkin's Disease Work Group. Follow-up of Hodgkin's Disease. [online publication]. Reston (VA): American College of Radiology (ACR); 2005. 6 p. [43 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 (revised 2005)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology--Hodgkin's Disease Work Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Andrea Ka-Min Ng, MD (*Review Author*); Louis S. Constine, MD (*Co-Author*); Richard L. Deming, MD (*Co-Author*); Harvey B. Wolkov, MD (*Co-Author*); Richard T. Hoppe, MD (*Hodgkin's Work Group Panel Chair*); Ross A. Abrams, MD ; Nancy P. Mendenhall, MD; David Eric Morris, MD; Joachim Yahalom, MD; Allen Chauvenet, MD; Melissa M. Hudson, MD; Jane N. Winter, MD; Peter M. Mauch, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previous version: Deming RL, Constine LS, Elman AJ, Hoppe RT, Mauch PM, Dosoretz DE, Pistenmaa DA, Prosnitz LR, Wolkov HB, Yahalom J, Chauvenet A, Connors JM, Glick JH, Leibel S. Follow-up of Hodgkin's disease. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1269-79.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable

Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 15, 2005. The updated information was verified by the guideline developer on January 19, 2006.

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