Complete Summary

GUIDELINE TITLE

Pediatric Hodgkin's disease.

BIBLIOGRAPHIC SOURCE(S)

Constine LS, Hoppe RT, Colman M, Deming RL, Mendenhall NP, Morris DE, Ng A, Wolkov HB, Yahalom J, Chauvenet AM, Hudson MM, Winter JN, Mauch PM, Expert Panel on Radiation Oncology-Hodgkin's Disease Work Group. Pediatric Hodgkin's disease. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 30 p. [131 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Constine LS, Wolkov HB, Yahalom J, Mauch PM, Deming RL, Dosoretz DE, Elman AJ, Hoppe RT, Pistenmaa DA, Prosnitz LR, Chauvenet A, Connors JM, Glick JH, Leibel S. Pediatric Hodgkin's disease. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1225-56.

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

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- January 24, 2008, Leukine (sargramostim): Voluntary market suspension of the current liquid formulation of sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), because of an upward trend in spontaneous reports of adverse reactions, including syncope (fainting). The lyophilized form of the drug is not affected. See the U.S. Food and Drug Administration (FDA) web site for more information.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
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SCOPE

DISEASE/CONDITION(S)

Hodgkin's disease

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Oncology
Pediatrics
Radiation Oncology
Radiology

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of radiologic treatment procedures for pediatric patients with Hodgkin's disease

TARGET POPULATION

Children with Hodgkin's disease

INTERVENTIONS AND PRACTICES CONSIDERED

1. Chemotherapy, including consideration of type and duration
2. Radiation therapy, including consideration of volume and therapy dose
3. Combination of chemotherapy and radiation therapy

4. Observation only

MAJOR OUTCOMES CONSIDERED

Overall, relapse-free, and event-free survival rate

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 stated

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: Pediatric Hodgkin's Disease

Variant 1: 12-year-old boy with CS IA (cervical) NSHD. Patient is Tanner 3.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	8	
Alone	4	
Chemotherapy Type		
ABVD	8	
OPPA (females); OEPA (males)	8	
VAMP	8	
OPPA/COPP or OEPA/COPP	4	
COPP/ABV hybrid	4	
COPP/ABVD alternating	4	
Chemotherapy Duration		
2 cycles	5	
3-4 cycles	8	
5-6 cycles	4	
>6 cycles	1	
Radiation Therapy (RT)		
Alone	1	
Chemo and radiation	8	
Radiation Volume		
Involved lymph node	2	
Involved field (nodal chain)	8	
Involved field + adjacent site(s)	4	

Treatment	Appropriateness Rating	Comments
Mantle	2	
Mantle + para-aortic/spleen	1	
Mantle + para-aortic/spleen + pelvis	1	
Radiation Therapy Dose		
15-20 Gy	7	
21-25 Gy	8	
26-30 Gy	4	
31-35 Gy	2	
36-40 Gy	1	
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: 6-year-old girl with CS IIA MCHD, three sites including mediastinum and bilateral neck, no bulk disease.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	7	
Alone	6	
Chemotherapy Type		
ABVD	8	
OPPA (females); OEPA (males)	7	
VAMP	8	
OPPA/COPP or OEPA/COPP	6	

Treatment	Appropriateness Rating	Comments
COPP/ABV hybrid	5	
COPP/ABVD alternating	5	
Chemotherapy Duration		
2 cycles	5	
3-4 cycles	8	
5-6 cycles	5	
>6 cycles	2	
Radiation Therapy (RT)		
Alone	1	
Chemo and radiation	7	
Radiation Volume		
Involved lymph nodes	2	
Involved field (nodal chain)	8	
Involved field + adjacent site(s)	3	
Mantle	2	
Mantle + para-aortic/spleen	1	
Mantle + para-aortic/spleen + pelvis	1	
Radiation Therapy Dose		
15-20 Gy	7	
21-25 Gy	8	
26-30 Gy	4	
31-35 Gy	2	
36-40 Gy	1	
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 3: 12-year-old girl with CS IA (left cervical) LPHD. Node has been excised. Patient is Tanner 3.

Treatment	Appropriateness Rating	Comments
Observation only (no chemo or RT)	5	
Chemotherapy (CT)		
Chemo and radiation therapy	7	
Alone	4	
Chemotherapy Type		
ABVD	7	
OPPA (females); OEPA (males)	7	
VAMP	8	
OPPA/COPP or OEPA/COPP	3	
COPP/ABV hybrid	2	
COPP/ABVD alternating	2	
Chemotherapy Duration		
2 cycles	7	
3-4 cycles	8	
5-6 cycles	2	
>6 cycles	1	
Radiation Therapy (RT)		
Alone	4	
Chemo and radiation	7	
Radiation Volume		
Involved lymph nodes	2	

Treatment	Appropriateness Rating	Comments
Involved field (nodal chain)	8	
Involved field + adjacent site(s)	4	
Mantle	1	
Mantle + para-aortic/spleen	1	
Mantle + para-aortic/spleen + pelvis	1	
Radiation Therapy Dose		
15-20 Gy	6	
21-25 Gy	8	
26-30 Gy	4	
31-35 Gy	2	
36-40 Gy	1	
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 4: 7-year-old boy with CS IIA LPHD isolated to the right iliac and inguinal nodes.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	8	
Alone	4	
Chemotherapy Type		
ABVD	7	
OPPA (females); OEPA	7	

Treatment	Appropriateness Rating	Comments
(males)		
VAMP	8	
COPP/ABV hybrid	2	
COPP/ABVD alternating	2	
Chemotherapy Duration		
2 cycles	7	
3-4 cycles	8	
5-6 cycles	2	
>6 cycles	1	
Radiation Volume		
Involved field	8	
Involved field + adjacent site(s) (para-aortic)	4	
Mantle + para-aortic/spleen + pelvis	1	
Pelvis	2	
Radiation Therapy Dose		
15-20 Gy	7	
21-25 Gy	7	
26-30 Gy	3	
31-35 Gy	2	
36-40 Gy	1	
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 5: 8-year-old boy with CS IIIA (neck, mediastinum, para-aortic) NSHD, no bulk disease.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	8	
Alone	6	
Chemotherapy Type		
ABVD	7	
OPPA (females); OEPA (males)	4	
VAMP	1	
COPP/ABV hybrid	6	
COPP/ABVD alternating	6	
Chemotherapy Duration		
2 cycles	2	
3-4 cycles	8	
5-6 cycles	7	
>6 cycles	2	
Radiation Volume		
Involved field	8	
Involved field + adjacent site(s)	4	
Mantle	1	
Mantle + para-aortic/spleen	2	
Mantle + para-aortic/spleen + pelvis	1	
Radiation Therapy Dose		
15-20 Gy	6	
21-25 Gy	8	
26-30 Gy	3	

Treatment	Appropriateness Rating	Comments
31-35 Gy	2	
36-40 Gy	1	
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 6: 3-year-old boy with CS IIIB (supraclavicular, mediastinum, para-aortic + splenomegaly) MCHD.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	6	
Alone	8	
Chemotherapy Type		
ABVD	4	
OPPA/COPP (females); OEPA/COPP (males)	3	
COPP/ABV hybrid	7	
COPP/ABVD alternating	7	
VAMP	1	
Chemotherapy Duration		
2 cycles	2	
3-4 cycles	5	
5-6 cycles	8	
>6 cycles	2	
Radiation Volume		
Involved field	8	

Treatment	Appropriateness Rating	Comments
Involved field + adjacent site(s)	1	
Mantle	1	
Mantle + para-aortic/spleen	1	
Mantle + para-aortic/spleen + pelvis	1	
Radiation Therapy Dose		
15-20 Gy	8	
21-25 Gy	6	
26-30 Gy	2	
31-35 Gy	1	
36-40 Gy	1	
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 7: 10-year-old girl with CS IIIB, MCHD with large mediastinal mass.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	8	
Alone	3	
Chemotherapy Type		
ABVD	4	
OPPA/COPP (females); OEPA/COPP (males)	3	
COPP/ABV hybrid	7	

Treatment	Appropriateness Rating	Comments
COPP/ABVD alternating	7	
VAMP	1	
Chemotherapy Duration		
2 cycles	1	
3-4 cycles	6	
5-6 cycles	8	
>6 cycles	2	
Radiation Volume		
Involved field	8	
Involved field + adjacent site(s)	4	
Radiation Therapy Dose		
15-20 Gy	5	
21-25 Gy	8	
26-30 Gy	4	
31-35 Gy	2	
36-40 Gy	1	
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 8: 7-year-old boy with CS IVB NSHD including pulmonary nodules and enlarged liver with focal defects. No bulk disease.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	7	

Treatment	Appropriateness Rating	Comments
Alone	6	
Chemotherapy Type		
ABVD	4	
OPPA/COPP (females); OEPA/COPP (males)	3	
COPP/ABV hybrid	7	
COPP/ABVD alternating	7	
VAMP	1	
Chemotherapy Duration		
2 cycles	1	
3-4 cycles	4	
5-6 cycles	8	
>6 cycles	3	
Radiation Volume		
Involved field	7	
Involved field + adjacent site(s)	1	
Radiation Therapy Dose		
10-15 Gy	8	
15-20 Gy	1	
21-25 Gy	1	
26-30 Gy	1	
31-35 Gy	1	
36-40 Gy	1	
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 9: 5-year-old girl with CS IVA MCHD with large mediastinal mass and positive BM.

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	8	
Alone	4	
Chemotherapy Type		
ABVD	4	
OPPA/COPP (females); OEPA/COPP (males)	3	
COPP/ABV hybrid	7	
COPP/ABVD alternating	7	
VAMP	1	
Chemotherapy Duration		
2 cycles	1	
3-4 cycles	4	
5-6 cycles	8	
>6 cycles	3	
Radiation Volume		
Involved field	7	
Involved field + adjacent site(s)	1	
Radiation Therapy Dose		
15-20 Gy	5	
21-25 Gy	8	
26-30 Gy	4	
31-35 Gy	2	
36-40 Gy	1	

Treatment	Appropriateness Rating	Comments
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 10: 16-year-old boy with CS IIA NSHD with small mediastinal mass.*

(*If fully grown, appropriateness criteria guidelines for early stage favorable disease in adults are appropriate.)

Treatment	Appropriateness Rating	Comments
Chemotherapy (CT)		
Chemo and radiation therapy	8	
Alone	4	
Chemotherapy Type		
ABVD	8	
OPPA (females); OEPA (males)	7	
VAMP	8	
COPP/ABV hybrid	4	
COPP/ABVD alternating	4	
Chemotherapy Duration		
2 cycles	6	
3-4 cycles	8	
5-6 cycles	3	
>6 cycles	1	
Radiation Volume		
Involved field	8	

Treatment	Appropriateness Rating	Comments
Involved field + adjacent site(s)	5	
Mantle	2	
Mantle + para-aortic spleen	1	
Mantle + para-aortic spleen + pelvis	1	
Radiation Therapy Dose		
15-20 Gy	6	
21-25 Gy	8	
26-30 Gy	6	
31-35 Gy	4	
36-40 Gy	1	
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.

The biology and natural history of Hodgkin's disease (HD) in children are similar to these in adults, but irradiation techniques and doses suitable for controlling disease in adults produce substantial morbidities (primarily musculoskeletal growth inhibition) in children. A desire to reduce morbidity motivated the development of new strategies for treating pediatric HD. Historically, children were thought to have a worse prognosis than adults. It is now apparent that the converse is true.

Please see the original guideline document for information about epidemiology, clinical presentation, pathologic classification, staging, diagnostic evaluation, and prognostic factors.

Selection of Therapy

HD is one of the pediatric malignancies that has an adult counterpart with a similar natural history and biology. Devising the optimal therapeutic approach for children with this disease is complicated by their increased risk of adverse effects. In particular, radiotherapy doses and fields used in adults can cause profound musculoskeletal retardation, including intraclavicular narrowing, shortened sitting height, decreased mandibular growth, and decreased muscle development in the

treated volume. Therefore, while adults with early stage HD may be treated with full dose radiation as a single modality, this approach in prepubertal children, despite a similar success rate, produces unacceptable sequelae. Further complicating the treatment of children are gender-specific differences in chemotherapy-induced gonadal injury.

The desire to cure young children with minimal side effects has stimulated attempts to reduce staging procedures, the intensity and types of chemotherapy, and the radiation dose and volume. Because of the differences in the age-related developmental status of children, and the gender-related sensitivity to chemotherapy, there is no single method of treatment that is ideal for all pediatric patients. In general, the use of radiation and chemotherapy broadens the spectrum of potential toxicities, while reducing the severity of individual (drug or radiation-related) toxicities. Current approaches, to be discussed subsequently, entail chemotherapy alone and in conjunction with reduced radiation doses. The volume of radiation and the intensity and duration of chemotherapy are risk-adapted or determined by prognostic factors at presentation, including presence of constitutional symptoms, disease stage, and bulk. Results for patients with early and favorable and advanced and unfavorable HD are summarized in Tables 3 and 4 in the original guideline document, and therapeutic recommendations are outlined in the Table, below.

Combination Chemotherapy

Chemotherapy with mechlorethamine, oncovin, procarbazine, and prednisolone (MOPP) was the standard regimen used in the United States for many years. The major toxicities include an associated risk of acute myeloid leukemia, azoospermia in more than 90% of males treated at any age, and a risk of sterility in females, which increases with age. Subsequently, the effectiveness of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line chemotherapy was established. Compared to MOPP, second malignancies and sterility were less common. The predominant adverse effects of ABVD are pulmonary toxicity related to bleomycin and cardiovascular toxicity secondary to adriamycin. These side effects may be exacerbated by the addition of mediastinal or mantle irradiation. Consequently, ABVD and MOPP were combined with the aim of improving disease control and reducing the risk of leukemogenesis and sterility related to the alkylating agents in the MOPP regimen. This alternating combination proved to be more effective than MOPP chemotherapy alone. Its use in pediatric patients also diminished the risk of cardiopulmonary dysfunction predisposed by the anthracycline and bleomycin in the ABVD regimen. Over the years, the MOPP and ABVD regimens underwent a variety of modifications, but the majority of the chemotherapeutic regimens used today are derived from these two combinations.

Combined Modality versus Chemotherapy Alone

The arguments that favor treatment with chemotherapy alone for all stages propose that this treatment approach eliminates the need for surgical staging and avoids the dysmorphic and carcinogenic consequences of irradiation. The disadvantages of the use of chemotherapy alone are the risks of treatment-related fatality, cardiopulmonary toxicity, infertility, and leukemogenesis due to the higher cumulative doses of anthracyclines, alkylating agents, and bleomycin, as well as an increased likelihood of disease recurrence in sites of bulk disease.

Generalization of treatment outcomes after these trials has been limited because most studies include small numbers of patients assigned to treatments in a nonrandom fashion. Also, long-term follow-up related to disease control and late treatment sequelae have not been reported.

Early chemotherapy trials used MOPP or similar regimens derived from MOPP and prescribed 6–12 months of chemotherapy. The longest follow-up data are from the Uganda experience, with only a 67% 9-year survival rate. Subgroups included CS I to IIIA patients with a 75% survival rate, and CS IIIB to IV patients with 60% and 47% survival rates at 5 and 10 years, respectively. One study reported a 90% 5-year survival rate for CS I to II children treated with MOPP or a similar program that substitutes chlorambucil for nitrogen mustard and vinblastine for vincristine (ChlVPP) (see Table 3 in the original guideline document), but the disease-free and overall survival rates were 40% and 55%, respectively, for children with advanced disease. A report from the Netherlands describes 37 children treated with 6 cycles of MOPP for "small" lymph node disease (defined as less than or equal to 4 cm or smaller), with the addition of 25 Gy involved-field radiation therapy for children with "large" lymph node disease. The disease-free survival with a median follow-up of 62+ months were 90% for the former (21 children) and 85.5% for the latter (16 children).

In an effort to avoid treatment complications associated with alkylating agent chemotherapy, contemporary chemotherapy alone trials have alternated MOPP-type regimens with ABVD or similar derivatives (MOPP/ABVD, COPP-ABV hybrid, CVPP/EBO) or by using combinations without alkylating agents (ABVD, VEEP, EVAP/ABV). Across all stages, event-free survival rates after treatment with 6-12 months of alternating MOPP/ABVD chemotherapy alone ranged from 77% at 4 years to 91% at 10 years; several of these investigations required pathologic staging to confirm eligibility for reduced therapy. Across all stages, event-free survival rates after treatment with 6-12 months of alternating MOPP/ABVD chemotherapy alone ranged from 77% at 4 years to 91% at 10 years; several of these investigations required pathologic staging to confirm eligibility for reduced therapy. Nicaraguan investigators used 8-10 cycles COPP-ABV hybrid chemotherapy alone in clinically staged patients; 3-year event-free survival rates were 100% for the 25 patients with stages I, II, IIIA, but only 74.9% for the 23 patients with stages IIIB or IV. Similarly, Costa Rican investigators observed inferior outcomes for stage IV patients treated with 12 months of cyclophosphamide, vincristine, procarbazine, and prednisone (CVPP) and epirubicin, bleomycin, and Oncovin (EBO) chemotherapy (60% 5-year relapse-free survival rate). The use of ABVD or ABVD-derivative chemotherapy combinations produced unsatisfactory outcomes in advanced stage patients treated with 6 cycles of ABVD chemotherapy alone (71% 8-year disease-free survival rate) and 5-6 cycles of vincristine, etoposide, epirubicin, and prednisolone (VEEP) chemotherapy alone (78% 5-year disease-free survival rate).

Only 3 randomized controlled trials have prospectively evaluated chemotherapy alone versus combined modality therapy in children and adolescents with HD. The Children's Cancer Group compared 12 cycles of alternating MOPP/ABVD to 6 cycles of ABVD plus low-dose (21 Gy) radiation. The trend in event-free and overall survival rates suggested a survival advantage for the combined modality group (90% 4-year event-free survival rate) over the chemotherapy alone group (84% 4-year event-free survival rate), but this difference was not statistically

significant (Figures 1A and 1B in the original guideline document). The Pediatric Oncology Group evaluated the benefit of adding low-dose radiation to 4 cycles each of MOPP and ABVD (Table 4 in the original guideline document), the addition of radiation therapy did not improve disease-free or overall survival rates. However, statistical and quality assurance issues complicate interpretation of these data. Long term follow-up will be necessary to assess the toxicity from these 2 trials, but cardiopulmonary and neoplastic sequelae were observed in early follow-up and could potentially increase due to the cumulative doses of alkylating agent chemotherapy, anthracyclines, and bleomycin.

In a recent Children's Cancer Group trial, chemotherapy alone using the COPP/ABV hybrid regimen was compared to combined modality therapy, including low-dose, involved-field radiation. Treatment assignment was risk-adapted based on the presence of clinical features, including the presence of "B" symptoms, hilar adenopathy, mediastinal and peripheral lymph node bulk, and the number of involved nodal regions. Patients with favorable disease presentations received 4 cycles of COPP/ABV; those with unfavorable risk features received 6 cycles of COPP/ABV. Stage IV patients received sequential cycles of high-dose cytarabine and etoposide, COPP/ABV, and cyclophosphamide, vincristine, doxorubicin, and methylprednisolone. Patients achieving a complete response to chemotherapy were eligible for randomization to receive low-dose, involved-field radiation or no further therapy. The trial was prematurely terminated because of results indicating a significantly higher number of relapses among patients treated with chemotherapy alone. The 3-year event-free survival estimates according to patient randomization were 92% for patients treated with combined modality therapy and 87% for those treated with chemotherapy alone; the benefit of involved-field radiation therapy remained significant in the "as treated" analysis. The difference was most marked in stage IV patients who had a 90% event-free survival rate if randomized to receive involved-field radiation compared to 81% in those randomized to receive chemotherapy alone. Due to successful salvage therapy after relapse, estimates of overall survival rates are not different between the randomized groups in early follow-up. However, other investigations of long-term outcomes after treatment for pediatric HD implicate retrieval therapy after relapse as a significant risk factor for neoplastic complications and early mortality. Finally, in the German GPOG-HD 95 trial, the relapse-free survival rate was superior for patients treated with RT after partial response (93%) than for those without RT after CR (89%). The difference was significant for patients treated for advanced stage but not early stage disease.

In summary, numerous investigations have confirmed that chemotherapy alone is an effective treatment approach for pediatric HD. However, the higher cumulative doses used in these protocols predispose survivors to greater risks of acute and late toxicity associated with alkylating agents, anthracyclines, and bleomycin. Conversely, these protocols avoid radiation-associated treatment complications, including musculoskeletal growth impairment, cardiopulmonary dysfunction, and solid tumor carcinogenesis. Current information suggests that children with advanced and unfavorable symptomatic or bulky disease at presentation have better outcomes using a combined modality approach. Identification of the prognostic features of patients who require radiation to optimize disease control is a focus of many ongoing pediatric trials.

Risk-Adapted Therapy

Numerous investigations published in the 1990s supported the use of a risk-adapted treatment assignment based on clinical features at disease presentation. Parameters have varied according to individual studies, but those most frequently used in risk assessments include the presence of "B" symptoms, mediastinal and peripheral lymph node bulk, extranodal extension of disease to contiguous structures, hilar lymph node involvement, number of involved nodal regions and Ann Arbor stage. These studies uniformly evaluated treatment outcomes using a reduced number of multi-agent chemotherapy cycles in clinically staged patients with favorable clinical presentation. Novel treatment approaches have been explored in patients with intermediate and high risk features in an effort to improve long-term disease control and reduce late therapy-related complications. The results of these studies are summarized in Tables 3 and 4 in the original guideline document.

Treatment of Early Stage Disease

Early stage disease may present with favorable or unfavorable features. A favorable clinical presentation is typically defined as localized (stage I/II) nodal involvement in the absence of "B" symptoms and nodal bulk. Mediastinal lymphadenopathy is designated as bulky when the ratio of the maximum measurement of the mediastinal lymphadenopathy to that of the intrathoracic cavity on upright chest radiograph is 33% or more. The criterion for peripheral lymph node bulk has varied across studies from 4 to 10 cm. The presence of extranodal extension to contiguous sites, hilar lymphadenopathy, or involvement of more than 3 to 4 nodal regions typically moves the patient into an intermediate or high risk group. Children and adolescents with early stage/favorable presentations of HD are excellent candidates for reduced therapy. Several multiagent regimens have proved effective, including MOPP/ABVD, OPPA or OEPA/COPP, COPP/ABV hybrid, and a variety of non-alkylator regimens such as ABVD, OEPA, VAMP, VBVP, and DBVE (Table 3 in the original guideline document). Treatment for patients with a favorable clinical presentation typically involves 2 to 4 cycles of chemotherapy and low-dose, involved-field radiation. In some regimens, the dose of radiation has been reduced based on a favorable response to chemotherapy.

The German Pediatric Oncology Group (GBOG) pioneered the use of risk- and gender-adapted therapy featuring the OPPA regimen. Following demonstration of the efficacy of 2 cycles of OPPA chemotherapy in combination with 35 Gy involved field radiation in patients with favorable clinical presentations, the regimen was modified to OEPA for boys and the radiation dose reduced to 25 Gy for boys and girls achieving a sufficient remission after 2 cycles of OEPA or OPPA chemotherapy. The current German Pediatric Oncology Group HD-95 trial is evaluating if radiation therapy can be omitted in patients achieving a complete response to chemotherapy. Early results (median follow-up time of 38 months) indicate a 94% event-free survival rate for favorable risk patients and no difference in outcome in favorable patients treated with chemotherapy alone versus combined modality therapy. Notably, bulky lymphadenopathy is not used in the GPOG risk assessment as bulk has not influenced outcome in the German trials, which prescribe a 5-10 Gy boost in cases with an insufficient remission following chemotherapy.

French investigators initially determined that treatment outcomes were not compromised in patients with early/favorable clinical presentations who had therapy reduced to 4 cycles of chemotherapy (2 MOPP/2 ABVD or 4 ABVD) plus 20 Gy involved-field radiation. Their next trial evaluated a novel regimen without alkylators or anthracyclines, VBVP (etoposide, bleomycin, vinblastine, and prednisone), which produced a 91% 5-year event-free survival rate in patients achieving a good response following 4 cycles of chemotherapy and 20 Gy to involved fields. Similarly, Italian investigators demonstrated comparable outcomes (91% 7-year freedom from progression) using reduced therapy with 3 cycles of ABVD and 20 Gy involved-field radiation.

Several North American investigators have likewise observed excellent treatment results in combined modality trials for favorable risk HD. Pediatric Hodgkin's consortium investigators from Stanford, St. Jude, and Dana Farber recently reported treatment results using a novel non-alkylator regimen, VAMP for children with clinical I/II, non-bulky HD. Patients received 4 cycles of VAMP chemotherapy and involved-field radiation; the radiation dose was determined by early response after 2 cycles of chemotherapy. Patients achieving a complete response received 15 Gy, and those achieving a partial response received 25.5 Gy. At a median follow-up of 5.6 years (range 1.1-10.4 years) the 5-year event-free survival rate was 93%. Very good early treatment results have also been observed by Pediatric Oncology Group investigators using response-based DBVE (doxorubicin, bleomycin, vincristine, and etoposide) chemotherapy and low-dose, involved-field 25.5 Gy radiation. The two-year event-free survival rate for the entire cohort was 91%, with 93% event-free survival for rapid early responders treated with 2 cycles of DBVE and 89% event-free survival for slower responders treated with 4 cycles of DBVE.

Treatment of Advanced and Unfavorable Disease

In risk-adapted treatment regimens, early disease presenting with unfavorable features are sometimes treated similarly to advanced stage disease. Alternatively, an intermediate designation is given in some risk categorizations to patients with localized (stage IA, IIA) disease presentations that have one or more of the unfavorable features and to patients with stage IIIA disease. For example, the German Pediatric Oncology Group studies prescribe 4 cycles of chemotherapy (2 OPPA or 2 OEPA and 2 COPP) for patients with intermediate risk (designated as stage II_EA, IIB, IIIA) and 6 cycles (2 OPPA or 2 OEPA and 4 COPP) for patients with unfavorable and advanced disease. The criteria for unfavorable clinical presentations vary per investigation, but typically include the presence of "B" symptoms, bulky lymphadenopathy, hilar lymphadenopathy, involvement of 3 or more nodal regions, extranodal extension to contiguous structures, or advanced stage (IIIB-IV). Chemotherapy used for this group includes MOPP and ABVD or derivative combinations that incorporate etoposide in many cases. As illustrated in Table 4 in the original guideline document, radiation therapy for unfavorable and advanced HD is variable and protocol dependent. Although involved-field radiotherapy remains the standard in patients treated with combined modality therapy, restricting RT to areas of initial bulk disease (generally defined as 5 cm or more at the time of disease presentation), or post-chemotherapy residual disease (generally defined as 2 cm or more, or residual PET avidity), is under investigation.

Two primary treatment approaches have been used for patients with unfavorable and advanced disease presentations. A conventional treatment approach prescribes chemotherapy on a twice-monthly schedule for 6–8 months. An alternative strategy compacts treatment administration into 3–5 months to enhance dose intensity and reduce the risk of developing resistant disease. This is accomplished by alternating myelosuppressive and non-myelosuppressive agents in a weekly schedule and using colony stimulating factor to support neutrophil recovery. A summary of treatment results of published trials is provided in Table 4 in the original guideline document, which demonstrates event-free survival rates ranging from 70%-90%. Long-term follow-up is not yet available to determine if the abbreviated, dose-intensive treatment approach is superior to conventional treatment in maintaining disease control.

Radiotherapeutic Management

The curability of pediatric HD, the complexity of current treatment approaches, and the vulnerability of the developing child to both radiation and chemotherapy require the involved radiation oncologist to thoroughly understand the role of radiation and to deliver it with skill. Most newly diagnosed children will be treated with risk-adapted chemotherapy alone or with combined-modality therapy including low-dose, involved-field radiation. In the past, fully grown adolescents with favorable early stage disease were considered for full-dose extended field radiation therapy, using techniques that are standard for adults. This approach has been abandoned due to concerns primarily relating to cardiac toxicity and second malignant neoplasms.

Meticulous and judiciously designed fields are necessary for maximum success in terms of both disease control and normal tissue damage. The definitions of such fields depend on the anatomy of the region in terms of lymph node distribution, patterns of disease extension into regional areas, and consideration for match line problems should disease recur. Involved fields typically should include not just the identifiably abnormal lymph nodes but the entire lymph node region containing the involved nodes (Table 5 in the original guideline document). The traditional definitions of lymph node regions can be helpful but are not necessarily sufficient. For example, the cervical and supraclavicular lymph nodes are generally treated when abnormal nodes are located anywhere within this area; this is consistent with the anatomic definition of lymph node regions used for staging purposes. However, the hila are irradiated when the mediastinum is involved, despite the fact that the hila and mediastinum are separate lymph node regions. Similarly, the supraclavicular (SCV) is often treated when the axilla or the mediastinum is involved, and the ipsilateral external iliac nodes are often treated when the inguinal nodes are involved. However, in both these situations care must be taken to shield relevant normal tissues to the degree possible, such as the breast in the former situation and ovaries in the latter. Moreover, a decision to treat the axilla or mediastinum without the SCV, and the inguinal nodes without the iliacs, might be appropriate depending on the size and distribution of involved nodes at presentation. Field definitions are often protocol specific, but excessively small fields are usually inappropriate. In a very young child (under 5 years of age), consideration may be given to treating bilateral areas (e.g., both sides of the neck) to avoid growth asymmetry. However, this is less of a concern with low radiation doses, and thus unilateral fields are usually appropriate if the disease is unilateral.

Efforts to exclude unnecessary normal tissues, (e.g., breast tissue) are always important in a child with isolated mediastinal disease and no axillary involvement. Treatment of involved supradiaphragmatic fields or a mantle field requires precision because of the distribution of lymph nodes and the critical adjacent normal tissues. These fields can be simulated with the arms up over the head, or down with hands on the hips. The former pulls the axillary lymph nodes away from the lungs, allowing greater lung shielding. However, the axillary lymph nodes then move into the vicinity of the humeral heads, which should be blocked in growing children. Thus the position chosen involves weighing concerns regarding lymph nodes, lung, and humeral heads. Attempts should be made to exclude breast tissue or position it under the lung/axillary blocking. When the decision is made to include some or all of a critical organ in the radiation field, such as liver, kidney, or heart, then normal tissue constraints, depending on the chemotherapy used and patient age, are critical.

The most effective sequence of therapy in the setting of combined chemotherapy and irradiation is not unequivocally established. However, chemotherapy is usually the first modality. This allows assessment of drug response, maximization of the amount of drug treatment as well as shrinkage of disease, and more limited fields of irradiation. Occasionally, focal irradiation prior to chemotherapy will be necessary because of airway obstruction. Since most children are treated in institutional (or multi-institutional) studies, the radiation oncologist should confirm all aspects of the diagnostic workup and staging and must also understand study requirements in order to deliver appropriate radiation.

Summary Recommendations for Primary Disease

Optimal treatment planning involves a multidisciplinary approach beginning at diagnosis. This is best accomplished if the pediatric and radiation oncologist can meet to review staging studies following examination of the patient. The treatment approach should consider host factors such as age and gender that may enhance the risk of specific treatment complications, as well as disease factors (e. g., presence of "B" symptoms), bulky lymphadenopathy, and stage, and others discussed above. Recommended treatment approaches for favorable localized, intermediate, and advanced unfavorable disease presentations are summarized in the Table below.

See the original guideline document for a discussion of treatment for refractory and relapsed disease.

Table. Recommendations for Treatment Approach in Pediatric Hodgkin's Disease

Clinical Presentation	Stage	Recommended treatment approach
Early/favorable: Localized disease involving <3-4 nodal regions in absence of B symptoms, bulk, or extranodal extension	IA, IIA	**Recommended therapy**: 2-4 cycles non-cross-resistant chemotherapy without alkylators (ABVD or derivative) plus low-dose, involved field radiation (1500 cGy-2550 cGy)

Clinical Presentation	Stage	Recommended treatment approach
		Other considerations: 6 cycles non-cross-resistant chemotherapy alone (alternating COPP and ABVD or derivative) **In clinical trial setting only**: 4 cycles of chemotherapy alone
Localized unfavorable/intermediate: Localized disease involving ≥3-4 nodal regions in presence of bulky lymphadenopathy (mediastinal ratio ≥33%; lymph node mass ≥6-10 cm).	IA, IIAI IB* IIIA	**Recommended therapy**: 4-6 cycles (3-5 compacted, dose-intensive cycles) non-cross-resistant chemotherapy (alternating COPP and ABVD or derivative ± etoposide) plus low-dose, involved-field radiation (1500 cGy-2550 cGy). **Other considerations**: 6-8 cycles (5 compacted, dose-intensive) non-cross-resistant chemotherapy alone (alternating COPP and ABVD or derivative ± etoposide).
Advanced/unfavorable: Stage II patients with constitutional symptoms of fever or weight loss and any patient with advanced stage	IIB* IIIB IV	**Recommended therapy**: 6-8 cycles (5-6 compacted, dose-intensive cycles) of non-cross-resistant chemotherapy (alternating COPP and ABVD or derivative ± etoposide) plus low-dose, involved-field radiation (organs 1000-1500 cGy, nodes 1500 cGy-2550 cGy). **Other considerations** 8 cycles (6-7 compacted, dose-intensive cycles) non-cross-resistant chemotherapy alone (alternating COPP and ABVD or derivative ± etoposide).

*Stage IIB patients have been variably treated as intermediate or unfavorable risk. Some studies use associated factors, e.g., weight loss, bulk disease, extranodal extension, for further risk stratification.

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

Abbreviations

- ABV, Adriamycin, bleomycin, and vinblastine
- ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine
- BM, bone marrow
- CS, clinical stage
- COPP, cyclophosphamide, oncovin, prednisone, and procarbazine
- LPHD, lymphocyte-predominant Hodgkin's disease
- MCHD, mixed-cellularity Hodgkin's disease

- NSHD, nodular sclerosis Hodgkin's disease
- OEPA, Oncovin, etoposide, prednisone, and Adriamycin
- OPPA, Oncovin, procarbazine, prednisone, and Adriamycin
- VAMP, vinblastine, adriamycin, methotrexate, and prednisone

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 treatment for the management of pediatric Hodgkin's disease

POTENTIAL HARMS

- Use of *chemotherapy alone* is associated with the risks of treatment-related fatality, cardiopulmonary toxicity, infertility, and leukemogenesis due to the higher cumulative doses of anthracyclines, alkylating agents, and bleomycin, as well as an increased likelihood of disease recurrence in sites of bulk disease.
- *Radiation treatment* is associated with musculoskeletal growth impairment, cardiopulmonary dysfunction, and solid tumor carcinogenesis
- In general, the use or *radiation and chemotherapy* broadens the spectrum of potential toxicities, while reducing the severity of individual (drug or radiation-related) toxicities.

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

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Constine LS, Hoppe RT, Colman M, Deming RL, Mendenhall NP, Morris DE, Ng A, Wolkov HB, Yahalom J, Chauvenet AM, Hudson MM, Winter JN, Mauch PM, Expert Panel on Radiation Oncology-Hodgkin's Disease Work Group. Pediatric Hodgkin's disease. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 30 p. [131 references]

ADAPTATION

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

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1999 (revised 2006)

GUIDELINE DEVELOPER(S)

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GUIDELINE COMMITTEE

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

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Louis S. Constine, MD; Richard T. Hoppe, MD; Martin Colman, MD; Richard L. Deming, MD; Nancy P. Mendenhall, MD; David Eric Morris, MD; Andrea Ng, MD; Harvey B. Wolkov, MD; Joachim Yahalom, MD; Allen R. 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.

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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.

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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 August 28, 2006. This summary was updated by ECRI Institute on February 26, 2008 following the U.S. Food and Drug Administration advisory/voluntary market withdrawal of the liquid formulation of Leukine (sargramostim).

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