



A Cancer Journal for Clinicians

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CA Cancer J Clin 1975;25:306-319

DOI: 10.3322/canjclin.25.6.306

This information is current as of May 14, 2010

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Hodgkin's Disease: Current Recommendations for Management

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Since 1962, we have conducted a series of controlled clinical trials at Stanford University Medical Center aimed at optimizing the treatment of Hodgkin's disease. Design, eligibility criteria and interim results have been previously reported.¹⁻³ These and other clinical studies will undoubtedly continue to provide substantial additional information as more cases are accrued and observed for longer follow-up periods. However, the fact that certain aspects of treatment are in a state of flux creates difficulties for the practicing physician called on to manage a patient with Hodgkin's disease. This article sets forth a distillation of our current views concerning optimal management in relation to site(s) and stage of disease, constitutional symptoms and histopathology, both for the previously untreated patient and also for the previously treated, relapsing patient who poses a much more difficult problem. In most instances, recom-

mendations are based on the results of our clinical trials, but in some situations where definitive data are not yet available, we have relied on our best clinical judgment at this time.

Diagnostic Evaluation

Nearly 10 years of field testing have provided convincing evidence that the Rye histopathological classification does indeed correlate well with prognosis.⁴ Although most cases can be readily classified among the four categories described in Table 1, approximately 15 percent of patients present with features that make classification difficult; when therapeutic management depends on the outcome, consultation, preferably with hematopathologists, should be sought.

Although it is usually both feasible and desirable to complete the diagnostic workup (Table 2.) before undertaking treatment, not infrequently a modified approach is indicated.⁵ For example, the patient with massive mediastinal and/or hilar lymphadenopathy is *not* a good candidate for either lymphangiography or staging laparotomy until the thoracic lymph node masses have been appreciably reduced in size. This is accomplished by first delivering part of the planned course of mantle field radiotherapy (1500-2000 rads in two-two and a half weeks) and then performing the lymphangiogram and staging laparotomy during a planned 10-14 day interruption of treatment. The final treatment

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Presented in part at the American Cancer Society/National Cancer Institute's National Conference on Advances in Cancer Management, Part I: Treatment and Rehabilitation, New York City, November 25-27, 1974.

Adapted from: Kaplan, H.S., and Rosenberg, S.A.: The management of Hodgkin's disease. *Cancer* 36:796-803, 1975.

Table 1.
Histopathological Classification*

Type	Features	Relative Prognosis
Lymphocyte predominance (LP)	Abundant lymphocytic stroma; sparse Reed-Sternberg (R-S) cells.**	Most favorable
Nodular sclerosis (NS)	Nodules of lymphoid tissue of varying size, separated by bands of collagen and containing "lacunar" cell variants of R-S cells.	Favorable
Mixed cellularity (MC)	More numerous R-S cells in pleomorphic stroma rich in eosinophils, plasma cells, fibroblasts and lymphocytes.	Guarded
Lymphocyte depletion (LD)	Paucity of lymphocytes; diffuse, irregular fibrosis in some instances; bizarre, anaplastic R-S cells usually numerous.	Least favorable
*Rye classification.⁴ **R-S cells are essential for diagnosis of Hodgkin's disease, but are not pathognomonic; they may be seen in infectious mononucleosis, metastatic breast cancer, etc. It is therefore important to observe them in an appropriate stroma.		

plan is outlined only after the extent of subdiaphragmatic disease has been disclosed by these procedures.⁶ When mantle field treatment is resumed, new lead shielding blocks are prepared to provide greater protection for the lungs, while tightly matching the reduced mediastinal/hilar adenopathy silhouette. Intravenous urograms, upper GI series, barium enemas and liver-spleen scans have been omitted from the routine diagnostic workup since they have too low a yield in Hodgkin's disease. These procedures should, therefore, be added selectively when specifically indicated by

the patient's symptomatology.

Clinical Staging

The Ann Arbor Clinical Staging Classification adopted in 1971 has proven to be a practical and workable scheme.⁷ (Table 3.) It distinguishes between the Clinical Stage (CS), determined by initial biopsy, history and physical examination, laboratory tests and radiographic evidence, and the Pathological Stage (PS), which adds additional definitive histopathologic information obtained at staging laparotomy, exploratory thoracotomy and/or bone marrow biopsy.

Table 2.
Diagnostic Work-up

- A. Careful history, with special attention to unexplained fever, night sweats, weight loss of more than 10 percent in prior 6 months.
- B. Physical examination, emphasizing peripheral lymph node chains, liver, spleen and bony tenderness.
- C. Chest roentgenogram; whole-lung tomography if mediastinal/hilar adenopathy present.
- D. Bilateral lower extremity lymphangiography; identification of suspicious nodes.
- E. Laboratory tests, especially CBC and platelet count, serum alkaline phosphatase, ESR and serum Cu^{++} .
- F. Staging laparotomy (except when Stage IV disease is apparent); splenectomy and biopsy of suspicious para-aortic, celiac, porta hepatis, splenic hilar and/or iliac nodes, liver, and iliac crest bone marrow.⁵
- G. Radioisotopic scans (optional): ^{67}Ga , $^{99\text{m}}\text{TcEHDP}$, $^{111}\text{InCl}_3$.
- H. Delayed hypersensitivity skin tests (optional): natural intradermal antigens, DNCB.

Biopsy-proven lesions of the liver or bone marrow are invariably defined as Stage IV disease. Lesions of other extra-lymphatic tissues, such as the lung, pleura or bone, must be judged individually: they may be either "E" lesions, if localized, or Stage IV disease, if multiple or disseminated.

Radiotherapy

The "cardinal features" of modern radiotherapy for Hodgkin's disease with curative intent are set forth in Table 4. The technical aspects have been fully detailed elsewhere.⁸ The use of small ^{60}Co teletherapy units, operating at treatment distances of 80 cm. or less, results in a patchwork quilt of small treatment fields which invite frequent technical errors. The patient with previously untreated, potentially curable

Hodgkin's disease deserves optimal treatment the *first time*. When the requisite equipment and/or radiotherapeutic expertise are not available in his community, the patient should be referred to the nearest major medical center for high precision radiotherapy. A number of radiotherapeutic field distributions are now available to deal flexibly with a variety of clinical presentations. (Tables 5. and 6.)

Chemotherapy

The number of chemotherapeutic agents with demonstrated therapeutic efficacy in Hodgkin's disease has been growing rapidly in recent years. (Table 7.) Significantly, the sites of major toxicity of these agents are not all the same; although most are myelotoxic, some primarily effect the nervous system or gas-

Table 3.
Clinical Staging Classification*

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I _E).
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II _E).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III _S) or by localized involvement of an extralymphatic organ or site (III _E) or both (III _{SE}).
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement.

The presence or absence of fever, night sweats and/or unexplained loss of 10 percent or more of body weight in the six months preceding admission are denoted by the suffix letters B and A, respectively.

Biopsy-documented involvement of Stage IV sites is also denoted by letter suffixes: marrow = M+; lung = L+; liver = H+; pleura = P+; bone = O+; skin and subcutaneous tissue = D+.

*Adopted at the workshop on the Staging of Hodgkin's Disease held at Ann Arbor, Michigan, April, 1971.⁷

Table 4.
Radiotherapy: Cardinal Features

- A. Tumoricidal dose: 3,500 rads/3.5 weeks to 4,400 rads/4 weeks; local "boost" to 5,000 rads/5-6 weeks to exceptionally large or slowly regressing lymph node masses.
- B. Large fields: Shaped to encompass multiple lymph node chains (anterior and posterior opposed, except for Waldeyer).
- C. Megavoltage beam energies: Linear accelerator or ⁶⁰Co teletherapy apparatus with treatment distance capability of 100-140 cm.

Table 5. Radiotherapy Fields

Mantle Encompasses mediastinal, hilar, and bilateral supraclavicular, infraclavicular, cervical, and axillary node chains, with lead shields shaped to lungs, heart, spinal cord (after 2,000 rads).⁸
Inverted-Y Encompasses splenic or splenic pedicle, para-aortic iliac, inguinal, and femoral node chains, with lead shields for rectum and bladder, iliac and upper femoral bone marrow, and "gap" at junction with mantle field;⁸ Or
Spade Encompasses splenic or splenic pedicle, para-aortic and common iliac node chains, with double thickness lead shields for gonads and pelvic structures; Or
Para-aortic/hepatic Encompasses splenic hilar and para-aortic node chains and entire right lobe of liver (through 50 percent transmission lead block), usually joined across another "gap" by a separate pelvic field.⁹
Pelvic field Encompasses external iliac, inguinal, and femoral node chains, with lead shields for rectum and bladder, iliac, and upper femoral bone marrow.
"Waldeyer" Opposed lateral fields, encompasses pre-auricular nodes and lymphatic tissues of Waldeyer's ring when clinically involved or when adenopathy present in high cervical nodes.

trointestinal tract. Thus, modern combination chemotherapy regimens (Table 8.) seek to obtain the additive antitumor effects of three or more agents with non-overlapping normal tissue toxicities. At present, MOPP and its British variant, MVPP, are the most firmly established programs, but a number of other four- and five-drug regimens are currently under investigation. Management of the patient who relapses after an adequate trial of MOPP chemotherapy has been a particularly distressing problem. The recent, highly encouraging "crossover" experience with the ABVD and CAVE regimens may provide at least a partial solution to this problem.

Treatment of the Previously Untreated Patient

Our treatment recommendations for patients with previously untreated Hodgkin's disease are based on a graded sequence of options related to stage, symptoms, histopathology and presenting site. (Table 9.) Local, involved-field or limited radiotherapy still has a valid place in the management of certain Stage IA and IIA presentations (Table 9, situations 1-3), and subtotal radiotherapy in others (Table 9, situations 4 and 5). For more extensive or symptomatic Stage II disease, or in patients with unfavorable histologic patterns, however, total lymphoid radiotherapy

Table 6.
Special Adjustments and Refinements
of Radiotherapeutic Technique

Split course treatment of very large mediastinal masses; normally 1,500–2,000 rads/2 weeks, then 1–2 week interruption to permit regression (and staging laparotomy), followed by resumption and completion of mantle field radiotherapy with reduced mediastinal aperture.

Thin lung (30 percent transmission) blocks over one or both lungs when hilar adenopathy present, to deliver: $\sim 1,600$ rads/4 weeks to entire lung.¹⁰

Subcarinal blocks, added across lower mediastinal field, from about 5 cm. below carina down to diaphragm, to shield heart after dose of 3,000–3,500 rads has been delivered to the mantle field.

Horizontal decubitus upper abdominal fields for opposed lateral port irradiation of para-aortic and mesenteric nodes with kidneys shielded.

Minimantle field, similar to the mantle, but with the mediastinum and hilar regions shielded; thus, both supraclavicular, cervical, infraclavicular, and axillary node chains are treated.

must now be regarded as the treatment of choice, either alone or supplemented by six cycles of MOP combination chemotherapy (Table 9, situations 6-8). In Stage III_sA with documented involvement of the spleen by NS or LP type disease, total lymphoid radiotherapy may be optionally supplemented with either hepatic irradiation (2200 rads/four weeks) or six cycles of MOP chemotherapy;¹⁶ in the presence of constitutional symptoms and/or unfavorable histology, both hepatic irradiation and MOP chemotherapy are added to total lymphoid radiotherapy. Patients with Stage IV disease usually require combination chemotherapy as the mainstay of their management, but those treated with chemotherapy alone have a relatively high rate of relapse in sites of initially bulky lymphadenopathy. Hence, strategies which incorporate moderate dose radiotherapy either in a "split course" approach or at the end of multiple drug cycles, when complete remis-

sion has been attained, have come into use in many Stage IV situations (Table 9, situations 11-13). Such combined chemotherapy-radiotherapy programs are formidable, and should be used selectively in relatively young patients who are in good general health, reserving chemotherapy alone for elderly patients and those in frail condition.

Treatment of the Previously Treated Patient in Relapse

The nature and extent of previous treatment influences and often severely limits the treatment of relapsing disease. Nonetheless, modern treatment modalities make possible a very gratifying rate of salvage, especially in first relapses. When the full extent of disease is not apparent at the time of first relapse, a complete diagnostic workup should be performed, including a repeat lymphangiogram and, if necessary, laparotomy with splenectomy and biopsies of para-aortic nodes, liver and marrow. The

Table 7.
Single Agent Chemotherapy: Palliation in Advanced, Relapsing Disease

Agent	Usual Dose Route, Interval	Mechanism of Action	Major Toxicity
Nitrogen mustard (Mustargen, HN ₂)	0.4 mg./kg., IV every 4-8 weeks	Alkylation	Bone marrow, nausea, vomiting
Chlorambucil (Leukeran, CLB)	0.1-0.2 mg./kg./day, P.O.	Alkylation	Bone marrow
Cyclophosphamide (Cytosan, CTX)	50-200 mg./day, P.O. or 20-40 mg./kg., IV every 3-4 weeks	Alkylation	Bone marrow, cystitis, alopecia, nausea
Vinblastine (Velban, VLB)	3-6 mg./m. ² , IV every 1-2 weeks	Mitotic spindle poison	Granulocytopenia
Vincristine (Oncovin, VCR)	1-1.4 mg./m. ² , IV every 1-2 weeks	Mitotic spindle poison	Neuropathy
Procarbazine (Natulan, Matulane PCB)	50-250 mg./day, P.O.	Alkylation, oxidation?	Bone marrow, nausea, vomiting
Adriamycin (ADM)	25-80 mg./m. ² , IV every 3-4 weeks	Antibiotic, intercalation into DNA	Bone marrow, alopecia, cardiomyopathy
Bleomycin (BLM)	2.5-15 mg./m. ² , IV every week	Antibiotic	Anaphylactoid and febrile reactions, pulmonary fibrosis
Nitrosoureas (BCNU, CCNU)	70-130 mg./m. ² for 1-2 days (IV, P.O.)	Alkylation	Bone marrow
Dimethyl-triazeno-imidazole-carboxamide (DTIC)	150-200 mg./m. ² , IV for 4-5 days	Antimetabolite?	Gastrointestinal, bone marrow
Corticosteroids (Prednisone)	Variable, P.O.	Lympholytic	Cushing's syndrome

proper course of action cannot be arrived at without objective knowledge of the distribution of relapsing sites of disease. Treatment of relapses in lymph nodes, spleen or localized osseous or subcutaneous sites in patients previously treated with radiotherapy only (Table 10, situa-

tions 1-5 and 10) calls for high dose radiotherapy to the site(s) of relapse and previously untreated lymphoid regions, supplemented in most instances by six cycles of MOP chemotherapy. Relapses in liver, lung, bone marrow or multiple, disseminated sites in patients previously

Table 8.
Combination Chemotherapy Regimens

"MOPP" ¹¹

HN₂ 6 mg./m.², IV, days 1 & 8
VCR 1.0-1.4 mg./m.², IV, days 1 & 8
PCB 100 mg./m.²/day, P.O., days 1-14
PRD 40 mg./m.²/day, P.O., days 1-14

14-day cycles separated by 14-day rest periods; usually 6 or more cycles; PRD in cycles 1 & 4 only.

"MVPP" ¹²

HN₂ 6 mg./m.², IV, days 1 & 8
VLB 6 mg./m.², IV, days 1 & 8
PCB 100 mg./m.², P.O., days 1-14
PRD 40 mg./day, P.O., days 1-14

14-day cycles separated by 28-day rest periods; usually 6 or more cycles; PRD given in all cycles.

"ABVD" ¹³

ADM 25 mg./m.², IV, days 1 & 14
BLM 10 mg./m.², IV, days 1 & 14
VLB 6 mg./m.², IV, days 1 & 14
DTIC 150 mg./m.², IV, days 1-5

14-day cycles and 14-day rest periods. Advantage: no cross-resistance vs. MOPP; high rate of response in MOPP failures (~75-80 percent).

"CAVe" ¹⁴

CCNU 100 mg./m.², P.O., day 1
ADM 60 mg./m.², IV, day 1
VLB 5 mg./m.², IV, day 1

Cycles repeated every 6 weeks (if blood counts permit) to total of 9 cycles; about 50 percent response rate in MOPP failures.

"MOP"

Same as MOPP, except for the omission of prednisone in all cycles in patients previously treated with mantle field radiotherapy.¹⁵

treated with radiotherapy only, are best managed with MOP chemotherapy (six or more cycles), optionally supplemented in some instances with low to moderate dose radiotherapy to the site(s) of relapse (Table 10, situations 6, 8 and 9). Patients who relapse following

single-drug chemotherapy are often moderately to severely cytopenic and have limited tolerance for combination chemotherapy; in general, the regimen selected for these patients should be comprised of agents that have not yet produced resistance. Patients who de-

Table 9.
Therapeutic Recommendations for
Previously Untreated Patients

Clinical Situation	Recommended Treatment
1. Stage PS IA (LP or NS type) limited to one upper cervical region, with negative lymphangiogram and laparotomy.	Ipsilateral local cervical-supraclavicular or minimantle and Waldeyer field radiotherapy only.
2. Stage CS IA (NS type) limited to the mediastinal region, with clinically negative hilar and cervical-supraclavicular nodes and negative lymphangiogram (laparotomy optional).	Mantle field radiotherapy only.
3. Stages PS IA (LP or NS type) limited to one inguinal/femoral region, with negative lymphangiogram and laparotomy.	Inverted-Y (pelvis, para-aortic, and splenic pedicle) field radiotherapy only.
4a. Stage PS IA (LP or NS type) involving one lower cervical-supraclavicular region; or 4b. Stage PS IIA (LP or NS type) involving two or more lymph node regions above the diaphragm, with negative lymphangiogram and laparotomy.	Subtotal lymphoid radiotherapy (mantle and spade fields); Waldeyer field also when upper cervical nodes involved.
5. Stage PS IIA (LP or NS type) involving two or more lymph node regions below the diaphragm, with negative spleen, liver and bone marrow at laparotomy.	Subtotal lymphoid radiotherapy only (full inverted-Y and minimantle fields).
6. Any of the above with constitutional symptoms (fever, night sweats and/or weight loss): Stages IB or IIB.	Total lymphoid radiotherapy only (mantle and full inverted-Y fields; Waldeyer field also when upper cervical nodes involved).
7. As in 4b, 5 or 6, but with one or two associated localized extralymphatic site(s) of involvement: Stage IIE-A or IIE-B.	As in 4, 5 or 6, respectively, plus local irradiation of the extralymphatic lesion(s); after a 6-8 week rest-period followed by 6 cycles of MOP combination chemotherapy (omitting prednisone).

Table 9. (continued)

Clinical Situation	Recommended Treatment
8. Any of the above with MC or LD type histology.	Total lymphoid radiotherapy (mantle and full inverted-Y fields; Waldeyer field also when upper cervical node involved) alone or supplemented, after 6-8 week rest period, with 6 cycles of MOP combination chemotherapy. ¹⁶
9. PS III-A and III _S -A (LP or NS types).	Total lymphoid radiotherapy only (mantle and inverted-Y fields); in addition when spleen is involved either hepatic field irradiation or 6 cycles of MOP chemotherapy.
10. PS III-A, PS III _S -A (MC and LD types) and PS III-B, PS III _S -B (any type).	Total lymphoid radiotherapy (mantle, para-aortic/hepatic, and pelvic fields) followed after a 6-8 week rest period by 6 cycles of MOP combination chemotherapy (omitting Prednisone).
11. PS IV _{H+} -A or B (any type) with biopsy-proven liver involvement.	Split course therapy: 2-3 cycles of MOPP combination chemotherapy, then para-aortic/hepatic, mantle and pelvic field radiotherapy (sequence depending on relative extent of initial involvement), then after 8-12 week rest period, 4-8 more cycles of MOP chemotherapy (omitting Prednisone); alternatively, MOPP alone for 6-9 cycles to documented remission, preferably supplemented by moderate dose radiotherapy to areas of initially bulky disease and 2-4 consolidation cycles of MOP chemotherapy before optional maintenance chemotherapy (MOP every 2-3 months or VLB + CLB every month for 18-24 months).
12. CS IV _L -A or B (any type) with multiple bilateral pulmonary lesions or pulmonary and biopsy proven pleural lesions.	MOPP combination chemotherapy (6-9 cycles), preferably followed by moderate dose (2,500-3,000 rads) radiotherapy to regions of initially bulky lymph node involvement in patients entering complete remission; consolidation and optional maintenance as in 11.
13. CS IV _O , PS IV _{M+} , and other Stage IV (A or B, any type).	As in 12, followed by consolidation and optional maintenance chemotherapy as in 11.

Table 10.
Therapeutic Recommendations for
Previously Treated Patients in Relapse
(First Relapse)

Clinical Situation	Recommended Treatment
1. Recurrence in treated lymph node chain in patients previously treated with radiotherapy only.	Low dose (2,000–2,500 rads 2 to 2½ weeks) local radiotherapy plus 6 cycles of MOP combination chemotherapy.
2. Recurrence at margin of treated lymph node chain in patients previously treated with radiotherapy.	Local radiotherapy, with dose limited to 2,000–2,500 rads to previously irradiated area but carried to 4,000 rads/4 weeks to marginal recurrence; supplementary MOP chemotherapy optional.
3. Extension to previously untreated lymph node chain on same side of diaphragm.	High dose radiotherapy (4,000 rads/4 weeks) to newly involved chain and usually to all other previously unirradiated lymphoid regions on both sides of diaphragm; supplementary MOP chemotherapy optional.
4. Extension to previously untreated lymph node chains on opposite side of diaphragm. (a) Extension from below diaphragm to cervical-supraclavicular nodes. (b) Extension from above diaphragm to para-aortic nodes.	(a) Same as 3 above. (b) Laparotomy, if not previously done; if spleen or liver found to be involved, then as per 5 or 6, respectively; if nodes alone are involved and spleen removed, high dose radiotherapy to full inverted-Y field; supplementary MOP chemotherapy indicated in presence of MC or LD histology or "B" symptoms and optional in other histologies.
5. Extension to spleen, usually associated with para-aortic node involvement, in patients previously treated with radiotherapy above diaphragm.	Splenectomy with liver and bone marrow biopsies; if biopsies positive, then as per 6 or 7, respectively; if negative, high dose radiotherapy to para-aortic/hepatic field (4400 rads-2200 rads/4 weeks), then to pelvic field (4400 rads/4 weeks); supplementary MOP chemotherapy with MC or LD histology or "B" symptoms.
6. Biopsy-proven extension to liver, with or without evident lymph node disease, in patients previously treated with radiotherapy only.	Split course MOP chemotherapy (usually 3–4 cycles initially), then low dose radiotherapy (2,000 rads/3–4 weeks) to the liver and regions of bulky lymphadenopathy, then 3–6 more cycles of MOP.

Table 10 (continued)

Clinical Situation	Recommended Treatment
7. Biopsy-proven extension to bone marrow, with or without concurrent involvement of spleen and lymph nodes, in patients previously treated with radiotherapy only.	MOP chemotherapy (6-9 cycles), followed by 2-4 "consolidation" cycles of MOP chemotherapy in patients attaining documented remission; optional low dose (1,500-2,000 rads/2 weeks) radiotherapy to areas of bulky lymphadenopathy and optional maintenance chemotherapy as in Table 9., 11.
8. Solitary lesion in one lung in patients previously treated with radiotherapy only.	MOP chemotherapy (usually 6 cycles), supplemented by ipsilateral whole-lung irradiation (1,500 rads/3-4 weeks) with boost over involved area to ~2,000-2,500 rads.
9. Multiple lesions in both lungs in patients previously treated with radiotherapy only.	MOP chemotherapy (6 or more cycles) and optional low dose radiotherapy to both lung fields (1,200-1,500 rads/4 weeks).
10. Apparently solitary extension to bone or subcutaneous tissues previously treated with radiotherapy only.	Local radiotherapy (4,000 rads/4 weeks if region previously unirradiated; 1,500-2,000 rads/2 weeks plus MOP chemotherapy, 6 cycles, if region previously irradiated).
11. Multiple scattered osseous or subcutaneous lesions in patients previously treated with radiotherapy only.	MOP chemotherapy (6-9 cycles); optional low dose radiotherapy to sites of incomplete response.
12. In lymph node(s) in patients previously treated with single-drug chemotherapy only.	Careful diagnostic evaluation and re-staging, then high dose, total lymphoid radiotherapy if no extranodal disease is detected and hematologic tolerance is good; high dose local radiotherapy to involved areas plus 6 cycles of MOP chemotherapy is an acceptable alternative.
13. In extranodal site(s), such as bone marrow, liver, lungs, etc., in patients previously treated with single-drug chemotherapy only.	MOPP, ABVD or CAVe chemotherapy, selecting combination with agents to which resistance has not yet been demonstrated.
14. In patients previously treated with MOPP chemotherapy.	Renewed MOPP chemotherapy when first relapse occurs more than 12 months after first course of MOPP; for earlier relapses, "crossover" to other drug combinations, such as ABVD or CAVe, when hematologic tolerance is good; palliative single-drug chemotherapy and/or local radiotherapy (for localized relapses) when hematologic tolerance is too poor to permit intensive chemotherapy.

Table 11.
Therapeutic Recommendations for Previously Treated Patients In Relapse
(Second and Later Relapses)

MOP or other intensive combination chemotherapy when hematologic tolerance permits and relapse involves multiple or extranodal or heavily irradiated sites; local radiotherapy when relapse involves local nodal or osseous site and hematologic tolerance is poor; single-drug, palliative chemotherapy when relapse involves multiple or extranodal or heavily irradiated sites and hematologic tolerance is poor.

velop "late" relapses, more than 12 months after completion of the last MOPP cycle, usually do well on another course of MOPP; those relapsing earlier are best regarded as MOPP failures and treated with one of the new "crossover" combinations, such as ABVD or CAVe. Treatment options inevitably become more and more severely restricted in patients with multiple, sequential relapses (Table 11.), due both to the limitations on tissue tolerance imposed by prior therapy, and to the dwindling list of agents in which tumor resistance has not yet developed. Nonetheless, skillful use of the available options can give years of useful and productive life, even to the patient ultimately destined to die.

Prognosis

The dramatic improvement in the prognosis of Hodgkin's disease, which has resulted from the systematic application of modern diagnostic and therapeutic advances, has been fully described elsewhere,¹⁷ and only a brief summary of our current data on survival and freedom from relapse, for all stages and for each separate stage, is presented here. (Table 12.) It should be noted that five-year survival is now high not only in Stages I and II, but in Stage III as well. The curve for relapse-free, 10-year survival flattens out at about 50 percent and represents a minimum estimate of the permanent cure rate which can now be achieved in Hodgkin's disease. As

research aimed at the conquest of Stage IV and other advanced disease states goes forward in major medical centers, it is hoped that the judicious application of the treatment principles and recommendations set forth in this paper will help bring the benefits of modern therapy and improved prognosis to all patients with Hodgkin's disease. ©

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Table 12. Prognosis*

Group	5-Year Survival (Percent)	5-Year Relapse-free (Percent)
All stages, all cases	81.3	61.5
Stage PS I (A & B)	86.0	72.5
Stage PS II (A & B)	93.6	69.0
Stage PS III (A & B)	81.3	61.1
Stage PS IV (A & B)	39.0	26.9

At 10 years, the curve for relapse-free survival has flattened out at about 50 percent, suggesting that at least half of all cases may now be permanently cured of their once inevitably fatal disease by meticulous diagnostic evaluation and staging, and the judicious selection and skillful administration of megavoltage radiotherapy and/or multi-agent combination chemotherapy.

*Based on data from a series of 504 consecutive biopsy-proved, previously untreated patients with Hodgkin's disease routinely staged with lymphangiography and laparotomy with splenectomy, most of whom were treated with high dose, total lymphoid radiotherapy in Stages IA, IB, IIA, IIB, and III_SA; total lymphoid radiation supplemented with either hepatic radiotherapy or MOPP chemotherapy in Stages III_S-B and IV_H+A or B; and MOPP chemotherapy with or without supplementary radiotherapy in Stage IV_M+A or B and IV_LA or B.

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