RADIATION THERAPY ALONE VERSUS RADIATION THERAPY AND CHEMOTHERAPY IN THE MANAGEMENT OF HODGKIN'S DISEASE

Luther D. Glenn, MD, and P. Pradeep Kumar, MD
Omaha, Nebraska

Forty-four patients with histologically proven Hodgkin's disease underwent initial treatment with extended-field radiation therapy. Nineteen of these patients also received combination chemotherapy. For analysis, patients were assigned to three treatment groups: group 1 received radiation therapy only (25 patients); group 2 received combination chemotherapy followed by consolidative (low-dose extended-field) radiation therapy; and group 3 was treated with alternate chemotherapy and radiation therapy using the sandwich technique. The actuarial 5-year disease-free survival rates were 83% (group 1), 83% (group 2), and 100% (group 3). The overall actuarial survival rates were 96% (group 1), 92% (group 2), and 100% (group 3). No factor was identified as being of prognostic value in predicting relapse. We conclude that extended-field radiation therapy delivered in this manner is a safe and effective approach to the initial management of Hodgkin's disease.

From the Department of Internal Medicine, Division of Medical Oncology; and the Department of Radiology, Division of Radiation Oncology, University of Nebraska Medical Center, Omaha. Requests for reprints should be addressed to Dr P.P. Kumar, Division of Radiation Oncology, University of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NB 68105.

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In the early 1900s, radiation therapy (RT) was shown to be effective in the management of Hodgkin's disease (HD),[1-3] and it has remained a mainstay in therapy to this day.[4] The institution of standard extended-field radiation ports with prophylactic irradiation of adjacent but uninvolved lymph node chains,[5-9] the development of megavoltage linear accelerators,[10] and the establishment of the dose-response relationship[11-13] have all contributed to improved results in the management of HD.

Certain presentations of HD, however, do not seem to be amenable to RT as a single modality or to be conducive to long-term disease-free survival. These cases include patients with systemic symptoms (B symptoms),[14-19] hepatic involvement,[20] bone marrow involvement,[15] bulky disease,[16,18,21] large mediastinal disease,[17,19,22-33] age,[14,25,34,35] extensive splenic involvement,[36,37] relapse following RT,[38] and extensive nodal disease (anatomic substage IIIA2).[39-43] For these presentations, multi-agent chemotherapy (CT), with or without RT, has been advocated as the therapy of choice.[42,44-47]

At the University of Nebraska Medical Center, we employ a 100 cm effective target-to-axis distance (TAD) isocentric technique to deliver extended-field radiotherapy, which may be coupled with multi-agent CT in the treatment of HD. This technique allows an

increase in the field size to 35 to 40 cm and improves field matching and the treatment set-up accuracy and reproducibility. This article reports the results of this technique of radiotherapy in the management of HD.

METHODS AND MATERIALS

All patients with newly diagnosed HD referred to the University of Nebraska Medical Center Division of Radiation Oncology between October 1979 and January 1988 were considered for treatment with extended-field radiation, using the isocentric technique. The disease was clinically staged by patient history and physical examination, chest x-ray (posterior-anterior and lateral views), and bone marrow aspiration and biopsy. In addition, most patients underwent whole lung tomography to evaluate the chest and lymphangiography to evaluate the abdomen. In more recent years, computerized tomography of the chest and abdomen were occasionally performed in lieu of whole lung tomography and lymphangiography. Liver spleen scans, gallium scans, and abdominal ultrasounds were obtained when clinically indicated. Patients were also evaluated with routine blood tests, including complete blood counts with differential, platelet count, chemistry profile, and serum electrolytes. Although not required for treatment, patients were strongly urged to undergo staging laparotomy with splenectomy. All cases were staged according to the Ann Arbor classification.[49]

Following the completion of staging, patients were treated with extended-field radiation. Radiation therapy was administered using the isocentric technique with either a 4 MV or 10 MV linear accelerator utilizing a 100 cm effective TAD. In all instances, large lymphatic fields received a prophylactic dose of 3000 to 3600 cGy in 200 cGy fractions 4 days a week, with areas of known tumor involvement boosted to a total dose of 4000 to 4600 cGy. Patients who received CT in conjunction with RT did not receive the boost dose to known sites of disease. A description of the fields used has been published previously.[48]

No uniformity in CT regimens used was made, as the referral base of this population included several oncologists; however, ChlVPP (chlorambucil, vincristine, procarbazine, and prednisone) was the regimen most often used. Other regimens used were MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)[51] and COPP-ABVD (cyclophosphamide, vincristine, procarbazine, and prednisone, alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine).[52] Most patients receiving CT as part of their primary treatment received either six cycles of ChlVPP followed by RT (group 2 consolidation, 12 patients) or two cycles of MOPP followed by RT, with the remaining cycles of MOPP following the completion of radiation therapy (group 3, sandwich technique, 7 patients).

A complete response to treatment was defined as complete disappearance of all known sites of disease upon repeat staging or greater than 50% reduction in the product of the perpendicular diameters of residual disease with no evidence of progression for 24 months following treatment. A partial response to treatment was defined as greater than 50% reduction in the product of the perpendicular diameters of residual disease with progression within 24 months following treatment. Progressive disease was defined as any evidence of new or enlarging HD, which was confirmed histologically. Follow-up consisted of blood counts and chest x-rays at 1-month intervals for the first year after treatment, at 3-month intervals for the next 2 years, and at 6-month intervals thereafter.

Disease-free survival was defined as the interval between the completion of primary treatment (RT with or without CT) and the date of progressive disease or most recent follow-up. Overall survival was defined as the interval between the date of diagnosis and the date of death or most recent follow-up. Follow-up for all patients is reported through 31 August 1988 or time of death, with a median follow-up of 51 months. The distribution of disease-free survival and overall survival was estimated by the product-limit method of Kaplan and Meier.[53] The log-rank test was used to assess the statistical significance of differences in disease-free survival and overall survival among groups.[54]

RESULTS

Forty-nine patients with HD diagnosed between March 1979 and January 1988 were referred for treatment with radiation therapy. Five patients were considered inevaluable and were excluded from further analysis. Of the 44 evaluable patients, 29 were male and 15 were female, with a median age of 23 years (range 11 to 63 years). The median age for females was 20 years compared with 24 years for males. Histology showed that 4 patients had lymphocyte predominance, 29 had nodular sclerosis, 9 had mixed cellularity, and 2 were unclassified.

Twenty-four patients underwent staging laparotomy; reasons for not performing staging laparotomy included

TABLE 1. PATIENT CHARACTERISTICS

	Radiation Only (Group 1)	Combination Chemotherapy Radiation Therapy (Group 2)	Radiation Therapy Sandwiched Between Cycles of Chemotherapy (Group 3)
Number of patients	25	12	7
Median age	24 (14-63)	24 (15-59)	15 (11-56)
Sex (M:F)	13:12	10:2	6:1
Histology			
Lymphocyte predominance	3	1	
Nodular sclerosis	14	11	4
Mixed cellularity	7		2
Unclassified	1		1
Staging (A:B)			
I	8:1		2:0
II	15:1	2:1	0:1
III		3:5	2:0
IV		1:0	1:1
Subdiaphragmatic disease only	1	1	
Extranodal disease			
Spleen		4	
Bone marrow		1	
Thyroid	1		
Lung			1
Mediastinal mass	14	9	4

age less than or equal to 16 years (6 patients), age over 60 years (2 patients), subdiaphragmatic disease documented by biopsy (3 patients), stage III disease documented radiographically (3 patients), physician preference (3 patients), patient refusal (2 patients), and bone marrow involvement (1 patient). Staging laparotomy resulted in higher staging in 5 patients (20%). Among cases staged clinically, 5 patients had stage I disease, 7 had stage II, 5 had stage III, and 3 had stage IV. Among cases staged pathologically, 7 patients had stage I disease, 12 had stage II, and 5 had stage III.

Of the patients with limited stage disease, only 2 had subdiaphragmatic disease (2 of 31, or 6%). Twenty-seven of the 42 patients with supradiaphragmatic disease (67%) had mediastinal masses seen on chest x-ray. Sites of extranodal disease included the spleen (4 patients), bone marrow (1 patient), thyroid (1 patient), and lung (1 patient). These patient characteristics, divided into treatment groups, are summarized in Table 1. Median duration of follow-up for all patients was 51 months.

Twenty-five patients underwent extended-field radiation as the only initial therapy of HD. Twenty-two patients (88%) in this group achieved a complete response; although in 3 patients, the disease progressed while receiving RT. Two patients had mediastinal masses and received mantle irradiation; both patients developed lung parenchymal involvement adjacent to the radiation port and progression was documented by open lung biopsy in both instances. One patient was treated with 12 cycles of COPP and is now free of disease 71 months after completion of salvage therapy and 85 months following initial diagnosis. The other patient treated with six cycles of MOPP is now free of disease 78 months after completion of salvage therapy and 89 months following diagnosis. One other patient had bone marrow involvement documented while receiving RT. Of the 22 patients, one patient relapsed outside the field in the lung, and one patient relapsed in field in the left axilla. Both patients were salvaged with six cycles of CT and remain alive and disease-free at 71 and 74 months after initial diagnosis.

Twelve patients were treated with extended field RT as consolidation therapy administered within 4 weeks of the completion of CT (group 2), including 3 patients with stage II disease, 8 with stage III, and 1 with stage

TABLE 2. TOXICITY OF ISOCENTRIC TECHNIQUE OF EXTENDED FIELD RADIATION THERAPY

Short-term	
Hematologic	17
Leukopenia (WBC<3000 cmmM-1)	14
Thrombocytopenia	4
Anemia (hgb<11.0 gm%)	6
Gastrointestinal	12
Nausea/vomiting	7
Esophagitis	6
Constipation	1
Diarrhea	1
Small bowel obstruction	1
Dry mouth	1
Decreased appetite	1
Dermatologic	7
Fatigue	1
Long-term	
Infectious	3
Gram-negative sepsis	2
Herpes zoster	1
Hypothyroidism	6

IV. Seven patients had B symptoms. Ten patients were treated with ChlVPP, one patient was treated with COPP for six cycles, and one patient was treated with MOPP for six cycles, all prior to the commencement of RT.

All 12 group 2 patients treated with consolidation RT attained a complete response to therapy, however, 2 patients (16.6%) have relapsed. One patient with stage IV disease presented 6 weeks after completion of RT with a left supraclavicular mass, which was biopsied and found to be recurrent HD. He was started on salvage CT with ABVD and died during the fifth cycle of CT with gram-negative sepsis. The other patient presented 8 months after completion of RT with palpable inguinal nodes and characteristic changes in the inguinal and paraaortic nodes, although a confirmatory biopsy was not performed. The patient received an additional 2000 cGy to a pelvic field followed by nine cycles of COPP/ABVD. This patient remains in complete response 70 months following the completion of salvage CT and 105 months after initial diagnosis. Both of these patients relapsed outside the consolidation radiation fields. Of the 7 patients in the sandwich group 3, 6 were treated with MOPP and 1 was treated with COPP/ABVD. All patients in this group attained a complete response, and no relapses have been reported to date.

Seven patients received two cycles of CT prior to extended-field RT, with the remaining cycles being administered after the completion of RT (sandwich therapy group 3). Included in this group were 6 males and 1 female, with a median age of 15 years. Two patients had stage I disease, 1 patient had stage II disease, 2 patients had stage III disease, and 2 patients had stage IV disease. Six patients were treated with six total cycles of MOPP and 1 patient was treated with 12 total cycles of COPP/ABVD. Patients in this group attained a complete response, and no relapses have been reported to date.

The disease-free survival for each group, as well as the entire patient population, is shown in Figure 1. The actuarial disease-free survival at 5 years for patients in group 1 is 83% compared with 83% for the patients in group 2, and 100% for the patients in group 3. These differences are not significant because of the small patient numbers. The actuarial 5-year disease-free survival of all patients is 88%.

The overall actuarial survival for patients treated with extended-field RT for HD is shown in Figure 2. The 5-year actuarial survival for the entire group is 93%: group 1 (96%), group 2 (92%), and group 3 (100%). Again, these differences are not statistically significant.

The toxicities associated with therapy were mild and well tolerated (Table 2). The most common toxicity was hematologic, with the more severe abnormalities seen in patients who had received prior chemotherapy. Gastrointestinal and dermatologic complications were generally mild and easily tolerable. Hypothyroidism has been documented in 6 patients following therapy. No second malignancies have been identified. Various factors were assessed for their prognostic value in predicting disease-free survival or overall survival. Age, sex, histology, stage, presence of B symptoms, and mediastinal disease were evaluated; none had prognostic significance (data not shown). Too few patients were included in other factor groups of potential predictive value to warrant statistical evaluation.

DISCUSSION

This series of 44 patients with HD treated with

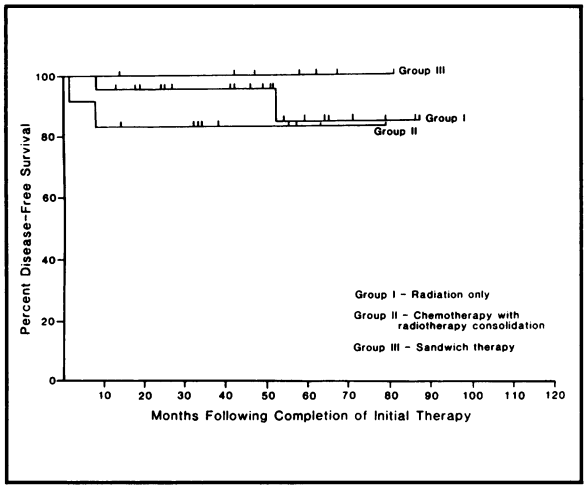

Figure 1. Disease-free survival following therapy with isocentric radiation therapy.

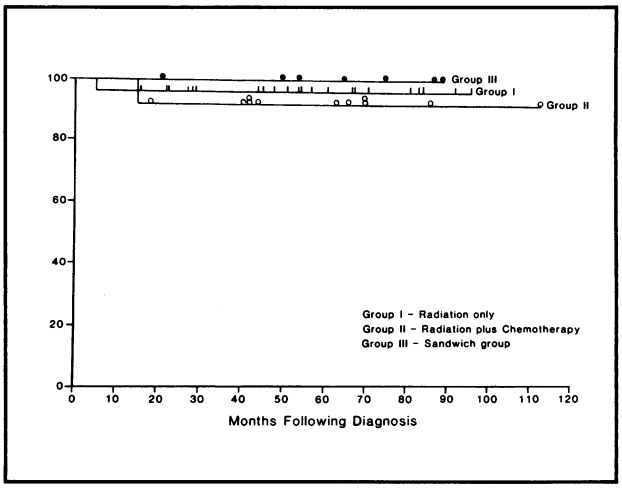

Figure 2. Overall survival following therapy with isocentric radiation therapy.

extended-field RT using an isocentric technique with a 100 cm TAD, either alone or in combination with CT, attests to the effectiveness and relatively low toxicity of such therapy. Of the 25 patients receiving extended-field RT as the only modality of therapy, 22 attained a complete remission (92%). These patients have maintained an 83% 5-year actuarial disease-free survival and a 96% 5-year actuarial overall survival with a median follow-up of more than 51 months. These results are in accord with results reported at other centers using modern radiotherapy techniques.[55-58]

Patients treated initially with a combination of RT and CT also fared quite well. In patients treated with CT followed by consolidative RT (group 2), the 5-year actuarial disease-free survival was 83% and the 5-year actuarial overall survival was 92%. For group 3 patients, the 5-year actuarial disease-free survival and overall survival were both 100%. These figures also compare favorably with other series using modern radiotherapeutic techniques and chemotherapeutic regimens.[18,27,59,60]

Patients tolerated the radiation therapy well, with very few adverse effects having been reported during treatment and no second malignancies having been noted in up to 113 months of observation. Further time will be needed to see if this trend persists. In addition, only 3 patients failed to achieve a complete response, and 2 of these patients have been effectively salvaged with CT. Of the 41 patients who achieved a complete response, only 4 have relapsed to date and 3 have been rendered disease-free with salvage chemotherapy.

In summary, we presented treatment results of 44 patients who underwent extended-field RT using an isocentric technique as the initial therapy for HD. Nineteen of these patients also received combination CT. In patients with stage I and II disease, RT alone achieved superb disease control with minimal toxicity. Patients with more advanced disease were effectively treated with combination CT and extended-field RT.

Literature Cited

1. Pusey ES. Cases of sarcoma and of Hodgkin's disease treated by exposure to x-rays. *J Am Med Assoc.* 1902;28:166-169.

2. Williams FH. *The Roentgen Rays in Medicine and Surgery.* 2nd ed. New York: MacMillan; 1903.

3. Senn N. Therapeutic value of roentgen ray in treatment of pseudoleucaemia. *NY Med J.* 1903:77:665-668.

4. Kennedy BJ, Loeb Jr V, Peterson VM, et al. National survey of patterns of care for Hodgkin's disease. *Cancer* 1985;56:2547-2556.

5. Gilbert R, Babaiantx L. Notre methods de roentgentherapie de la lymphogranulomatose (Hodgkin) resultats eloignes. *Acta Radio.* 12:523-529, 1931.

6. Peters MV. Prophylactic treatment of adjacent areas in Hodgkin's disease. *Cancer Res.* 1966;26:1232-1243.

7. Carmel RJ, Kaplan HS.Mantle irradiation in Hodgkin's disease: an analysis of technique, tumor irradication,and complications. *Cancer.* 1976;37:2813-2825.

8. Page V, Gardner A, Katmark CJ. Physical and dosimetric aspects of the radiotherapy of malignant lymphoma. I.The mantle technique. *Radiology.* 1970;96:609-618.

9. Page V, Gardner A, Karzmark CJ. Physical and dosimetric aspects of the radiotherapy of malignant lymphoma. II.The inverted-Y technique. *Radiology.* 1970;96:619-626.

10. Hoppe RT. Radiation therapy in the treatment of Hodgkin's disease. *Semin Oncol.* 1980;7:144-154.

11. Seydel HG, Bloedorn FG, Wizenberg MJ. Time-dose-

volume relationship in Hodgkin's disease. *Radiology.* 1967;89:919-922.

12. Kaplan HS. Evidence for a tumoricidal dose level in the radiotherapy of Hodgkin's disease. *Cancer Res.* 1966;26:1221-1224.

13. Fuller LM, Jing B-S, Shullenberger CC, Butler JJ. Radiotherapeutic managanent of localised Hodgkin's disease involving the mediastinum. *Br J Radiol.* 1967;40:9l3-925.

14. Prosnitz LR, Farber LR, Kapp DS,et al. Combined modality therapy for advanced Hodgkin's disease: long-term follow-up data. *Cancer Treat Rev.* 1982;66:871-879.

15. Peters MV, Middlemiss KCH. A study of Hodgkin's disease treated by irradiation. *Am J Roentgenol Radiat Ther.* 1958;79:114-121.

16. Yarnold JR, Jelliffe AM, Vaughan Hudson G. Patterns of relapse following radiotherapy for Hodgkin's disease. *Clin Radiol.* 1982;33:137-140.

17. Jones SE, Coltman Jr CA, Grozea PN, et al. Conclusions from clinical trials of the Southwest Oncology Group. *Cancer Treat Res.* 1982;66:847-853.

18. Anderson H, Deakin DP, Wagstaff J, et al. A randomised study of adjuvant chemotherapy after mantle radiotherapy in supradiaphragmatic Hodgkin's disease PSIA-IIB: A report from the Manchester lymphoma group. *Br J Cancer.* 1984;695-702.

19. Cramer P, Andrieu JM. Hodgkin's disease in childhood and adolescence: results of chemotherapy-radiotherapy in clinical stages IA-IIB. *J Clin Oncol.* 1985;3:1495-1502.

20. Rosenberg SA, Moore MR, Bull JM, et al. Combination chemotherapy and radiotherapy for Hodgkin's disease. *Cancer.* 1972;30:1505-1510.

21. Prosnitz LR, Cooper D, Cox EB, et al. Treatment selection for stage IIIA Hodgkin's disease patients. *Int J Radiat Oncol Biol Phys.* 1985;11:1431-1437.

22. Fuller LM, Gamble JF, Ibrahim E, et al. Stage II Hodgkin's disease. *Radiology.* 1973;109:429-435.

23. Mauch P, Goodman R, Hellman S. The significance of mediastinal involvement in early stage Hodgkin's disease. *Cancer.* 1978;42:1039-1045.

24. Lee CKK, Bloomfield CD, Goldman AI, Levitt SH. Prognostic significance of mediastinal involvement in Hodgkin's discase treated with curative radiotherapy. *Cancer.* 1980;46:2403-2409.

25. Fuller LM, Gamble JF, Velazquez WS, et al. Evaluation of the significance of prognostic factors in stage III Hodgkin's disease treated with MOPP and radiotherapy. *Cancer.* 1980;45:1352-1364.

26. Hagmeister FB, Fuller LM, Sullivan JA, et al. Treatment of stage I and II mediastinal Hodgkin's disease: a comparison of involved fields, extended fields, and involved fields followed by MOPP in patients staged by laparotomy. *Radiology.* 1981;144:783-789.

27. Hagemeister FB, Fuller LM, Velasquez WS, et al. Stage I and II Hodgkin's disease: involved-field radiotherapy versus extended-field radiotherapy versus involved-field radiotherapy followed by six cycles of MOPP. *Cancer Treat Res.* 1982;66:789-798.

28. Hoppe RT, Coleman CN, Cox RS, et al. The managament of stage I-II Hodgkin's disease with irradiation alone of combined modality therapy: The Stanford experience. *Blood.* 1982; 59:455-465.

29. Mauch P, Gorshein D, Cunningham J, Hellman S. Influence of mediastinal adenopathy on site and frequency of relapse in patients with Hodgkin's disease. *Cancer Treat Res.* 1982;66:809-817.

30. Schomberg PJ, Evans RG, O'Connell MJ, et al. Prognostic significance of mediastinal mass in adult Hodgkin's disease. *Cancer.* 1984;53:324-328.

31. Anderson H, Jenkinins JPR, Brigg DJ,et al. The prognostic significance of mediastinal bulk in patients with stage IA-IVB Hodgkin's disease: A report from the Manchester Lymphoma Group. *Clin Radiol.* 1985;36:449-454.

32. Leslie NT, Mauch PM, Hellman S. Stage IA to IIB supradiaphragmatic Hodgkin's disease: Long-term survival and relapse frequency. *Cancer.* 1985; 55:2072-2078.

33. Ryoo MC, Kagan AR, Wollin M, et al. Observations on the treatment of mediastinal masses in Hodgkin's disease emphasizing site of failure. *Am J Clin Oncol.* 1987;10:185-193.

34. Ibrahim E, Fuller LM, Gamble JF, et al. Stage I Hodgkin's disease. *Radiology.* 1972;104:145-152.

35. Sutcliffe SB, Gospodarowicz MK, Bergsagel DE, et al. Prognostic groups for management of localized Hodgkin's disease. *J Clin Oncol.* 1985;3:393-401.

36. Hoppe RT, Rosenberg SA, Kaplan HS, Cox RS. Prognostic factors in pathologic stage IIIA Hodgkin's disease. *Cancer.* 1980;46:1240-1246.

37. Hoppe RT, Cox RS, Rosenberg SA, Kaplan HS. Prognostic factors in pathologic stage III Hodgkin's disease. *Cancer Treat Res.* 1982;66:743-749.

38. Weller SA, Glatstein E, Castellino RA, et al. Initial relapse in previously treated Hodgkin's disease--II; retrograde transdiaphragmatic extension. *Int J Radiat Oncol Biol Phys.* 1977;2:863-872.

39. Stein RS, Golomb HM, Diggs CH, et al. Anatomic substages of stage III-A Hodgkin's disease: a collaborative study. *Ann Intern Med.* 1980;92:159-165.

40. Desser RK, Golomb HM, Ultmann JE, et al. Prognostic classification of Hodgkin's disease in pathologic stage III, based on anatomic considerations. *Blood.* 1977;49:883-893.

41. Stein RS, Hilborn RM, Flexner JM, et al. Anatomic substages of stage III Hodgkin's disease: implications for staging, therapy, and experimental design. *Cancer.* 1978;42:429-436.

42. Stein RS, Golomb HM, Wiernik PH, et al. Anatomic substages of stage IIIA Hodgkin's disease: followup of a collaborative study. *Cancer Treat Res.* 1982;66:733-741.

43. Willett CG, Linggood RM, Meyer J, et al. Results of treatment of stage 3A Hodgkin's disease. *Cancer.* 1987;59:27-30.

44. Prosnitz LR, Montalvo RL, Fischer DB, et al. Treatment of stage IIIA Hodgkin's disease: Is radiotherapy alone adequate? *Int J Radiat Oncol Biol Phys.* 1978;4:781-787.

45. Rodger RW, Fuller LM, Hagemeister FB, et al. Reassessment of prognostic factors in stage IIIA and IIIB Hodgkin's disease treated with MOPP and radiotherapy. *Cancer.* 1981;47:2196-2203.

46. Young CW, Straus DJ, Myers J, et al. Multidisciplinary treatment of advanced Hodgkin's disease by an alternating chemotherapeutic regimen of MOPP/ABVD and low-dose radiation therapy restricted to originally bulky disease. *Cancer Treat Res.* 1982;66:907-914.

47. Hellman S, Mauch P. Role of radiation therapy in the treatment of Hodgkin's disease. *Cancer Treat Res.*

1982;66:915-923.

48. Kumar PP, Good RR, Jones EO, et al. Extended-field isocentric irradiation for Hodgkin's disease. *J Natl Med Assoc.* 1987;79:969-980.

49. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. *Cancer Res.* 1971;31:1860-1861.

50. Armitage J, Vose J, Weisenburger D, et al. ChlVPP: an effective and well tolerated alternative to MOPP. *Proc. American Society of Clinical Oncology.*1987;6:196.

51. Friedenberg WR, Dirks P, Beltaos E, et al. Improved survival in the treatment of advanced Hodgkin's disease at a nonuniversity institution (1970-1979). *Cancer.* 1986;57:12-17.

52. Bonadonna Valagassa P, Santoro A. Alternating non-cross-resistant combination chemotherapy or MOPP in stage IV Hodgkin's disease: report of 8-year results. *Ann Intern Med.* 1986;104:739-746.

53. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.

54. Peto R, Pike M. Conservatism of the approximation of $Z(O-E)^2/E$ in the log rank for survival data on tumor incidence data. *Biometrics.* 1973;29:579-584.

55. Rosenberg SA, Kaplan HS, Glatstein EJ, Portlock CS. Combined modality therapy of Hodgkin's disease: a report on the Stanford trials. *Cancer.* 1978;42:991-1000.

56. Hagemeister FB, Fuller LM, Sullivan JA, et al. Treatment of patients with stages I and II nonmediastinal Hodgkin's disease. *Cancer.* 1982;50:2307-2313.

57. Cornbleet MA, Vitolo U, Ultmann JE, et al. Pathologic stages IA and IIA Hodgkin's disease: results of treatment with radiotherapy alone (1968-1980). *J Clin Oncol.* 1985;3:758-768.

58. Koziner B, Myers J, Cirrincione C, et al. Treatment of stages I and II Hodgkin's disease with three different therapeutic modalities. *Am J Med.* 1986;80;1067-1078.

59. Gomez GA, Panahon AM, Stutzman L, et al. Large mediastinal mass in Hodgkin's disease: results of two treatment modalities. *Am J Clin Oncol.* 1984;6:65-73.

60. Zittoun RA, Audebert A, Hoerni B, et al. Extended versus involved fields irradiation combined with MOPP chemotherapy in early clinical stages of Hodgkin's disease. *J Clin Oncol.* 1985;3:2077-2214.