SWOG
Leading cancer research. Together.

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swog.org

June 15, 2011

TO: ALL SWOG MEMBER, CCOP CCOP AND CGOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS AND PATHOLOGISTS

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **SWOG-8736**, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

REVISION #14

Study Coordinator: Thomas P. Miller, M.D.
Phone number: 520/626-2667

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #14

The study referenced above has been revised as follows:

1. Page 14, Section 7.64: The following sentence has been added to the end of this section because follow-up is no longer deemed necessary: "(Note: It has been determined that follow-up until death is unnecessary, therefore, all follow-up on this study has ended **effective 7/1/2011.**)".

Please append this notice to the front of your copy of the protocol, insert the replacement pages and forward to the responsible Institutional Review Board.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.S.
Bryan Goldman, M.S.
Iris Syquia
Jeri Jardine

Southwest
Oncology Group
A National Clinical Research Group

May 15, 1998

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS AND PATHOLOGISTS

FROM: Tamra N. Oner, Protocol Coordinator

RE: **SWOG-8736**, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, A. Aref, and C. Spier.

REVISION #3

The study referenced above has been revised. A. Aref, M.D. replaces J. Robert Cassady, M.D. as the Radiation Oncology study coordinator for this study. This change is reflected on the face page. Additionally, the phone information for Drs. Miller and Spier has been updated on the face page.

This study remains permanently closed.

A replacement page is enclosed for the face page. Please append this notice to the front of your copy of the protocol and insert this replacement page.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.D.
Susan Carlin
Tracy Maher

Operations Office
14980 Omicron Drive•San Antonio, TX 78245-3217 • Telephone 210-677-8808 • FAX 210-677-0006 • http://www.oo.saci.org

Southwest
Oncology Group
A National Clinical Research Group

May 1, 1997

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS AND PATHOLOGISTS

FROM: Tamra N. Oner - Protocol Coordinator

RE: **SWOG-8736**, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

AMENDMENT #2

The study referenced above has been amended to no longer require patient follow-up at 3 month intervals until death.

Section 9.0 (Study Calendars ARM I and ARM II) has been amended as follows: Follow-up will still be required every 3 months while the patient is on treatment. After treatment is completed, follow-up will be required once every 6 months for the first 2 years, and then once annually after 2 years. Note: These follow up times are for the purposes of data collection for research purposes on this study. Patients may still need to be followed more closely than this for medical reasons at the discretion of their physician.

This study remains permanently closed.

Replacement pages are enclosed for pages 16 and 17.

This memorandum serves to inform the NCI and Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.D.
Diana Lowry
Evonne Mize
Susan Carlin

Southwest
Oncology Group
A National Clinical Research Group

February 15, 1996

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Oncologists and Pathologists

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-8736**, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

REVISION #12

Sections 12.114, 12.12, 12.13, and Section 14.6 were revised to indicate that pathology materials must be sent **directly to the pathology reviewer, Dr. Thomas Grogan**, rather than the Southwest Oncology Group Pathology Office.

Please note that materials must be identified with a hot pink "SWOG Pathology Materials" label affixed to the outside of each package. If this label is missing, the materials will not be able to be reviewed, rendering the patient ineligible. An initial supply of labels, will be sent to your institution for your use. To obtain additional labels, please call 206/ 667-4623 and ask for the Data Operations Technical Manager.

Also, the Study Specific Pathology Submission Form which includes the protocol number is also included and should be inserted into the Master Forms Set. This is reflected in Section 18.24.

This study is permanently closed.

Replacement pages are enclosed for pages 20, 22 and 29, as well as the new Study Specific Pathology Submission Form. Please insert them into your copy of the protocol.

This memorandum serves to inform the NCI and Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.D.
Diana Lowry
Evonne Mize
Susan Carlin

Southwest
Oncology Group
A National Clinical Research Group

June 15, 1995

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Oncologists and Pathologists

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: SWOG-8736, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

PERMANENT CLOSURE

The study referenced is permanently closed **effective immediately** as it has met its accrual goal and the closure has been approved by the Data and Safety Monitoring Committee.

This memorandum serves to notify the NCI and the Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Steve Dahlberg, M.S.
Danika Lew, M.A.
Diana Lowry
Evonne Mize
Susan Carlin

Operations Office
14980 Omicron Drive • San Antonio, TX 78245-3217 • Telephone 210-677-8808 • FAX 210-677-0006

Southwest
Oncology Group
A National Clinical Research Group

February 15, 1995

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Oncologists and Pathologists

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: SWOG-8736, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

TEMPORARY CLOSURE

The study referenced above will be temporarily closed **effective 3/1/95** as it has reached its accrual goal.

This memorandum serves to notify the NCI and the Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Steve Dahlberg, M.S.
Danika Lew, M.A.
Diana Lowry
Evonne Mize
Susan Carlin

Southwest
Oncology Group
A National Clinical Research Group

January 1, 1995

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Oncologists and Pathologists

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: SWOG-8736, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

REVISION #11

The Radiation Therapy Quality Assurance Center (QAC) for the Southwest Oncology Group has been moved to the new Chairman's office.

Effective January 1, 1995, all materials submitted for QAC review should be sent to the following address:

Jeffrey D. Forman, M.D.
Department of Radiation Oncology
3990 John R
Detroit, MI 48201
Phone: 313/745-2593

Sections 12.237 has been revised to reflect this change.

Revised page 21 is included for replacement into your copy of the study.

This memorandum serves to notify the NCI and the Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Steve Dahlberg, M.S.
Danika Lew, M.A.
Diana Lowry
Evonne Mize
Susan Carlin

Southwest
Oncology Group
A National Clinical Research Group

October 1, 1994

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Oncologists and Pathologists

FROM: Dana B. Sparks, M.A.T. - Protocol Coordinator

RE: **SWOG-8736**, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

AMENDMENT #1

The drug information sections and consent form toxicity sections for all the drugs in this study have been updated to include the most current information. Specifically the sections for Adriamycin, cyclophosphamide and vincristine have been updated to include information regarding the possible occurrence of acute leukemia in patients treated with anthracycline/alkylator combination chemotherapy.

This change was made as a result of a recent "Investigator's Letter" which was distributed by the Cancer Therapy Evaluation Program (CTEP) of the NCI.

Additionally, the Study Calendar for Arm II has been amended to correct the reference in the ++ footnote from "7.32" to "7.221". (The symbol for the footnote has also been changed from ++ to ν.) Also, the Operations Office telephone number in Section 16.41 was updated, and the form name on page 27 was updated from Form FDA 1639 to Form FDA 3500.

Replacement pages are enclosed for pages 4 - 6, 26 - 27 and 30 - 33. Please insert them into your copy of the protocol.To prevent extensive repagination, pages 6a, 6b and 33a have been added.

This memorandum serves to inform the NCI and Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Steve Dahlberg, M.S.
Diane Lowry
Evonne Mize
Susan Beatty

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5430 Fredericksburg R
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78229-6197
Phone 512/366-9300
FAX 512/349-4330

October 15, 1991

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Dana B. Sparks, Protocol Coordinator

RE: SWOG-8736, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T Miller, J.R. Cassady, and C. Spier.

REVISION #10

The study referenced above has been revised to allow submission of radiotherapy records for QAC review to be within 48 hours of initiation of treatment rather than 24 hours.

This revision is reflected in Section 12.23. A replacement page is enclosed for page 20 and should be inserted into your copy of the protocol.

This memorandum serves to inform the NCI and Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Steve Dahlberg, M.S.
Michael Wolf, M.S.
Evonne Mize
Susan Beatty

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FAX 512/349-433C

February 15, 1991

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Dana B. Sparks, Protocol Coordinator

RE: SWOG-8736, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

REVISION #9

The study referenced above has been editorially revised as follows:

The columns in the tables on pages 9 and 10 have been correctly aligned.

Section 14.3 was revised to correct the number of copies of forms to be sent to the Statistical Center.

Section 14.7 was revised to change the reference from Section 13.2 to the correct Section 12.2 (radiotherapy review).

Replacement pages are enclosed for pages 9, 10, 22 and 23. Please insert them into your copy of the protocol.

This memorandum serves to inform the NCI and Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Steve Dahlberg, M.S.
Michael Wolf, M.S.
~~Evonne Mize~~
Susan Beatty

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78229-6197
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FAX 512/349-433

November 1, 1990

TO: All Southwest Oncology Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Dana B. Sparks, Protocol Coordinator

RE: SWOG-8736, "Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy." Study Coordinators: Drs. T. Miller, J.R. Cassady, and C. Spier.

REVISION #8

The study referenced above has been revised to correct an editorial error. Section 7.2222 (maximum radiotherapy dose to the small bowel) now reads as follows:

> Significant volumes of small bowel (greater than 1500 cm^2) should not be irradiated to more than 4000 cGy. Small volumes of bowel (225 cm^2 or less) may be treated to a maximum of 4600 cGy.

In addition, the ADR reporting guidelines have been revised to correctly reflect the guidelines for reactions occurring with commercial agents.

Enclosed, please find a replacement page for page 11 and page 27.

This memorandum serves to inform the NCI and Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Steve Dahlberg, M.S.
Michael Wolf, M.S.
Evonne Mize
Susan Beatty

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August 15, 1990

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Southwest Oncology Group Operations Office

RE: SWOG-8736, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

MEMORANDUM

As a result of the Board of Governors action at the Spring 1990 Group Meeting, a clarification of the 14 day time limit on pretreatment tests follows:

> In calculating days of tests and measurements, the day the test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday two weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines.

Please attach this memo to the front of your protocol.

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FAX 512/349-4330

December 1, 1989

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Mary Adams

RE: **SWOG-8736**, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

REVISION #7

This protocol is being revised at this time because of the following radiation-therapy-related concerns: 1) adequacy of field; 2) difficulties in assessing adequacy of fields because of missing forms or inadequate documentation of extent of disease prior to any treatment (including surgery) on forms submitted and 3) an unsatisfactory time lag between patient registration and availability of radiation therapy planning and treatment information for radiation therapy study coordinator review and feedback.

To try to address these problems, a mechanism for early study coordinator review of sites of involvement and proposed radiation treatment plan has been defined. Changes in procedures will involve a more detailed documentation of the preregistration radiation therapy consultation already required for the study, as follows:

1) Submission of the radiation therapy initial consult note describing the proposed treatment plan (sites of involvement, doses, radiation portals, and technical factors) and

2) Mapping of proposed radiation therapy fields on the same lymphoma prestudy form diagrams used to indicate all initial sites of disease (in cases of head and neck location, the Lymphoma Head and Neck Radiotherapy Form should be used).

An error has been corrected in the Radiation Therapy Section (7.2234), the second sentence of which now states that, "the volume should be determined by the tumor status prior to the initiation of therapy (including surgical resection)."

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In eligibility, bulk of disease has been problematic for several Stage II patients registered thus far. Patients need to be carefully selected at the institutional level because of the increased chance for systemic spread with bulky stage II disease and treatment volumes needed for involved field radiation therapy. To section 5.2 has been added the sentence: "Staging and evaluation of bulk of disease for registration on this study are defined at the time of diagnosis, prior to any treatment, including surgical resection."

To section 5.11 has been added the sentence, "The radiation therapy consultation is to be documented as detailed in Section 7.221."

Other changes relating to this revision have been made in sections 7.221, 7.2234, the study calendars, sections 12.2, 14.0, 15.0 and 18.0.

Please note that, due to the method in which this protocol was originally prepared, it has been necessary to completely repaginate this study and recirculate it in its entirety. All previous revisions have been incorporated into this version. Please destroy old copies of the protocol.

This memo notifies the NCI and Statistical Center.

cc: Protocol and Information Office
Steve Dahlberg
Evonne Mize

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5430 Fredericksbu
Suite 618
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FAX 512 349-433

March 1, 1989

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Mary Adams, Protocol Coordinator

RE: SWOG-8736, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

REVISION #6

The protocol referenced above has been revised in conjunction with the activation of SWOG-8819, Central Lymphoma Repository Tissue Procurement Protocol. Participants on SWOG-8736 may now submit lymphoma specimens for Group credit. The model consent form (page 32) now refers to the laboratory testing of tissue samples.

Also, copies of the Radiation Therapy Lymphoma form and Change in Planned Radiotherapy form are attached; they were omitted from the protocol when it was activated.

This memorandum serves to notify the NCI and Statistical Center.

cc: Protocol and Information Office
Steve Dahlberg
Evonne Mize
Phyllis Goodman

Statistical Center–
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1124 Columbia St. MP-557
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FAX 512/349-433

November 15, 1988

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Mary Adams, Protocol Coordinator

RE: **SWOG-8736**, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

REVISION #5

Stratification factors in both the Eligibility Checklist and Section 6.0 of the protocol referenced above have been clarified. Question #3 under the Stratification section of the checklist now asks whether the patient's Working Formulation diagnosis is either G or H. Question #5 regarding disease status now includes residual non-measurable disease; this is reflected in Section 6.15 (page 10) of the protocol.

A new checklist and corresponding pages of the protocol are attached for your use.

This memorandum serves to notify the NCI and Statistical Center.

cc: Protocol and Information Office
Steve Dahlberg
Evonne Mize
Phyllis Goodman

Statistical Center–
Fred Hutchinson Cancer Research Center
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September 1, 1988

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Mary Adams, Protocol Coordinator

RE: SWOG-8736, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

REVISION #4

Attached for your use are new versions of the lymphoma prestudy and restaging forms (dated 8-88). Please discard the forms originally provided with this protocol and begin using the new ones as of this date. Instructions for using the forms may be found in the Data Managers Manual.

This memorandum serves to notify the NCI and Statistical Center.

cc: Protocol and Information Office
Steve Dahlberg
Evonne Mize
Phyllis Goodman

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5430 Fr
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August 1, 1988

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Mary Adams, Protocol Coordinator

RE: SWOG-8736, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

REVISION #3

To avoid confusion, allopurinol has been removed both study calendars (pages 17 and 18) as well as the flow sheet, as it is not documented elsewhere in the study. Copies of the revised pages are enclosed for inclusion in your version of the protocol.

This memorandum serves to notify the NCI and Statistical Center.

cc: Protocol and Information Office
Steve Dahlberg
Evonne Mize
Susan Beatty

Statistical Center–
Fred Hutchinson Cancer Research Center
1124 Columbia St., MP-557
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July 1, 1988

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists and Pathologists

FROM: Mary Adams, Protocol Coordinator

RE: **SWOG-8736**, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

REVISION #2

The Southwest Oncology Group Pathology Office has recently moved from Salt Lake City, Utah to Seattle, Washington. The office's new address appears in Section 12.12 (page 21) of this protocol. Sections 5.10 (page 9) and 14.6 (page 23) have also been modified in response to this change. Replacement pages are attached for inclusion in your copy of the study.

This memorandum serves to notify the NCI and Statistical Center.

cc: Protocol and Information Office
Steve Dahlberg
Evonne Mize

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FAX 512/349-4330

June 1, 1988

TO: All Group, CCOP and CGOP Medical Oncologists, Radiation Therapists

FROM: Mary Adams, Protocol Coordinator

RE: **SWOG-8736**, Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

REVISION #1

This protocol is being revised to correct an error in the dose of prednisone occurring in the study calendars and flow sheet. The dose now reads 100 mg/day, days 1-5. Replacement pages for the calendars (pages 16 and 17) and a new flow sheet are enclosed for inclusion in your copy of the protocol.

This memorandum serves to notify the NCI and Statistical Center.

cc: Protocol and Information Office
Steve Dahlberg
Evonne Mize
Sally Boynton

Statistical Center–
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Southwest Oncology Group Operations Office, 5430 Fredericksburg Road, Suite 618, San Antonio, TX 78229-3533, (512) 366-9300

March 15, 1988

Revised **December 1, 1989**

SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street MP557
Seattle, WA 98104-2092
Patient registration (206) 467-4623

SWOG Patient No. _____

Treatment No. _____

Patient name _____ Patient birthdate _____

Patient's zip code _____ Patient sex and race _____

Institution _____ Date of IRB approval _____

Investigator _____ Date of informed consent _____

Investigator No. _____ Projected start date of treatment _____

SWOG 8736 Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy

Patients registered to this protocol may also be registered to the lymphoma tissue procurement protocol, SWOG 8819. Please refer to SWOG 8819 for details.

Eligibility Checklist

Each of the questions in the following two sections must be answered appropriately for a patient to be considered eligible for registration. The checklist should be entirely filled out and should be referred to during the phone registration. A copy must be submitted with the prestudy form and initial flow sheet.

Criteria for Eligibility (All responses must be *yes*)

Yes ***No***

___ ___ 1. Have all pretreatment laboratory values (blood work and x-rays/scans/ultrasounds) which will be utilized for tumor measurement been obtained within 14 days prior to registration, and have baseline exams for screening (EKG, MUGA, etc.) and x-rays/scans/ultrasounds of uninvolved organs which are not utilized for tumor measurement been performed within 42 days prior to registration?

___ ___ 2. Does the patient have biopsy proven non-Hodgkin's lymphoma of intermediate or high grade histology (Working Formulation Categories D through H and J) EXCEPT lymphoblastic lymphoma (Category I)?
Histology _____

___ ___ 3. Does the patient have clinical or pathologic Stage I or I_e, or non-bulky stage II or II_e disease?

Note: Stage II patients must have non-bulky disease. Bulky disease is defined as mediastinal mass > 1/3 chest diameter or any mass ≥ 10 cm.

___ ___ 4. Does the patient have a performance status of 0, 1 or 2 according to Southwest Oncology Group criteria?
Performance Status _____

Southwest Oncology Group Operations Office, 5430 Fredericksburg Road, Suite 618, San Antonio, TX 78229-3533, (512) 366-9300

SWOG Patient No. _____

Eligibility Checklist SWOG 8736

Yes	No		
___	___	5.	Is the patient at least 16 years of age?
___	___	6.	Does the patient have adequate myocardial function to begin treatment at full doses and potentially receive 400 mg/M^2 of doxorubicin? If the patient's history of cardiac disease is questionable, did the baseline MUGA scan show an ejection fraction of ≥ 50%? MUGA % _____ Indicate N/A if this question does not apply to your patient.
___	___	7.	Will adequate diagnostic tissue specimen be available for pathology review?
___	___	8.	Has the patient been seen in consultation by both a medical oncologist and radiation therapist (Southwest Oncology Group members) PRIOR to this registration and will proposed radiotherapy fields be mapped on the appropriate prestudy diagram?

Criteria for Exclusion (All responses must be *no*)

Yes	No		
___	___	1.	Has the patient had prior chemotherapy or radiation therapy for any condition?
___	___	2.	Is the patient known to have central nervous system disease?
___	___	3.	Is the patient known to have AIDS syndrome or HIV associated complex?

Stratification (Response does not affect eligibility)

Yes	No		
___	___	1.	Is the patient age 65 or older?
___	___	2.	Does the patient have non-bulky stage II or IIe disease?
___	___	3.	Is the patient's Working Formulation diagnosis either G or H?
		4.	Location of Involvement: _____ GI _____ Non-GI, Abdominal _____ Non-GI, Other (specify) _____
		5.	Disease Status: _____ All disease resected _____ Residual measurable disease _____ Residual non-measurable disease

Southwest Oncology Group

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March 15, 1988
Last **Revised December 1, 1989**

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Patient registration (206) 467-4623

SWOG Patient No.	
Treatment No.	

Investigator No.		Radiation therapist	
Investigator		PATIENT NAME (last, first, m.i.)	
Institution		Patient's sex and race	
Date of IRB approval		Patient's birthdate	
Date of informed consent		Patient's Soc. Sec. No.	
Projected start date of treatment		Patient's zip code	
Radiation facility No.		Planned radiation therapy date	
Radiotherapy facility			

SWOG 8736 Treatment of Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy.

Radiotherapy Checklist

Each of the questions in the following two sections must be answered appropriately for a patient to be considered eligible for registration. The checklist should be entirely filled out and should be referred to during the phone registration.

Criteria for Eligibility (All responses must be YES)

Yes *No*

___ ___ 1. 1. Has the patient completed the third cycle of CHOP on SWOG Study 8736?

SOUTHWEST ONCOLOGY GROUP

TREATMENT OF LOCALIZED NON-HODGKIN'S LYMPHOMA: COMPARISON OF CHEMOTHERAPY (CHOP) TO CHEMOTHERAPY PLUS RADIATION THERAPY

PHASE III

PARTICIPANTS: **ALL GROUP AND CCOP MEMBER INSTITUTIONS OPEN TO ALL CGOP MEMBERS**

STUDY COORDINATORS:

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AGENTS:

Doxorubicin (NSC-123127)
Cyclophosphamide
(NSC-11987)
Prednisone (NSC-10023)
Vincristine (NSC-6754)

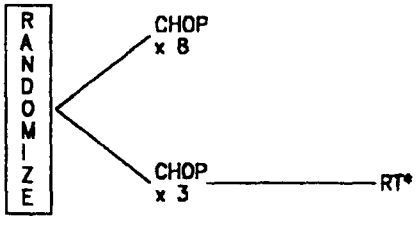
Southwest Oncology Group Protocol 8736

Schema

Stratifications: All patients will be stratified at the time of initial registration by each of the following:

1) Age (< 65 years vs ≥ 65 years)
2) Stage (I or I_e vs non-bulky II or II_e)
3) Histology (Diffuse large Cell vs Other)
4) Location of disease (GI involved vs non-GI, abdominal vs non-GI, other)
5) All disease resected vs residual measurable disease

Treatment:



*Re-register prior to starting RT

CHOP:

Cyclophosphamide, 750 mg/M^2 IV,day 1.
Doxorubicin, 50 mg/M^2 IV, day 1.
Vincristine, 1.4 mg/M^2 IV, day 1 (max 2.0).
Prednisone, 100 mg/day po x 5 days (days 1-5).

Radiotherapy:

Doses of 180 to 200 cGy given 5 days per week for a minimum total tumor dose of 4000 cGy.
Radiotherapy to start immediately after completion of the third course of CHOP (normally week 10).

1.0 OBJECTIVES

1.1 The primary study objective is to evaluate, in a cooperative group setting, the difference in survival, time to treatment failure and toxicity of two curative approaches to the treatment of patients with localized, intermediate or high grade, non-Hodgkin's lymphoma. The first treatment approach is chemotherapy using Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) for eight cycles. The second uses CHOP for three cycles followed by involved field radiation therapy.

1.2 Secondary study objectives are:

1.21 To establish the complete response rate (CR%) by treatment arm for this population of localized non-Hodgkin's lymphoma patients.

1.22 To determine if differences in the CR rate translate into longer survival and time to treatment failure.

1.23 To establish the response rate, survival duration, time to treatment failure and toxicities for separate localized histologies (diffuse large cell, diffuse small cleaved, diffuse mixed, follicular large cell and diffuse undifferentiated).

1.24 To determine if any subgroups (based on location of disease, histology, age, stage) have significant prognostic importance with regard to complete response per cent, survival duration, time to treatment failure and toxicity.

2.0 BACKGROUND

2.1 Initial Chemotherapy: This study proposes to use some initial chemotherapy for all patients with non-bulky Stage I or II unfavorable non-Hodgkin's lymphomas (NHL). That decision is primarily based on several pilot studies demonstrating large differences in relapse-free survival and overall survival for patients receiving some initial chemotherapy compared to historical trials of radiation therapy alone, and on consideration of the known clinical biology of these diseases. The rationale for using initial chemotherapy has been discussed previously *(1,2)* and is summarized here. Unfavorable NHL's are characterized by relatively rapid growth, and a propensity for early hematogenous spread making predictions of patterns of dissemination unreliable. Initial systemic treatment (chemotherapy) obviates the need for aggressive surgical staging, an important consideration for this group of patients who are frequently elderly. Initial chemotherapy reduces or eliminates the spread of disease in 10 - 20% of patients who are treated with initial regional radiation therapy. *(3,4)* In addition, the results of several large prospective trials using initial chemotherapy has resulted in consistent improvements in relapse-free survival *(2,3,5)* compared to trials of radiation therapy alone. *(6,7)* These differences have been large with at least a doubling of long-term survival in patients treated with initial chemotherapy.

2.2 Chemotherapy Regimen: The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) has been chosen for initial chemotherapy based on the following considerations. First, all reported series testing initial chemotherapy in patients with localized unfavorable NHL have used either CVP (cyclophosphamide, vincristine and prednisone) or CHOP and CHOP-like regimens. The Milan group has shown a survival advantage for patients treated with BACOP compared to those treated with CVP. *(3)* Furthermore, CHOP has a proven curative potential in unfavorable NHL, whereas CVP does not. *(8)* There is no published data to indicate that more aggressive regimens (second and third generation combinations) are more effective or safe for this elderly group of patients (median age approximately 60 years). Furthermore, it is unlikely that third generation regimens will improve the proportion of patients cured compared to results obtained with CHOP for several reasons. First, treatment with initial

chemotherapy using CHOP (with or without radiation therapy) results in a very high proportion of patients apparently cured. For example, a recent update of two series *(2,5)* resulted in a 98% CR rate in 142 patients with Stage I and II diffuse large cell NHL. Only 22 patients have relapsed resulting in a relapse-free survival of 80% at five years with a median follow-up time of 3.5 years. Among 61 patients with Stage I disease, there have only been six relapses and two deaths. It is unlikely that more aggressive treatment can be proven to improve these results, and it is likely that more aggressive treatment would not be tolerated by the significant proportion of elderly patients. Finally, there is no compelling proof that more aggressive regimens improve the outcome of patients with advanced unfavorable NHL compared to results achieved with CHOP in a cooperative group setting. *(10)*

2.3 Role of Radiotherapy: The role of radiotherapy when combined with initial chemotherapy is largely undefined. *(1,9)* However, several clinical observations suggest the combination of initial chemotherapy followed by consolidative radiation therapy may improve outcome and reduce toxicity (especially in elderly patients). First, radiation therapy alone is known to cure a proportion of patients with unfavorable NHL. *(6,7)* In the largest series reported (148 patients from Stanford), that proportion was approximately 50%. *(6)* The proportion can be increased with careful patient selection and aggressive surgical staging. *(11)* Second, the addition of consolidative radiation therapy to initial chemotherapy may decrease the amount of initial chemotherapy necessary to achieve cure *(2,5,9)* , an important consideration for elderly patients. Third, consolidative radiation therapy may increase the proportion cured compared to chemotherapy alone. This last possibility is suggested by the selection process used to determine treatment in the non-randomized series from Arizona. *(2)* Patients who could not tolerate full doses of CHOP, or who failed to achieve a CR within a few cycles of CHOP, generally received consolidative radiation therapy resulting in identical outcomes for patients receiving CHOP alone. Finally, chemotherapy with CHOP in patients with advanced disease results in an age dependent probability of cure. *(12)* Since a high proportion of patients with localized NHL are elderly, CHOP alone may result in a high relapse rate.

2.4 Duration of Chemotherapy: The current study is designed to compare the effectiveness and toxicity of two known curative approaches to patients with localized NHL. This study is not a test to determine if radiation therapy adds to chemotherapy (such a trial is currently underway by ECOG and compares eight cycles of CHOP to eight cycles of CHOP followed by radiation therapy). From pilot data, it would appear that radiation therapy adds to chemotherapy by at least allowing fewer cycles of chemotherapy to be given with equivalent results, by reducing the toxicity of chemotherapy, by allowing chemotherapy to be given to older patients (less chemotherapy), and possibly improving results after considering selection criteria of previous studies.*(2,5,9)* The optimal number of chemotherapy doses to be given prior to radiation therapy is not known *(2)* , but three cycles appear to result in a high proportion of patients cured, and is well tolerated by older patients.*(5,9)* In general, the relevant clinical question is not how to improve on the results of eight cycles of CHOP using additional treatment but how to make treatment acceptable to a wider spectrum of patients and still result in a high proportion of cures. Because less chemotherapy when combined with radiation therapy will be applicable and tolerable to larger numbers of patients, the proportion of all patients cured may increase.

3.0 DRUG INFORMATION

3. 1 Adriamycin (Doxorubicin) (NSC-123127)

a. DESCRIPTION

Mechanism of Action: Adriamycin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position.

Adriamycin is produced by fermentation from S. *Peucetius* var. *caesius*. Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

b. TOXICOLOGY

Human Toxicology: Studies with Adriamycin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2 - 3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phlebosclerosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5 - 10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nailbeds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/M^2. Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of the blood counts approximately two and a half weeks after a single injection generally permits an every three week schedule. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, patients with hepatic dysfunction may need to have reduced dosage or to be excluded from therapy. Renal excretion of Adriamycin is minimal, but enough to color the urine red; thus impaired renal function does not appear to increase the toxicity of Adriamycin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Adriamycin is supplied in 10, 20 and 50 mg single-use vials, and 150 mg multidose vials as a red-orange, lyophilized powder which has a storage stability of at least two years - see expiration date on vial. Adriamycin should be reconstituted with 5, 10, 25 and 75 ml respectively, of Sodium Chloride Injection, USP (0.9%) to give a final concentration of 2 mg/ml.

Storage and Stability: The reconstituted doxorubicin is stable for 24 hours at room temperature and 48 hours under refrigeration (2° - 8° C). It should be protected from exposure to sunlight. Discard any unused solution from the vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Adriamycin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing intravenous infusion with great care taken to avoid extravasation.

Supplier: This drug is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.2 Cyclophosphamide (Cytoxan®) (NSC-26271)

a. DESCRIPTION

2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which cross-link to tumor cell DNA.

b. TOXICOLOGY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration, nausea, vomiting, anorexia, abdominal discomfort, diarrhea, stomatitis, hemorrhagic colitis, jaundice, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration, hematuria, ureteritis, tubular necrosis, fibrosis of the bladder, cardiac toxicity which may potentiate doxorubicin-induced cardiotoxicity, rare anaphylactic reaction, skin rash, hyperpigmentation of the skin and nails, interstitial pulmonary fibrosis, and cross sensitivity with other aklylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. It may occur several years after treatment has been discontinued. It interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. It has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosupression may be seen with chronic administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. Five to twenty-five percent of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP, and may be diluted in either normal saline or D5W. The PO form is supplied as 50 mg and 25 mg tablets.

Storage and Stability: Although the reconstituted cyclophosphamide is stable for six days under refrigeration, it contains no preservatives and therefore should be used within 6 hours. Tablets are stable at room temperature.

Administration: The drug should be diluted in about 150 cc of normal saline or D5W and infused IV. An added dose of IV fluids may help prevent bladder toxicity. The tablet form of the drug may also be administered PO.

Supplier: This drug is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.3 Prednisone (NSC-10023)

a. DESCRIPTION

Prednisone is a glucocorticoid rapidly absorbed from the GI tract.

b. TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of prednisone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbitol and ephedrin enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is very slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are as follows:

Dexamethasone	Methyl-prednisolone Cortisone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	
0.75 mg	4 mg	5 mg	20 mg	25 mg

Formulation: Prednisone is available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

Storage and Stability: Prednisone should be stored at room temperature.

Supplier: Prednisone is commercially available and should be purchased by third party. Prednisone will not be supplied by the NCI.

3.4 Vincristine (Oncovin) (NSC-67574)

a. DESCRIPTION

Chemistry: Vincristine is one of the so-called vinca-alkaloids and is extracted from the plant cantharanthus roseus (vinca rosea).

Biochemistry: This drug appears to produce the arrest of mitosis in animal cells by interfering with microtubule function.

b. TOXICOLOGY

Human Toxicology: The primary toxic effects of vincristine are neurological with paresthesia, weakness, muscle wasting, motor difficulties including difficulty walking and slapping gait, loss of deep tendon reflexes, sensory loss, neuritic pain, paralytic ileus, bladder atony, and constipation. Rarely, it produces myelosuppression. Other side effects may include alopecia, allergic reactions, (including rare anaphylaxis, rash and edema), jaw pain, hypertension, hypotension, nausea, vomiting, diarrhea, fever, headache, oral ulceration, optic atrophy with blindness, ptosis, diplopia and photophobia. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: After IV administration, a triphasic serum decay pattern follows with half-lives of 5 minutes, 2-3 hours, and 85 hours. The range of terminal half-life is 19-155 hours. Excretion is 80% in the feces and 10-20 % in the urine.

The liver is the major excretory organ in humans and animals, and biliary obstruction causes increased toxicity in man.

Formulation: 1 mg/1 ml, 2 mg/2 ml, and 5 mg/5 ml vials containing solution. It is also available in 1 mg/ml and 2 mg/2 ml disposable syringes.

Storage and Stability: It should be stored under refrigeration. Vincristine is available with and without preservatives so the time-frame for use once the vial has been entered varies. The intact vials have a labelled expiration date. Protect from light. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration: Vincristine should be administered intravenously through a freely-running IV. If it extravasates, it produces a severe local reaction with skin slough. **FATAL IF GIVEN INTRATHECALLY, FOR INTRAVENOUS USE ONLY.**

Supplier: Vincristine is commercially available, and should be purchased through a third party. This drug will NOT be supplied by the NCI.

4.0 STAGING/HISTOLOGY CRITERIA

4.1 All patients must have any Stage I or I_E, or non-bulky Stage 2 or 2_E disease. The following standard tests must be performed in order to determine stage of disease: 1) Complete history and physical; 2) Routine peripheral blood counts; 3) Liver Enzyme tests; 4) Chest radiograph; 5) Abdominal CT scan; and 6) Bone marrow biopsy.

4.11 Any additional radiographic tests that may be required to rule out a symptom as being caused by lymphoma must be performed. For example, bone pain should be followed with a bone scan; central nervous system complaints should be assessed using a CT scan of the brain and lumbar puncture.

4.2 Patients must have intermediate or high grade histologies, Groups D through H and J except lymphoblastic lymphoma as defined below:

THE NEW WORKING FORMULATION OF MALIGNANT LYMPHOMAS (ML)
(with Rappaport classification equivalent)

NEW TYPE	NOMENCLATURE	OLDER TERM (RAPPAPORT)
FAVORABLE	**Low-Grade Malignancy**	
A	ML, Diffuse, small, lymphocytic (= plasmacytic features)	DLWD
B	ML, Follicular, small, cleaved	NLPD
C	ML, Follicular, mixed, small cleaved and large cell	NM
UNFAVORABLE	**Intermediate-Grade Malignancy**	
D	ML, Follicular, large cell	NH
E	ML, Diffuse, small, cleaved	DLPD (some)
F	ML, Diffuse, mixed, small, cleaved and large cell (includes Lennert's lymhoma)	DM
G	ML, Diffuse, large cell (cleaved, non-cleaved = sclerosis)	DH
UNFAVORABLE	**High-Grade Malignancy**	
H	ML, Diffuse, immunoblastic spyroninophilic (B): clear cell (T) spleomorphic	DH
I	ML, Diffuse, lymphoblastic (convoluted, nonconvoluted)	DLPD
J	ML, small, noncleaved (follicular rare, diffuse) Burkitt's	DU or Burkitt's

5.0 PATIENT ELIGIBILITY

5.1 All patients must have biopsy proven non-Hodgkin's lymphoma of intermediate and high grade histologies (Working Formulation, Groups D through H and J) except lymphoblastic lymphoma. (See Section 4.2, Working Formulation)

5.2 **Stage:** Patients must be clinically or pathologically staged, with any Stage I or I_E, or non-bulky Stage II or II_E disease eligible. (For disease $\geq$ 10 cm largest diameter or a mediastinal mass greater than one-third the maximum chest diameter, refer to SWOG-8516.) Staging and evaluation of bulk of disease for registration on this study are defined at the time of diagnosis, prior to any treatment including surgical resection.

5.3 **Prior Treatment:** No prior chemotherapy or radiation therapy will be allowed.

5.4 **Performance Status:** All patients must have a performance status of 0, 1 or 2 according to Southwest Oncology Group criteria (see Section 10.8).

5.5 **Age:** Patients must be at least 16 years of age.

5.6 **Sites of Disease:** Patients with known central nervous system disease are not eligible.

5.7 **Excised Tumor:** Patients having all visible tumor removed (excisional biopsy) are eligible. Response will not be measured.

5.8 **Organ Impairment:** Patients must have clinically adequate liver and myocardial function to begin treatment at full doses and to potentially receive 400 mg/M^2 of doxorubicin. If the patient's history of cardiac disease is questionable, a MUGA scan should be performed (patients having an abnormal ejection fraction on MUGA scan are ineligible).

5.9 **Previous Cancer:** Patients having a previous cancer with a possibility for a recurrence which might effect survival are ineligible. Previous chemotherapy or radiation therapy for any condition is not allowed (see Section 5.3).

5.10 **Pathology Review:** Adequate diagnostic tissue for expert review is required. Send diagnostic sections to the Southwest Oncology Group's Pathology Office as outlined in Section 12.0.

5.11 **Consultation:** Patients must be seen in consultation by both a medical oncologist and radiation therapist (Southwest Oncology Group members) prior to registration. The radiation therapy consultation is to be documented as detailed in Section 7.221.

5.12 Patients with known AIDS syndrome or HIV associated complex are not eligible.

5.13 Pretreatment laboratory values (blood work) and x-rays/scans/ultrasounds which will be utilized for tumor measurement must be obtained within 14 days of patient registration. Baseline exams for screening and x-rays/scans/ultrasounds of uninvolved organs which are not utilized for tumor measurement must have been performed within 42 days of registration.

5.14 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institutional and FDA guidelines.

5.15 The date of institutional review board approval must be provided at the time of registration. Failure to provide the approval date will render the patient ineligible.

6.0 STRATIFICATIONS/DESCRIPTIVE FACTORS

6.1 A dynamic patient allocation schema will be used to randomize patients equally between two treatment arms: ARM I - CHOP (eight cycles); or ARM II - CHOP (three cycles) plus involved field radiation therapy. The method of Pocock and Simon *(13)* will be used to balance patients across the following stratification factors:

6.11 Age (65 years or older versus younger than 65).

6.12 Stage (I or I_E versus non-bulky II or II_E).

6.13 Histology (Diffuse large cell versus others).

6.14 Location of disease (GI involved versus non-GI abdominal versus other).

6.15 All disease resected versus residual measurable disease vs. residual non-measurable disease.

7.0 TREATMENT PLAN

7.1 **ARM I - CHOP ALONE** (all patients randomized to this arm will initially receive full starting doses of CHOP except as indicated below):

AGENT	DOSE	ROUTE	DAYS	RETX INTERVAL	NOTES
Cyclophosphamide	750 mg/M^2	IV	1	Q 21 days	
Doxorubicin	50 mg/M^2	IV	1	Q 21 days	
Vincristine	1.4 mg/M^2	IV	1	Q 21 days	Maximum dose of 2.0 mg
Prednisone	100 mg	PO	1-5	Q 21 days	Omit if active peptic ulcer disease is present.

7.11 A complete course of chemotherapy will consist of the administration of CHOP every 21 days for eight consecutive cycles unless progressive disease develops.

7.2 **ARM II - CHOP + RADIATION THERAPY** (all patients randomized to this arm will initially receive full starting doses of CHOP except as indicated below):

7.21 **Chemotherapy:**

AGENT	DOSE	ROUTE	DAYS	RETX INTERVAL	NOTES
Cyclophosphamide	750 mg/M^2	IV	1	Q 21 days	
Doxorubicin	50 mg/M^2	IV	1	Q 21 days	
Vincristine	1.4 mg/M^2	IV	1	Q 21 days	Maximum dose of 2.0 mg
Prednisone	100 mg	PO	1-5	Q 21 days	Omit if active peptic ulcer disease is present.

7.211 A complete course of chemotherapy will consist of the administration of CHOP every 21 days for three consecutive cycles unless progressive disease develops.

7.22 **Radiation Therapy** (to begin after the completion of the third cycle of CHOP, approximately week 10 of study) (Patients should be re-registered at Statistical Center as in Section 13.4):

7.221 General Concepts of Treatment:

Multiagent chemotherapy is to be relied on to treat potential microscopic disease. Therefore, an involved field approach with irradiation is to be used. Lymph node regions or organs known to have been involved by overt disease prior to initiation of therapy are to be treated. It is therefore required that the attending radiation oncologist examine the patient prior to initiation of therapy (see Section 5.10). The radiation oncologist and medical oncologist should then jointly agree on the necessary treatment volume to treat clinically involved lymph node groups or regions. Clinical examination, radiographic evaluation and use of other imaging modalities (i.e., magnetic resonance imaging) are all suitable techniques for assessment of overt disease - see Section 9.0, Study Calendar).

All lymph node regions or organs known to be involved prior to any treatment (including surgical resection) and all proposed treatment volumes are to be mapped on pages 4 and 6 of the new Lymphoma Prestudy Form to be submitted with 14 days of registration (in cases of head and neck location, the SWOG Radiotherapy Head and Neck Form should be added to more clearly demonstrate anatomic location of the tumor and structures to be included in the fields). A copy of the written radiation therapy consultation note describing the proposed treatment plan (sites of involvement, doses, radiation portals and technical factors) is to be submitted along with the prestudy form.

7.222 Doses (all doses to be calculated at midplane of target volumes): A minimum tumor dose of 4000 cGy should be delivered to the tumor volume and dose maximum to this volume should be 4600 cGy. A small boost volume may be treated to a maximum of 5000 - 5500 cGy if overt disease remains following chemotherapy and initial irradiation.

7.2221 **Tumor Dose:** A minimum of 4000 cGy will be delivered to the tumor volume (See Section 7.223). A small boost volume may be taken to a maximum of 5000-5500 cGy if overt disease remains following chemotherapy and initial irradiation.

Doses to the following sites will be calculated if included in the treatment field:

Right Neck -- at midplane
Left neck -- at midplane
Right supraclavicular -- at 3 cm depth
Left supraclavicular -- at 3 cm depth
Mediastinum -- at midplane
Right axilla -- at midplane
Left axilla -- at midplane
Para-aortic nodes -- at midplane
Right iliac -- at midplane
Left iliac -- at midplane
Right inguinal -- at 3 cm depth
Left inguinal -- at 3 cm depth

7.2222 Maximum Dose to Critical Structures

Spinal Cord: Spinal cord dose is not to exceed 4500 cGy delivered at fraction sizes specified in Section 7.3245. Where possible, exclusion of the spinal cord after it has received 4000 cGy is desirable.

Heart: Total dose to a portion of the heart is not to exceed 4000 cGy. When a substantial (> 50%) portion of the heart must be encompassed by treatment fields, the total dose to this volume should be kept less than 3500 cGy.

Lungs: It is permissible to treat lung volumes proximate to known tumor sites with full radiation doses (i.e., margin of 1 - 2 cm). When oblique or lateral field techniques are utilized, the transit normal lung dose should be maintained at less than 1500 cGy where possible and should not exceed 1800 cGy. (uncorrected for lung inhomogeneity.)

Small Bowel: Significant volumes of small bowel (greater than 1500 cm^2)should not be irradiated to more than 4000 cGy. Small volumes of bowel (225 cm^2 or less) may be treated to a maximum of 4600 cGy.

Kidney: It is desirable to maintain renal doses less than 2000 cGy where possible. When both kidneys are to be treated, maximum renal dose to one normal kidney is 1800 cGy. Calculation is made at mid-plane of the kidney.

7.223 Radiation Portals (Volume to be Irradiated):

7.2231 All radiation fields will be simulated. Radiation fields will be planned to minimize irradiation of normal (transit) tissue not deemed to be affected by overt lymphoma. As an illustration of this, a patient with clinical unilateral pre-auricular disease should be treated by a photon or electron technique designed to exclude the unaffected pre-auricular region (and parotid gland) and, thereby, prevent treatment associated xerostomia.

Please refer to Appendix II for examples of radiation fields.

7.2232 When two lymph node groups are affected with an intervening region of clinically uninvolved lymph nodes, it is acceptable to encompass the entire volume within the treatment portals. As an example, when the left cervical and left axillary lymph nodes have been clinically involved initially, it is acceptable to irradiate the left supraclavicular fossa in addition to the axilla and cervical region.

7.2233 Treatment planning approaches and blocking techniques will be utilized to minimize normal tissue irradiation.

7.2234 A minimum margin of 1 - 1.5 cm of normal tissue should be included in the treatment volume carried to the minimum specified dose. The volume should be determined by the tumor status prior to the initiation of therapy (including surgical resection).

7.2235 When an organ such as the stomach is the primary disease site, radiation fields are to encompass that organ and any regionally affected lymph nodes. However, no attempt at routine treatment of the entire peritoneal contents should be made in this situation.

7.2236 When primary lymphoma of the bone is to be treated, the initial field will encompass the entire bone (and any overt regionally affected lymph node regions). Smaller volumes of clinically and/or radiographically affected tissues may be boosted to higher doses (see Section 7.2245).

7.224 Technical Factors:

7.2241 **Beam Energy:** Megavoltage equipment is required. Minimal acceptable energy will be ^{60}CO or 2 MV or greater x-rays. If treatment of lymph node sites located close to the surface of the skin is necessary (i.e., supraclavicular fossa) and beam energies of greater than 8-10 MV are be used, care must be taken (i.e., by use of bolus) so that superficial structures are not underdosed. For certain sites, electron beams of adequate energy may be appropriate (i.e., pre-auricular region). Electron doses should be calculated at the 90% isodose line.

7.2242 **Treatment Distance:** The minimal treatment distance should be 80 cm for either SSD or SAD technique.

7.2243 **Blocking:** Individually contoured blocks will be routinely used to protect areas not requiring irradiation from treatment. Thickness of blocks should be equal or greater than 6 half value layers ($\geq$ 6 HvL) and blocks should be fabricated so that divergence is appropriate to treatment set-up.

7.2244 **Compensating Filters:** When difference in separation within the treatment volume is sufficient to produce dose heterogeneity of greater than 10% at the isocenter or mid-plane, compensating filters should be utilized.

7.2245 **Fractionation:** Each field will be treated daily, five days a week. Daily doses will be 180-200 cGy.

7.2246 **Therapy Interruption:** Should skin or mucosal irritation, myelosuppression, bowel symptoms (i.e., diarrhea) or similar normal tissue difficulty develop, short interruptions in treatment may take place. When possible, these should be limited to less than one week; should interruptions of more than two weeks be necessary, the radiation oncology Study Coordinator must be informed and the "Change in Planned Radiation Therapy" form should be completed and submitted to the Statistical Center.

7.2247 **Treatment Planning:** All fields will be simulated and simulation fields utilized for fabrication of individualized blocks.

7.2248 **Localization Films:** Localization films taken on simulators and portal films taken on treatment machines will be necessary in all cases. Polaroid pictures of portals in treatment position are required.

7.3 **CNS Prophylaxis:** There will be no CNS prophylaxis for patients randomized to either treatment arm.

7.4 **Duration of Therapy:**

7.41 Patients with documented progressive disease at any time may be taken off protocol treatment. It is important that all patients be allowed to complete six weeks of therapy on their assigned treatment arm unless life-threatening progression or toxicity precludes completion of the trial period.

7.42 Patients will be restaged upon completion of the treatment program to assess response. Patients whose clinical disease (e.g., palpable adenopathy, mediastinal mass, etc.) has disappeared and who thereafter appear to be in complete remission should undergo a complete and thorough laboratory and radiographic search for evidence of persistent lymphoma approximately one month after the completion of therapy.

7.43 Patients with less than a complete response at restaging will be removed from protocol treatment.

7.5 **Treatment at Progression or Relapse:**

7.51 Patients who develop objective evidence of disease progression during treatment, patients who relapse following a complete remission, and patients who fail to achieve a complete remission after completing the specified protocol treatment may be treated according to physician preference (consider Southwest Oncology Group studies of bone marrow transplantation or new agents).

7.6 **Criteria for Removal From Protocol Treatment:**

7.61 Treatment may be discontinued if disease progression is documented at any time (see Section 7.51) or if a complete response is not obtained upon completion of the treatment program.

7.62 Unacceptable toxicity -- this must be documented on the flow sheet.

7.63 A patient may withdraw from protocol treatment at any time. Reasons must be documented on the flow sheet.

7.64 All patients will be followed until death. (Note: It has been determined that follow-up until death is unnecessary, therefore, all follow-up on this study has ended **effective 7/1/2011.**)

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 CHOP:

8.11 Dose Modifications for Hematologic Toxicity: The CHOP regimen should be given by the above schedule if both the WBC is ≥3,000 cells/µl (granulocytes ≥ 1,500 cells/µl) and the platelets are ≥ 75,000 cells/µl by the time the next cycle is due. If the blood counts have not recovered, treatment should be delayed one week and counts repeated. If, after two weeks, counts have not yet recovered, the patient should be treated at 75% of the dose of doxorubicin (37.5 mg/M^2) and cyclophosphamide (562.5 mg/M^2). No change in the dosage of vincristine or prednisone should be made for hematologic toxicity.

Severe infection due to chemotherapy related neutropenia would necessitate a decrease in the doses of doxorubicin and cyclophosphamide to 75% of the baseline.

8.12 Cyclophosphamide will be discontinued if hemorrhagic cystitis resulting from this drug occurs. Adequate fluid intake is recommended during therapy. Continue on protocol treatment with HOP only (doxorubicin, vincristine and prednisone).

8.13 Doxorubicin will be administered by rapid IV push or infusion. A total dosage of 550 mg/M^2 should not be exceeded. Doxorubicin should be discontinued if evidence of congestive heart failure develops.

8.14 Impaired Hepatic Function: All eligible patients should be able to receive a full initial dose of doxorubicin. If the bilirubin is > 1.2 mg/ml, the doxorubicin dose must be reduce to 25 mg/M^2 to avoid undue myelotoxicity. With subsequent cycles of treatment and with improved hepatic function, escalation of the doxorubicin dose by 12.5 mg/M^2 increments (e.g., from 25 mg/M^2 to 37.5 mg/M^2) should be made.

8.15 Vincristine should be given at a dose of 1.4 mg/M^2 (maximum 2.0 mg). Vincristine should be reduced by 50% (.7 mg/M^2) if the patient develops moderate (Grade 2) neuropathy and interrupted only if the patient becomes incapacitated. Paresthesias or loss of deep tendon reflexes alone is not sufficient reason to justify a vincristine dosage reduction. With the improvement of neuropathy or symptoms, a gradual escalation of the dose (50% increments) towards the targeted amount should be administered.

8.16 Prednisone will only be employed during the first five days of each treatment cycle at 100 mg daily in single or divided doses. Prednisone should be omitted if the patient has a history of recent active peptic ulcer disease or if peptic ulcer symptoms occur during treatment. The flow sheets must include the reason for stopping this drug.

8.2 Unexpected or fatal toxicities must be reported to the Operations Office (Mary Adams) and the NCI (including <u>suspected</u> reactions). The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR - ARM I (CHOP ALONE)

REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	£
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Every 3
PHYSICAL																												Months
History & Physical Exam	X				X			X			X			X			X			X			X					
Weight,BSA & Performance Status	X				X			X			X			X			X			X			X				X	X
Tumor Measurement	X				X			X			X			X			X			X			X				X	X
Toxicity Notation		X			X			X			X			X			X			X			X				X	X
																	X			X			X				X	X
LABORATORY																												
CBC, Platelets & Differential	X				X			X			X			X			X			X			X					
Serum Creatinine	X*																										X	X
LDH & SGOT	X										X																X	
Alkaline Phosphatase	X										X																X	
Bilirubin	X										X																X	
Bone Marrow Biopsy	X*																										X	
OTHER STUDIES																												
Chest X-Ray	X																											
CT Scan - Abdomen	X*																										X	X**
X-rays/scans needed for tumor mea	X@																										X	X**
EKG	X#																											X**
MUGA	X++																											
TREATMENT																												
Cyclophosphamide 750 mg/M2 D1		X			X			X			X			X			X			X			X					
Doxorubicin 50 mg/M2 D1		X			X			X			X			X			X			X			X					
Vincristine 1.4 mg/M2 D1		X			X			X			X			X			X			X			X					
Prednisone 100 mg/day D 1-5		X			X			X			X			X			X			X			X					
XRT Consult	X																											
FORMS																												
Lymphoma Prestudy Form	X																											
Eligibility Checklist	X																											
Pathology Materials					X																							
Restaging Form																												
Study Specific Flow Sheets	X				X			X			X			X			X			X			X				X	
																											X	X

* Required prior to registration. Repeat only if clinically indicated.

@ Not required. Obtain additional x-rays/scans if needed to measure response.

Perform pretreatment; repeat only as indicated.

++Not required unless patient history of cardiac disease is questionable (see Section 5.8).

** Repeat as necessary for tumor measurement.

THE SAME SCANNING PROCEDURE SHOULD BE USED THROUGHOUT THE PATIENT'S CLINICAL COURSE TO ALLOW UNIFORMITY OF RESULTS.

A complete course of chemotherapy consists of CHOP given every 21 days for eight consecutive cycles unless progressive disease develops.

£ ALL PATIENTS ARE FOLLOWED AT Q 3 MONTH INTERVALS UNTIL TREATMENT IS COMPLETED, THEN ONCE EVERY 6 MONTHS FOR TWO YEARS, THEN ONCE ANNUALLY UNTIL DEATH.

9.0 STUDY CALENDAR - ARM II (CHOP + RADIOTHERAPY)

£

REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Every 3
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Months
PHYSICAL																						
History & Physical Exam	X				X			X			X			X			X				X	X
Weight,BSA & Performance Status	X				X			X			X			X			X				X	X
Tumor Measurement	X				X			X			X			X			X				X	X
Toxicity Notation		X			X			X			X			X			X				X	
LABORATORY																						
CBC, Platelets & Differential	X				X			X			X			X			X				X	X
Serum Creatinine	X*																					
LDH & SGOT	X										X										X	
Alkaline Phosphatase	X										X										X	
Bilirubin	X										X										X	
Bone Marrow Biopsy	X*																					
OTHER STUDIES																						
Chest X-Ray	X																				X	X**
CT Scan - Abdomen	X*																				X	X**
X-rays/scans needed for tumor mea	X@																					X**
EKG	X#																					
MUGA	X¶																					
TREATMENT																						
Cyclophosphamide 750 mg/M2 D1		X			X			X														
Doxorubicin 50 mg/M2 D1		X			X			X														
Vincristine 1.4 mg/M2 D1		X			X			X														
Prednisone 100 mg/day D 1-5		X			X			X														
XRT Consult	X																					
Radiation Therapy √											X	X	X	X	X	X	X					
FORMS																						
Lymphoma Prestudy Form	X																					
Eligibility Checklist	X																					
Pathology Materals					X																	
Radiation Therapy Materials											X										X	
Radiotherapy Checklist											X											
Restaging Form																					X	
Study Specific Flow Sheets	X				X			X			X			X			X				X	X

* Required prior to registration. Repeat only if clinically indicated.

@ Not required. Obtain additional x-rays/scans if needed to measure response.

Perform pretreatment; repeat only as indicated.

¶ Not required unless patient history of cardiac disease is questionable (see Section 5.8).

**Repeat as necessary for tumor measurement.

THE SAME SCANNING PROCEDURE MUST BE USED THROUGHOUT THE PATIENT'S CLINICAL COURSE TO ALLOW UNIFORMITY OF RESULTS.

√ Radiation therapy dose and duration, and treatment volume will be determined jointly by the radiation oncologist and medical oncologist. (see 7.221)

A complete course of chemotherapy consists of CHOP given every 21 days for three consecutive cycles unless progressive disease develops

£ ALL PATIENTS ARE FOLLOWED AT Q 3 MONTH INTERVALS UNTIL TREATMENT IS COMPLETED, THEN ONCE EVERY 6 MONTHS FOR TWO YEARS, THEN ONCE ANUALLY UNTIL DEATH

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 All tumor measurements must be recorded in centimeters using the same tests throughout and should consist of the longest diameter and the perpendicular diameter at the widest portion of the tumor. Liver size measurements should be recorded at the xiphoid line and 8 cm lateral to the xiphoid lines, both sides.

10.2 Complete Remission: Disappearance of all clinical evidence of active tumor. The patient must be free of any symptoms of cancer. Patients with all disease resected are not evaluable for complete response. (Single bone lesion: Some radiographic evidence of healing, no new lesions, and normal enzymes.)

10.3 Partial Remission: 50% or greater decrease in the sum of the products of all diameters of measured lesions. No simultaneous increase in the size of any lesion or appearance of any new lesions may occur. Patients with all disease resected are not evaluable for partial response.

10.4 Stable Disease: Steady state or response less than a partial remission or progression. There may be no appearance of new lesions and no worsening of the symptoms.

10.5 Progression: Unequivocal increase of at least 25% in the size of any measurable lesions or appearance of new lesions.

10.6 Relapse:

10.61 The appearance of new lesions for patients in complete or partial remission.

10.62 The reappearance of old lesions in patients who were in complete remission.

10.63 For patients in partial remission, an increase of 50% or more in the sum of the products of the diameters of all measured tumors over than which was obtained at the time of maximum regression.

10.7 Performance Status: Patients will be graded according to the current Southwest Oncology Group grading scales:

GRADE	SCALE
0	Fully active; able to carry on all predisease activities without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnosfky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Study Objective: The primary objective is to assess the difference in survival of patients with localized, intermediate or high grade NHL treated with chemotherapy using eight cycles of CHOP compared to patients treated with three courses of CHOP followed by radiotherapy. Evaluation of early and late toxicities as well as the estimation of the relapse-free survival for each treatment regimen is also a primary study objective.

11.2 Randomization: Each patient will be randomly assigned to one of the two treatment regimens prior to the start of any therapy. The method of Pocock and Simon *(13)* will be used to balance patient accrual across the stratification factors defined in Section 5.0. Institution will also be used as an additional stratification factor. Therefore, each institution and each stratification factor will have approximately equal numbers of patients in each treatment arm.

11.3 Sample Size and Patient Accrual: It is anticipated that at least 80 eligible patients per year will be registered on this study. Long term (five-year) survival of 75% is consistent with previous experience using chemotherapy in this disease. Five years of patient accrual and two years of additional follow-up will provide 200 patients for each of the treatment arms and statistical power of approximately 0.80 to detect a difference in long term survival from 75% to 86% (two-sided test with critical alpha level = 0.05). This power calculation is based on the use of a parametric test to compare duration of survival, which is exponentially distributed. This provides an adequate approximation to the power of the logrank test which will be used in the final analysis.

11.4 Study Monitoring, Stopping Guidelines, Interim Analysis:

11.41 Study results will be monitored throughout the accrual and follow-up period by the Data Monitoring Committee which includes the Southwest Oncology Group Chairman, Lymphoma Committee Chairman, Study Coordinator(s) and Study Biostatistician.

11.42 Three formal interim analyses of survival will be performed at approximately two years, four years and five years after the start of patient accrual. These times are determined by when approximately equal numbers of deaths may be expected to be observed. The Data Monitoring Committee will consider the results of these interim analyses when determining either early study termination or early disclosure of study results.

To insure the overall two-sided critical level of alpha = 0.05, the three interim analyses will be done at the 0.0017, 0.0019 and 0.0023 critical levels, respectively, and the final analysis at the 0.0484 level. The probability that an interim test will indicate an apparently significant difference when the probability of survival of the two treatment groups is equivalent is 0.05.

11.43 The group-sequential boundaries described previously will be used by the Data Monitoring Committee as guidelines to be carefully considered, not as strict rules which solely determine whether the study is terminated early. Such a decision will also take into consideration the characteristics of the patients treated, type and degree of toxicity, quality of remissions obtained and other pertinent information. Interim results will not be presented outside the Data Monitoring Committee unless a decision is made to terminate accrual and report the study findings early.

11.44 Secondary study objectives include examination of subsets of patients base on histology, location of disease, age and stage. Endpoints of CR%, survival, relapse-free survival and time to progression will be analyzed. Interpretation and reporting of results from these analyses will incorporate multiple comparison and sample size considerations.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review:

12.11 Pathology review for this study is mandatory. The following pathology materials must be submitted within 30 days of registration:

12.111 Representative H&E stained slides from the original diagnostic specimen.

12.112 One representative paraffin block which will be conserved (no more than eight additional slides will be cut) and returned to the submitter.

12.113 A copy of the operative and pathology report.

12.114 A copy of the Southwest Oncology Group Lymphoma Prestudy Form and a copy of the Study Specific Pathology Submission Form.

12.12 The materials are to be forwarded to:

Thomas M. Grogan, M.D.
Dept of Pathology
Arizona Cancer Center
1501 N. Campbell Ave
Tucson, AZ 85724-0001
Phone: 602/626-2212

A copy of the Study Specific Pathology Submission Form must be submitted to the Statistical Center each time submissions are made to Dr. Grogan.

The materials must be identified with a "SWOG Pathology Materials" label on the outside of each package. If this label is missing, the materials will not be reviewed, rendering the patient ineligible. These labels will be provided by the Statistical Center. To obtain additional labels, please call 206/667-4623 and ask for the Data Operations Technical Manager.

12.13 Each slide (and block) must be numbered with the surgical pathology number or date obtained.

12.14 Pathology materials should be reviewed by the institutional pathologist prior to initial patient registration and submission to Dr. Grogan. Tumors must fit into the nomenclature designated for this protocol.

12.2 Radiation Therapy Review: (see Section 7.22 for treatment guidelines)

12.21 Early radiation therapy study coordinator review of sites of involvement and proposed treatment plan will be performed on the basis of materials submitted at the time of registration on study. Review results will be forwarded to QAC. Institutions will also be notified directly if there are any problems with the proposed radiation therapy treatment plan. (NOTE: The name and phone numbers of the SWOG radiation therapist and the data manager should be clearly indicated.)

12.22 Dosimetry Monitoring: The Radiological Physics Center may conduct a field survey and may do equipment quality control in the participating radiotherapy facilities.

12.23 Submission of Radiotherapy Records to QAC for Early Review (within 48 hours of initiation of treatment):

12.231 Treatment prescription and date of first treatment.

12.232 Copies of daily treatment sheets documenting treatment to date.

12.233 Calculation of tumor doses and computer assisted dosimetry if performed: Pertinent patient data, depth, field size, SSD and SAD, tray factors, machine ID#, machine energy, etc.

12.234 Copy of port and simulator films of treatment port used for therapy with tumor volumes outlined.

12.235 Copy of Southwest Oncology Group Lymphoma Prestudy Form and, if a head and neck site, a copy of the Lymphoma Head and Neck Radiotherapy Form.

12.236 Name, institution and telephone number of the treating radiotherapist and data manager.

12.237 The QAC will forward all films to the Statistical Center to avoid unnecessary duplication of the films.

All data should be forwarded to the Quality Assurance Center:

Jeffrey D. Forman, M.D.
Department of Radiation Oncology
3990 John R
Detroit, MI 48201
Phone: 313/745-2593

12.24 Submission of completed Radiotherapy Records to the Statistical Center (within 30 days of completion of radiation therapy):

12.241 Copy of daily dose records.

12.242 Copy of pertinent port and simulation films (if not previously sent).

12.243 Copy of any films showing any changes during therapy.

12.244 Treatment plan computations.

12.245 Photographs of patient with fields indicated.

12.246 Radiation Therapy Lymphoma Form.

12.25 Change in Radiotherapy Plans: If a patient receives the planned radiotherapy, if the patient receives radiotherapy at a non-Southwest Oncology Group approved radiotherapy facility, if the patient will not complete the planned radiotherapy course or if there will be a delay of 14 days or more in the completion of radiotherapy, the Change in Radiotherapy Plans Form should be completed and submitted to the Statistical Center.

13.0 REGISTRATION GUIDELINES

13.1 All patients must be registered through the Statistical Center by phoning 206/467-4623 during normal working hours. Patients will be stratified as follows:

13.11 Age (65 years or older versus younger than 65).

13.12 Stage (I or I_E versus non-bulky II or II_E).

13.13 Histology (Diffuse large cell versus others).

13.14 Location (GI involved versus abdominal non-GI involved versus others).

13.15 All disease resected versus residual measurable disease.

13.2 At the time of registration, the caller must be prepared to answer every question on the Eligibility Checklist, and provide descriptive factor/stratification information.

13.3 Exceptions to the current registration policies will not be permitted. Therefore, late registrations (after initiation of treatment), exceptions to eligibility requirements, participation by an institution/member not identified as eligible **AND/OR** cancellations will not be allowed.

13.4 Patients initially randomized to ARM II (CHOP plus radiation therapy) must be re-registered with the Statistical Center a second time and the Radiotherapy Eligibility Checklist completed prior to the start of radiation therapy (on or about Week 10 on protocol treatment).

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible.

14.2 Patients with inadequate documentation to determine eligibility will be deemed ineligible.

14.3 Group members, full member CCOP's (Community Clinical Oncology Program) and CGOP members (Cooperative Group Outreach Program) must submit three copies of all forms directly to the Statistical Center in Seattle.

14.4 Copies of all forms used for this study are included in the Master Forms Set in Section 18.0. These forms should be photocopied, completed and submitted for all patients.

14.5 The Lymphoma Prestudy Form must be completed and submitted along with a copy of the Eligibility Checklist, operative and pathology report, and the initial flow sheet documenting initial doses and dose calculations within 14 days of registration. NOTE: The Lymphoma Prestudy must include documentation of all disease sites and all proposed radiation therapy treatment volumes as detailed in Section 7.221. A copy of the written radiation therapy consult note must also be submitted at this time.

14.6 Histopathologic materials along with a copy of the operative and pathology reports are to be forwarded to Dr. Thomas Grogan within 30 days of registration (see Section 12.0).

A copy of the Study Specific Pathology Submission Form must be submitted to the Statistical Center each time submissions are made to Dr. Grogan.

14.7 All radiotherapy materials must be submitted for patients randomized to ARM II as outlined in Section 12.2 (Discipline Review).

14.8 The Study Specific Solid Tumor Flow Sheets must be completed and submitted (with results of the inital staging studies recorded) on active protocol patients at monthlyintervals.

14.9 An Off Treatment Notice must be completed and submitted to summarize a patient's treatment and document why a patient was taken off study (completion of treatment,progressive disease or relapse, patient refusal of further treatment or to report a patient's death). Any other survival status information should be documented in supplemental flow sheets. The Off Treatment Notice must be submitted within 14 days of the event outlined. A Notice of Death should be submitted when the patient dies.

15.0 DISTRIBUTION OF MATERIALS FOR ANALYSIS

15.1 Dr. Miller, Medical Oncology Coordinator, will receive the following from the Statistical Center for analysis:

15.11 Lymphoma Prestudy Forms (copies to be forwarded to Dr. Cassady)

15.12 Eligibility Checklists.

15.13 Study Specific Solid Tumor Flow Sheets (copies to be forwarded to Dr. Cassady)

15.14 Off Treatment Notice and Notice of Death.

15.15 Copies of operative and pathology reports.

15.16 Radiation Therapy Consult Note (copies to be forwarded to Dr. Cassady)

15.2 Dr. Cassady, Radiation Therapy Coordinator, will receive the following from the Statistical Center for analysis:

15.21 Radiation Therapy Films/Materials.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

16.1 Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations. In seeking informed consent, the following information shall be provided in a language understandable to the subject.

16.11 **Basic Elements of Informed Consent:** The following are the basic elements of informed consent which should be provided to each subject:

16.111 A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subjects participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

16.112 A description of any reasonably foreseeable risks or discomforts to the subject.

16.113 A description of any benefits to the subject or to others which may reasonably be expected from the research.

16.114 A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

16.115 A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.

16.116 For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

16.117 An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.

16.118 A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

16.12 **Additional Elements of Informed Consent:** When appropriate, one or more of the following elements of information shall also be provided to each subject:

16.121 A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, is the subject to or may become pregnant) which are currently foreseeable.

16.122 Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

16.123 Any additional costs to the subject that may result from participation in the research.

16.124 The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

16.125 A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

16.126 The approximate number of subjects involved in the study.

16.13 A subject (or the subject's legally authorized representative) must give his/her written consent to participate in the study. This consent must be witnessed and dated and retained by the investigator as part of the study records.

16.14 If Experimental Subject's Bill of Rights is applicable in your state, this form must also be prepared and signed by each subject and retained as part of the required study records.

16.15 A copy of the proposed consent form must be submitted to the Institutional Review Board together with the protocol for approval. Each subject's signed informed consent form must be kept on file by the investigator for FDA inspection at any time.

16.2 Institutional Review

16.21 This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56).

16.22 The protocol and informed consent form for this study, must be approved in writing by the appropriate Institutional Review Board (IRB). The IRB must be from an institution which has a valid Multiple Project Assurance, Single Project Assurance or Cooperative Oncology Group Assurance on file with the Office for Protection from Research Risks, National Institutes of Health. The institution must be in compliance with regulations of the Food and Drug Administration and the Department of Health and Human Services.

16.23 Significant changes to the protocol, as well as a change of principal investigator, must also be approved by the Board and documentation of this approval provided to the study monitor. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and final report within 3 months of study completion or termination. The investigator must maintain an accurate and complete record of all submissions made to the Institutional Review Board, including a list of all reports and documents submitted.

16.3 Drug Accountability

16.31 For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained.

16.32 The ledger will be maintained routinely for all studies regardless of study design, and will identify for each shipment the subject number (as applicable) and the quantity of drugs contained in the shipment. The ledger will consist of drug

Accountability Record Forms supplied by the NCI. One form for each investigational drug used on each research protocol will be kept. If a protocol contains more than one investigational drug, a separate Accountability Form should be used. A separate drug Accountability Form should also be maintained for each different strength or dosage form of the particular drug being used.

16.33 The Accountability Form will be used at each location at which drug is stored for patient administration, i.e., main pharmacy, satellite pharmacy, physician's office or other dispensing areas. The form is also designed to accommodate both dispensing accountability and any other types of drug transactions (receipts,transfers, returns, broken vials, etc.). The Accountability Form requires information related to the specific protocol and drug transactions such as dispensing to individual patients, drug receipts, transfers to and returns from satellite pharmacies, drug returns.

16.34 Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger: the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; subjects should return empty containers to the investigator, and the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

16.35 One copy of all Accountability Forms and the return statement are retained by the investigator for his files; the ledger containing copies of the inventory sheets are included in the return shipment of drug supplies.

16.4 Adverse Experiences

16.41 Any adverse experience, if deemed drug related, must be reported to the Operations Office Adverse Drug Reaction (ADR) representative (210/677-8808), who will obtain information on the ADR. Depending on the nature of the reaction and whether it was caused by an investigational or commercial agent, the ADR representative will advise whether the report to the NCI should be phoned in, written in, or both. See guidelines below. All deaths considered drug-related must be reported immediately to the ADR representative. On double-blinded studies, if the investigator must know what treatment the subject received to make therapeutic decisions, the code for that particular subject can be broken by phoning the Operations Office.

16.42 An unexpected adverse experience must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Office.

16.43 All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medication(s) (i.e., "probable", "possible" or "unrelated").

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRS) OCCURRING WITH **COMMERCIAL** AGENTS

The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) **should be reported by telephone to the Operations Office (210/677-8808), within 24 hours of occurrence, your Institutional Review Board (IRB) and by written notification to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:**

(a) Any ADR which is **BOTH** serious (life threatening [Grade 4] or fatal [Grade 5])and unexpected.[1,2,3]

(b) Any increased incidence of a known ADR which has been reported in the package insert or the literature.

(c) Any death on study if **CLEARLY** related to the commercial agent(s).

The ADR report should be documented on Form FDA-3500 and mailed to the address.

Investigational Drug Branch
P. O. Box 30012
Bethesda, MD 20824

Send a copy of the Form FDA-3500, all data records and a copy of documentation of notification of your IRB to the Operations Office within 10 days.

ATTN: ADR Program
Southwest Oncology Group
14980 Omicron Drive
San Antonio, TX 78245-3217

1. See Section 19.0, Southwest Oncology Group Toxicity Criteria.

2. A list of all known toxicities can be found in either the Background section, Drug Information or Informed Consent Form of the protocol.

3. Reactions judged definitely not to be treatment related should not be reported. However, a report shall be submitted if there is only a reasonable suspicion of drug effect.

17.0 BIBLIOGRAPHY

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4. Landberg TG, Hakanssan LG, Moller TR, Mattsson WKI, Ladys KE, Johansson BG, Killander DCF, Molin BF, Westing PF, Lennet PH, Dahl OG. CVP-remission-maintenance in stage I or II non-Hogkin's lymphomas. Preliminary results of a randomized study. Cancer 1979; 44: 831-838.

5. Connors JM, Klimo P, Fairey RN, Voss N. Brief chemotherapy and involved field radiation therapy for limited-stage histologically aggressive lymphoma. Ann of Int Med 1987; 107: 25-30.

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13. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103-115.

14. Fleming TR, Green SJ, Harrington DP. Considerations for monitoring and evaluating treatment effects in clinical trials. Controlled Clinical Trials 1984; 5: 55-66.

18.0 MASTER FORMS SET

18.1 Attached are copies of all data forms which must be completed for this study. The model informed consent form is also included in this packet, which must be reviewed and approved by the institutional review board prior to registration and treatment of patients on this study.

18.2 Forms to be used for patients treated on this study include:

18.21 Lymphoma Prestudy Form.

18.22 Study Specific Solid Tumor Flow Sheet.

18.23 Radiation Therapy Forms:

18.231 Radiation Therapy Lymphoma Form.

18.232 Change in Planned Radiotherapy Form.

18.24 Study Specific Pathology Submission Form.

18.25 Off Treatment Notice and Notice of Death.

18.26 Southwest Oncology Group Lymphoma Head and Neck Radiotherapy Form.

APPENDIX

CONSENT FORM AND INFORMATION ABOUT

SWOG-8736, "Treatment of Localized Non-Hodkgin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation Therapy, Phase III"

TO BE CONDUCTED AT

_____

_____

_____

I. You are invited to take part in this research study because you have intermediate or high-grade non-Hodgkin's lymphoma. We want to find out how well patients respond (stop growth or cause your cancer to reduce or disappear) and how long their response lasts when treated with a combination of drugs (combination chemotherapy), given either with or without radiation therapy. We also want to find out what kind of side effects each treatment causes.

We cannot and do not guarantee you will benefit if you take part in this study. The treatment you receive may even be harmful.

II. If you decide to take part in this study, your treatment will be decided in a way like picking numbers out of a hat called randomization. You will be randomized to one of two treatments (arms).

If you are assigned to the first treatment (Arm I), you will receive four drugs which consist of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP). These treatments will be repeated every three weeks for a total of eight cycles. Cyclophosphamide, Doxorubicin and Vincristine will be administered through a vein, in a solution (intravenous). Cyclophosphamide will be given over a period of 15-20 minutes, doxorubicin over 5-10 minutes, and vincristine over a period of 2-3 minutes. The intravenous drugs will be given on the first day of each treatment cycle. Prednisone shall be administered in a tablet (oral). The oral drug will be given on the first five days of each treatment cycle.

If you are assigned treatment to Arm II, you receive CHOP chemotherapy as for ARM I. However, treatment on this arm will be given for a total of three cycles only. At approximately Week 10 on this study, you will begin radiation therapy to the areas of your body affected by cancer. Your exact treatment (location and length) will be determined by your physician. Every effort will be made to treat only the diseased areas and not normal organs/tissue. It most cases, radiation therapy will last a total of six weeks.

If your disease gets worse at any time, your doctor will take you off the study and offer you other therapy. If, at the end of your treatment on this study, you do not have complete disappearance of the disease, you will be removed from the study and offered other treatment.

You will have x-rays, laboratory and other tests, including blood tests, during your therapy (approximately every three weeks) so your doctor can see how your body is responding to

treatments. Also, tissue samples that your doctor has already obtained might be used for special laboratory tests. This testing is for research purposes and will not influence the treatment of your cancer.

Administration of the drug will be (provided free of charge/charged in the usual way). The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate).

All of the drugs used in this study are commercially available.

III. Some of the side effects some people have had with Cyclophosphamide, Doxorubicin, Prednisone, Vincristine and radiation therapy are summarized below:

Cyclophosphamide (Cytoxan®)

This drug can affect several organs (or parts) of your body in addition to the cancer cells. The gastrointestinal tract (stomach and intestine) can be affected which could cause you to experience abdominal pain, diarrhea, ulcers in the mouth or stomach, loss of appetite, nausea and/or vomiting. These usually appear six hours after the drug is given and usually last less than four hours. Temporary hair loss (not only from the scalp but possibly underarms, beard, eyelashes and pubic area) can occur. The loss is occasionally total but the hair does grow back when drug treatment is stopped.

Cyclophosphamide can decrease the blood cells produced in the bone marrow. This can lead to:

1) decreased white cells which may make you more vulnerable to infection.
2) lower number of red cells which may make you short of breath, weak and fatigued.
3) lower platelets which may result in easy bruising or bleeding for a longer time.

These effects may not show up for several weeks after treatment is given.

The drug's effect on the bone marrow is temporary and transfusions are available if needed to counteract decreases in these cells until your bone marrow recovers. Blood samples will be taken frequently to monitor these effects of the drug on your bone marrow.

There is a small chance of irritating the urinary bladder (where urine is stored). This can cause pain and the appearance of blood in the urine and scarring of the bladder. However, this is almost always avoidable by drinking 8 to 10 glasses of water a day and emptying your bladder every 2 to 3 hours for three days, especially before bedtime.

Taking the drug for an extended length of time can damage the male (testes) or female (ovaries) sex glands. In men, the number of sperm may be reduced without the loss of the ability to have intercourse. Women, who are still menstruating may have irregular periods or cease to menstruate altogether for a time. The ability to have children may be permanently impaired.

Very rarely with prolonged administration the drug has been reported to cause scarring of the lungs which could cause you to experience coughing spells and shortness of breath. Heart failure has also been reported (rarely) at high doses. There is also a small chance with prolonged administration of this drug of developing a second cancer (i.e., leukemia). Therefore, the risks of not treating your disease will be weighed against this hazard.

Side-effects may be increased by using other drugs with cyclophosphamide. Phenobarbital increases the effect of cyclophosphamide on your blood cells. Other drug interactions have been reported. A list of all medications you are currently taking should be given to your physician. You

should not receive any anesthesia within 10 days of receiving cyclophosphamide. Other side-effects include skin rash, yellowing of the skin, allergic reactions and discoloration of the skin and nails. Your immune system may be affected, which would make you more vulnerable to infection. Cyclophosphamide has also been reported to have more severe side-effects in people who have had a adrenal gland removed.

This drug has been known to cause malformations in the unborn child. Therefore, precautions should be taken against becoming pregnant. This drug can also be secreted in breast milk. Therefore it is advised that nursing mothers discontinue nursing while receiving cyclophosphamide.

The occurrence of acute leukemia has been reported rarely in patients treated with combination chemotherapy using this type of drug.

Adriamycin (Doxorubicin)

This drug can affect several organs (or parts) of your body in addition to the cancer cells. The gastrointestinal tract (stomach and intestine) can be affected which could cause you to experience loss of appetite, nausea and/or vomiting, diarrhea and ulcers. The nausea and vomiting usually develop shortly after the drug is administered and usually last less than 24 hours. Some patients who have taken this drug with another drug called cytarabine have had severe ulcers in the colon.

There is a chance of experiencing soreness or painful ulcers of the mouth and throat lasting a couple of days, skin rash and appearance of dark patches on your skin. Temporary hair loss (not only from the scalp but possibly underarms, beard, eyelashes and pubic area) can occur. The loss is occasionally total but the hair does grow back when drug treatment is stopped.

If you have previously received radiation, this drug may cause you to have a rash. Adriamycin can cause your fingernails and toenails to be discolored and/or become loose. It may also cause discoloration of your skin.

Adriamycin can decrease the blood cells produced in the bone marrow. This can lead to:

1) decreased white cells which may make you more vulnerable to infection.
2) lower number of red cells which can give you symptoms of shortness of breath, weakness and fatigue.
3) lower platelets which can result in easy bruising or bleeding for a longer time.

The drug's effect on the bone marrow is only temporary and transfusions are available if needed to counteract decreases in these cells until your bone marrow recovers. Blood samples will be taken frequently to monitor these effects of the drug on your bone marrow.

Adriamycin can change the way your heart beats and how your heart transfers the beats to other parts of the heart. These effects may appear as electrocardiographic (EKG) changes and generally go away within a few hours to weeks. The drug can also affect the heart's strength to a point of the heart not pumping appropriately. The risk of developing pump failure increases after each dose of drug regardless of how long it has been since previously receiving the drug; therefore, a total lifetime dose has been determined which is not exceeded. However, even at this dose (550 mg/square meter), the chances of developing heart failure is not common. Your heart function will be monitored while receiving the drug regardless of your current total dose.

If some of the drug accidently leaks out of the vein where it is being injected, severe irritation and/or death of the tissue can occur. The vein where the drug is administered may become inflamed. All necessary precautions will be taken to prevent this from occurring. While receiving this drug, report any pain or unusual sensations so the vein can be checked. Even if the drug

does not leak out of the vein, you may experience blistering, itching, streaking of the skin and hardening of the vein.

Due to the red color of doxorubicin, your urine may turn red for 1 to 2 days after being given the drug; but this is harmless.

This drug may also cause fever, chills, facial flushing, itching, an allergic reaction, itchy or swollen eyelids and cause your eyes to water.

The occurrence of acute leukemia has been reported rarely in patients treated with combination chemotherapy using this type of drug.

Prednisone

This drug can affect several organs (or parts) of your body, in addition, to the cancer cells. In susceptible individuals, the drug can cause stomach ulcers or aggravate existing ulcers. It may also cause ulcers in the throat and problems with your pancreas.

This drug can change your physical appearance, namely in the form of increased weight gain around your stomach and a puffy appearance, especially in the face. Prednisone has a property of causing the body to retain salt and fluids which could cause an increase in blood pressure. People who are prone to heart disease may also experience heart failure. In addition, the drug may alter the body's process of handling sugar causing the sugar content of the blood to rise; however, sugar diabetes is rare. The drug may also cause problems with the level of potassium in your blood.

Additionally, patients may experience muscle weakness, brittle bones, menstrual changes, itching and other allergic reactions (including severe allergic reactions). Rarely, patients may experience mood swings, depression, trouble with sleeping, changes in personality, convulsions and dizziness.

Persons with glaucoma or a family history of glaucoma may experience a rise of their inner eye pressure or glaucoma. Prolonged administration (greater than one year in doses of 15 mg or greater) can cause cataracts. Prednisone may affect the skin by causing stretch marks (stomach, lower back, breasts and groin area), slow wound healing, increased sweating and easy bruisability. Continued use (greater than 25 mg for two weeks) can suppress the body's adrenal glands. Prednisone can alter the body's defense system increasing the susceptibility to infections.

Vincristine (Oncovin)

This drug can affect several parts of your body in addition to the cancer cells. This drug can cause loss of muscle or nerve function in the lower parts of the arms and legs which may cause tingling, numbness or weakness similar to having one's hand "fall asleep", and may be associated with some clumsiness of movement. Most of these disappear when the drug treatment is stopped. The drug can cause constipation and stomach pain. These can usually be avoided by the using stool softeners and having daily bowel movements. This drug can cause sores to appear in the mouth and temporary hair loss (not only from the scalp but possibly underarms, beard, eyelashes and pubic area) can occur. The loss is occasionally total but the hair does grow back when drug treatment is stopped.

Vincristine can decrease the blood cells produced in the bone marrow. This can lead to:

1) decreased white cells which may make you more vulnerable to infection.
2) lower number of red cells which may make you short of breath, weak and fatigued.
3) lower platelets which may result in easy bruising or bleeding for a longer time.

These effects may not show up for several weeks after treatment is given.

The drug's effect on bone marrow is temporary and transfusions are available if needed to counteract decreases in these cells until your bone marrow recovers. Blood samples will be taken frequently to monitor these effects of the drug on your bone marrow.

Some patients have experienced nausea, vomiting, diarrhea, high or low blood pressure, allergic reactions, jaw pain, headaches, fever, bladder problems and eye and vision problems (and even blindness). Some patients also experience problems with walking, problems with their reflexes and problems with their senses.

The occurrence of acute leukemia has been reported rarely in patients treated with combination chemotherapy using this type of drug.

Radiation Therapy

Possible side effects from irradiation, which have been observed in some patients are:

As radiation therapy affects several organs (or parts) of your body, in addition to the cancer cells, your gastrointestinal tract (throat, stomach and intestines) can be affected which may cause you to experience a sore throat, difficulty swallowing, loss of appetite, nausea and/or vomiting. This condition begins to improve approximately three to five days after radiation therapy is stopped. Gastrointestinal side effects will occur only if that area is being treated with radiation therapy.

Temporary hair loss (not only from the scalp but the underarms, beard, and eyelashes) can occur in the area of treatment. The loss is sometimes total but the hair usually does grow back when treatment is stopped.

You may also develop a skin reaction in the area of treatment, much like a sunburn (redness and irritation of skin).

Although the drugs and radiation therapy have been tested previously in several patients with the side effects observed listed above, there is the possibility of other side effects occuring which have not been seen previously.

IV. There may be other treatments for your cancer, such as radiation therapy (alone or in combination with other treatment) or other investigational or standard chemotherapy.

V. If you are pregnant, you cannot take part in this study. You will take a urine test to see if you are pregnant before you start treatment. If you are sexually active, we strongly recommend you take precautions to avoid the possibility of becoming pregnant because we do not know how this drug could affect an unborn child.

VI. In the event of injury or illness resulting from the research procedures, emergency medical treatment will (or will not) be provided without cost. Continuing medical care and/or hospitalization will not be provided free of charge nor will financial compensation be available.

VII. We will keep any information we learn from this study confidential and disclose it only with your permission. By signing this form, however, you allow us to make your records available to the National Cancer Institute, the Food and Drug Administration and the Quality Assurance Committee of the Southwest Oncology Group. If we publish the information we learn from this study in a medical journal, you will not be identified by name.

VIII. The doctor(s) involved with your care can answer <u>any</u> questions you may have about the drug program. In case of a problem or emergency, you can call the doctors listed below day or night.

	<u>Office</u>	<u>Home</u>
Dr.		
Dr.		
Dr.		

You can also call the Institutional Review Board (#_____) if you have any questions, comments or concerns about the study or your rights as a research subject.

IX. I understand that I have the right to refuse to participate in this research study (thereby refusing to sign this consent form) if I so desire without any fear of prejudice to additional treatment. In addition, I understand that I may refuse to continue on this study at any time after the start of therapy without fear of prejudice to additional treatment. I acknowledge receipt of a copy of this consent form, and my signature indicates that I have volunteered to participate in the study having read the information provided.

_____ _____
Date Signature of Subject

_____ _____
Signature of Witness Signature of Investigator

_____
Time

LYMPHOMA PRESTUDY

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

Institution / Member _____ S.S. No ☐☐☐-☐☐-☐☐☐☐

Physician _____ Hospital No. _____

Groups other than SWOG: Group Name/Study No./Pt. No. _____ / _____ / _____

Amended data: ☐ Yes, mark amended data in red.

Instructions: All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

PATIENT CHARACTERISTICS

Date of Birth ☐☐-☐☐-☐☐

Sex ☐ Male ☐ Female

Race ☐ White ☐ Black ☐ Other ☐ Unknown

Weight ☐☐☐.☐ kg

Height ☐☐☐ cm

BSA ☐.☐☐ m^2

Performance status

- ☐ 0–Fully active
- ☐ 1–Symptoms but ambulatory and able to do light work
- ☐ 2–No work but self care and active >50% of waking hours
- ☐ 3–Limited self care, confined to bed or chair >50% of waking hours
- ☐ 4–Completely disabled

Is patient known to have AIDS or HIV Associated Complex or known to be HIV positive?

☐ No ☐ Yes

DISEASE DESCRIPTION

Date first pathologic diagnosis: ☐☐-☐☐-☐☐

LYMPHOMA HISTOLOGIC TYPE

Hodgkin's Disease

- ☐ Nodular Sclerosis (NS)
- ☐ Mixed Cellularity (MC)
- ☐ Lymphocyte Predominant (LP)
- ☐ Lymphocyte Depleted (LD)
- ☐ Other Hodgkin's (OH), specify: _____

LYMPHOMA HISTOLOGIC TYPE (cont.)

Non-Hodgkin's Lymphoma

Note: Enter both Working Formulation and Rappaport Codes

WORKING FORMULATION

Low Grade

- ☐ A Malignant lymphoma, small lymphocytic
- ☐ B Malignant lymphoma, follicular, small cleaved cell
- ☐ C Malignant lymphoma, follicular, mixed, small and large cell

Intermediate Grade

- ☐ D Malignant lymphoma, follicular, large cell
- ☐ E Malignant lymphoma, diffuse, small cleaved cell
- ☐ F Malignant lymphoma, diffuse, mixed, small and large cell
- ☐ G Malignant lymphoma, diffuse, large cell

High Grade

- ☐ H Malignant lymphoma, large cell, immunoblastic
- ☐ I Malignant lymphoma, lymphoblastic
- ☐ J Malignant lymphoma, small, non-cleaved cell

RAPPAPORT

- ☐ DLWD Diffuse, well-differentiated lymphocytic
- ☐ NLPD Nodular, poorly differentiated lymphocytic
- ☐ NM Nodular, mixed, lymphocytic-histiocytic
- ☐ NH Nodular, histiocytic
- ☐ DLPD Diffuse, poorly differentiated lymphocytic
- ☐ DM Diffuse, mixed, lymphocytic-histiocytic
- ☐ DH Diffuse, histiocytic
- ☐ DLB Diffuse, lymphoblastic
- ☐ DU Diffuse, undifferentiated

NON-CLASSIFIED NON-HODGKIN'S

Use only when Working Formulation and Rappaport are not applicable.

☐ Specify: _____

Other Diseases

- ☐ Mycosis Fungoides
- ☐ Other, specify: _____

LYMPHOMA PRESTUDY

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

Amended data: ☐ Yes, mark amended items in red

CURRENT LABORATORY VALUES

HGB (g%)	☐☐.☐	
PLTS (x10³)	☐☐☐☐	
WBC (x10³)	☐☐☐.☐	
Lymphs (%)	☐☐	
Polys (%)	☐☐	
BUN (mg%)	☐☐☐	ULN ☐☐☐
SGOT (U/l)	☐☐☐	ULN ☐☐☐
LDH (U/l)	☐☐☐☐☐	ULN ☐☐☐☐☐
Uric Acid (g%)	☐☐.☐	
Calcium (mg%)	☐☐.☐☐	
Creatinine (mg%)	☐☐.☐☐	ULN ☐☐.☐☐
Total Bilirubin (mg%)	☐☐.☐☐	ULN ☐☐.☐☐
Alk. Phos. (U/l)	☐☐☐.☐	ULN ☐☐☐.☐

DIAGNOSTIC PROCEDURES

	No	Yes	Unknown
Bone marrow biopsy/aspiration	☐	☐	☐
Staging laparotomy	☐	☐	☐
Lymphangiogram	☐	☐	☐

Notes:

PRIOR TREATMENT related to this cancer

INSTRUCTIONS: All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Prior RADIATION THERAPY ☐ No (skip to next section) ☐ Yes

Start Date	Stop Date	Site / Dose	• Best Response
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		

Prior SYSTEMIC THERAPY ☐ No (skip to next section) ☐ Yes

Start Date	Stop Date	Treatment Description	• Best Response
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐		

• Best Response: 1=CR 2=PR 3=Response, NOS 4=Stable 5=Progressive disease 6=Not applicable 9=Unknown

LYMPHOMA PRESTUDY

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

Amended data: ☐ Yes, mark amended items in red

CURRENT NODAL INVOLVEMENT

		---Involvement--- ----Yes---- No	Yes, meas or eval	Yes, not meas and not eval	Unk	Tests done indicating involvement*				---Involvement--- ----Yes---- No	Yes, meas or eval	Yes, not meas and not eval	Unk	Tests done indicating involvement*		
Anterior Cervical	L ☐ R ☐	☐	☐	☐	☐	☐☐	☐☐	☐☐		☐	☐	☐	☐	☐☐	☐☐	☐☐
Post Cervical	L ☐ R ☐	☐	☐	☐	☐	☐☐	☐☐	☐☐		☐	☐	☐	☐	☐☐	☐☐	☐☐
Supraclavicular	L ☐ R ☐	☐	☐	☐	☐	☐☐	☐☐	☐☐		☐	☐	☐	☐	☐☐	☐☐	☐☐
Axillary	L ☐ R ☐	☐	☐	☐	☐	☐☐	☐☐	☐☐		☐	☐	☐	☐	☐☐	☐☐	☐☐
Hilar	L ☐ R ☐	☐	☐	☐	☐	☐☐	☐☐	☐☐		☐	☐	☐	☐	☐☐	☐☐	☐☐
Iliac	L ☐ R ☐	☐	☐	☐	☐	☐☐	☐☐	☐☐		☐	☐	☐	☐	☐☐	☐☐	☐☐
Inguinal or Femoral	L ☐ R ☐	☐	☐	☐	☐	☐☐	☐☐	☐☐		☐	☐	☐	☐	☐☐	☐☐	☐☐
Mediastinal		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Spleen		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Splenic Hilar		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Porta Hepatic		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Paraaortic		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Celiac		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Mesenteric or Large Intestine		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Waldeyer's Ring		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Other head & neck		☐	☐	☐	☐	☐☐	☐☐	☐☐								
Other, NOS specify: _____		☐	☐	☐	☐	☐☐	☐☐	☐☐								

Indicate the site and size of all measurable or evaluable nodes which will be followed to determine response to therapy.

Measurable/Evaluable node: Size of node (cm)

_____ ☐☐.☐ X ☐☐.☐

_____ ☐☐.☐ X ☐☐.☐

_____ ☐☐.☐ X ☐☐.☐

_____ ☐☐.☐ X ☐☐.☐

_____ ☐☐.☐ X ☐☐.☐

_____ ☐☐.☐ X ☐☐.☐

_____ ☐☐.☐ X ☐☐.☐

_____ ☐☐.☐ X ☐☐.☐

* Test codes:

01–Palpation
02–Not applicable
03–Endoscopy
10–Plain film/X-ray
11–Not applicable
12–CT scan
13–MRI scan
14–Radioisotope scan
15–Ultrasound
20–Histologic confirmation
21–Cytologic confirmation
99–Other

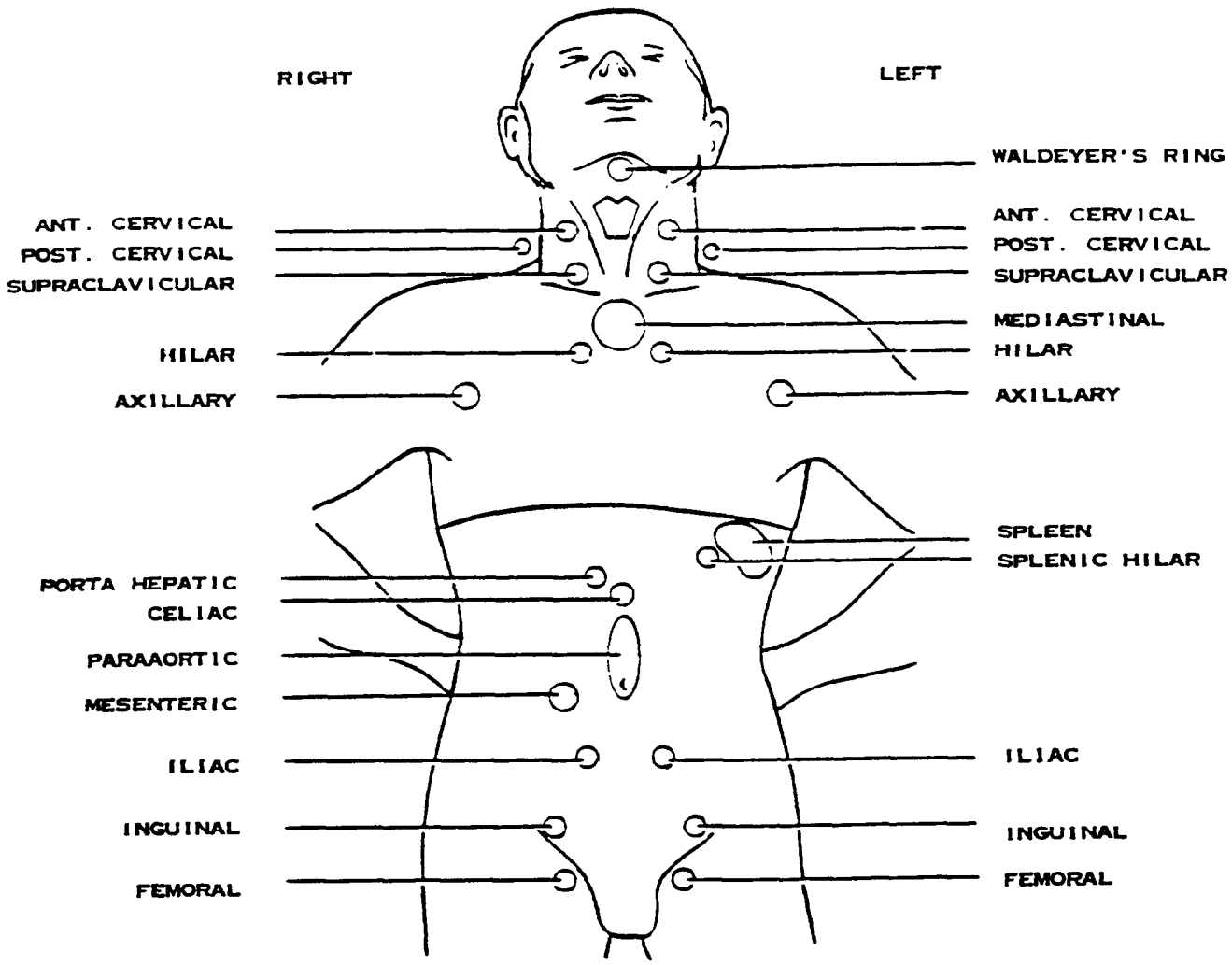
Notes:

LYMPHOMA PRESTUDY SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

☐ No current nodal involvement

INDICATE DISEASE BY COLORING IN SCHEMATIC LYMPH NODES AND/OR SPLEEN



OTHER HEAD AND NECK _____

OTHER THORAX _____

OTHER ABDOMEN, PELVIS LOWER TRUNK _____

OTHER, SPECIFY _____

LYMPHOMA PRESTUDY

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L,F,M)

Amended data: ☐ Yes, mark amended items in red

INSTRUCTIONS: For each site, indicate disease involvement as well as how this was determined. If measurable disease is present indicate largest bidimensional size of mass.

CURRENT EXTRA-NODAL INVOLVEMENT

	---Involvement--- ----Yes----					
	No	Yes, meas or eval	Yes, not meas and not eval	Unk	Tests done indicating involvement*	Size (cm) of measurable/evaluable disease
Bone Marrow	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	
Lung	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Pleura	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Stomach	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Liver	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Kidney	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Bone	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
CNS/Brain	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Head and Neck	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Skin/subcutaneous	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
GI Tract	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
Additional Involved Sites:						
_____	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
_____	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐
_____	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐

* Test codes:
01-Palpation
02-Not applicable
03-Endoscopy
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11-Not applicable
12-CT scan
13-MRI scan
14-Radioisotope scan
15-Ultrasound
20-Histologic confirmation
21-Cytologic confirmation
99-Other

STAGE OF DISEASE AT DIAGNOSIS

☐ I ☐ II ☐ III ☐ IV

E-Extranodal/Direct Extension ☐ No ☐ Yes ☐ Unknown

S-Spleen involvement ☐ No ☐ Yes ☐ Unknown

☐ A ☐ B-Symptoms

☐ Weight loss Kg lost _____

☐ Fever

☐ Night sweats

For stage III Hodgkin's Disease, indicate substage: ☐ III_1 ☐ III_2

For non-Hodgkin's Lymphoma, indicate Bulky Disease: ☐ No ☐ Yes

If Bulky Disease, indicate:

Mediastinal mass diameter ☐☐.☐ cm and Chest diameter ☐☐.☐ cm

or Mass diameter ☐☐.☐ cm Site _____

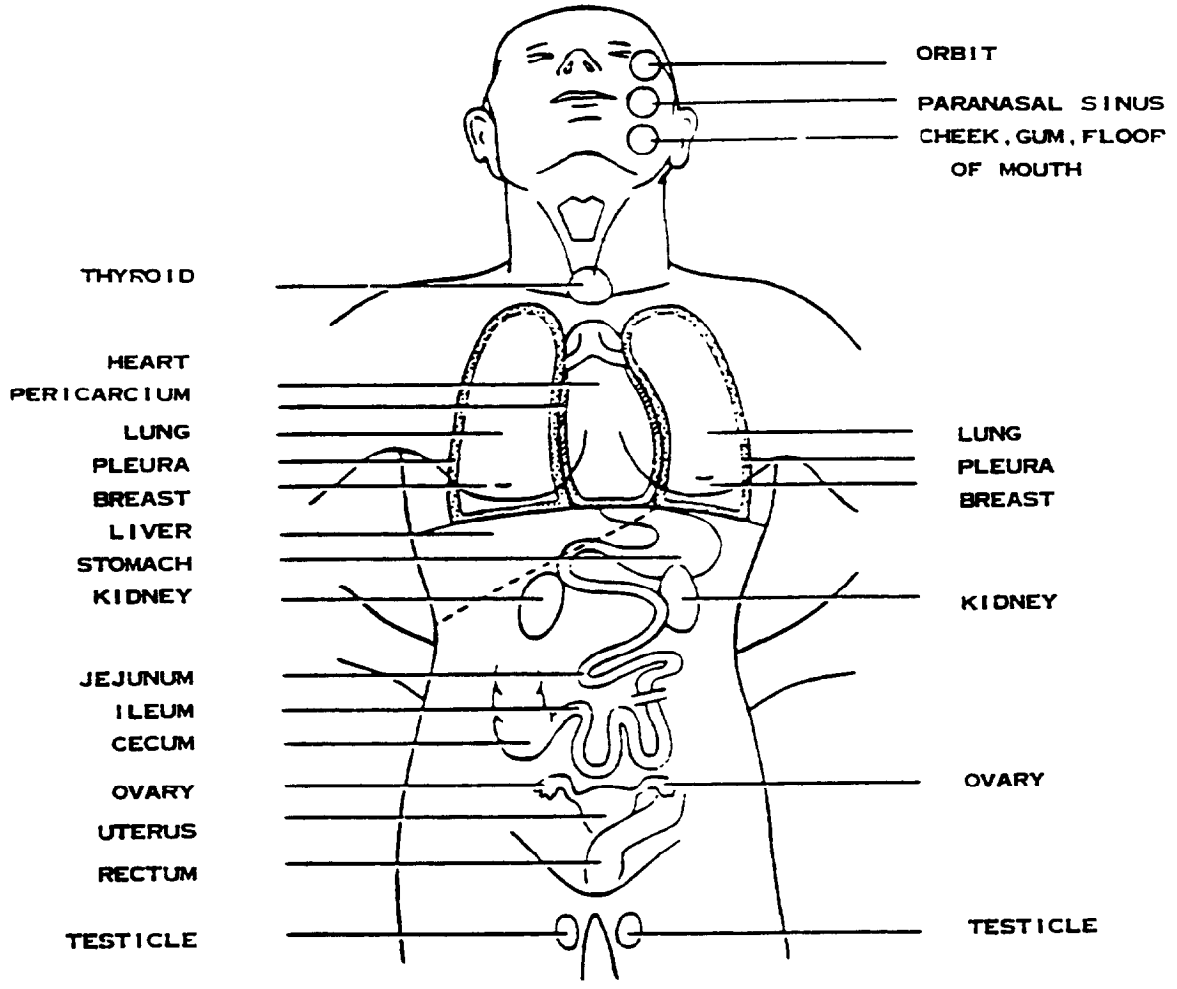
LYMPHOMA PRESTUDY

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

☐ No current extranodal involvement

INDICATE DISEASE BY COLORING IN SCHEMATIC ORGANS ON BI-SEX FIGURE



SKIN/SUBCUTANEOUS ○

BONE ○

BONE MARROW ○

BRAIN ○

OTHER, SPECIFY ○

BY: _____ DATE: _____

Revised 6/1/88
Revised 8/1/88

SOLID TUMOR FLOW SHEET SWOG- 8736

PT. # REG DATE

UNIT # PAGE

PATIENT

INVESTIG.

INSTITUTION

STUDY # 8736 RX. #

DISEASE CAT Localized NHL

PROGRESS NOTES (DATE EACH)

DATE 19 Mo./Day					
DAY ON STUDY					
TREATMENT					
BSA					
Cyclophos 750 mg/M2 D1					
Doxorubicin 50 mg/M2 D1					
Vincristine 1.4 mg/M2 D1					
Pred100 mg/day po D1-5					
Cumulative cGy *					
Cumulative cGy*					
Antibiotics					
MARROW BIOPSY					
CELLULARITY					
TUMOR CELLS					
BLOOD					
HGB					
HCT					
PLATLETS/μl					
WBC/μl					
NEUTROPHILES					
LYMPHOCYTES					
MONOCYTES					
EOSINOPHILES					
LAB					
Serum Creatinine					
LDH					
SGOT					
Alkaline Phosphatase					
Bilirubin					
EKG					
MUGA					
Chest X-ray					
CT of Abdomen					
PHYSICAL					
TEMP					
WEIGHT (KG) (LB)					
INFECTION					
LESIONS					
#1					
#2					
#3					
#4					
#5					
#6					
SYMPTOMS					
Performance Status					
TOXICITY					
Nausea/Vomiting (N/V)					
Hemorrhagic Cystitis					
Infection/Hepatic					
Neuropathy					
Peptic Ulcers					
Cardiac/Pneumonitis					
Xerostomia/Dental					
Diff Swallowing/Sore Throat					
Skin Reactions					
RESPONSE					
OBJECTIVE					

*Indicate site of radiation therapy in Progress

LYMPHOMA RESTAGING

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L,F,M)

Institution / Member _____ S.S. No ☐☐☐-☐☐-☐☐☐☐

Physician _____ Hospital No. _____

Groups other than SWOG: Group Name/Study No./Pt. No. _____ / _____ / _____

Amended data: ☐ Yes, mark amended items in red

INVESTIGATOR ASSESSMENT OF RESPONSE

☐
1 – CR
2 – PR
3 – Improvement
4 – Stable
5 – Increasing Disease
6 – Early Death

CURRENT NODAL INVOLVEMENT

		---Involvement--- ----Yes----					---Involvement--- ----Yes----				
		No	Yes, meas or eval	Yes, not meas and not eval	Unk	Tests done indicating involvement*		No	Yes, meas or eval	Yes, not meas and not eval	Unk	Tests done indicating involvement*
Anterior Cervical	L / R	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐	☐	☐	☐	☐	☐☐ ☐☐ ☐☐
Post Cervical	L / R	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐	☐	☐	☐	☐	☐☐ ☐☐ ☐☐
Supraclavicular	L / R	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐	☐	☐	☐	☐	☐☐ ☐☐ ☐☐
Axillary	L / R	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐	☐	☐	☐	☐	☐☐ ☐☐ ☐☐
Hilar	L / R	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐	☐	☐	☐	☐	☐☐ ☐☐ ☐☐
Iliac	L / R	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐	☐	☐	☐	☐	☐☐ ☐☐ ☐☐
Inguinal or Femoral	L / R	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐	☐	☐	☐	☐	☐☐ ☐☐ ☐☐
Mediastinal		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
Spleen		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
Splenic Hilar		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
Porta Hepatic		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
Paraaortic		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
Celiac		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
Mesenteric or Large Intestine		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
Waldeyer's Ring		☐	☐	☐	☐	☐☐ ☐☐ ☐☐						
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Indicate the site and size of all measurable or evaluable nodes which will be followed to determine response to therapy.

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LYMPHOMA RESTAGING SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

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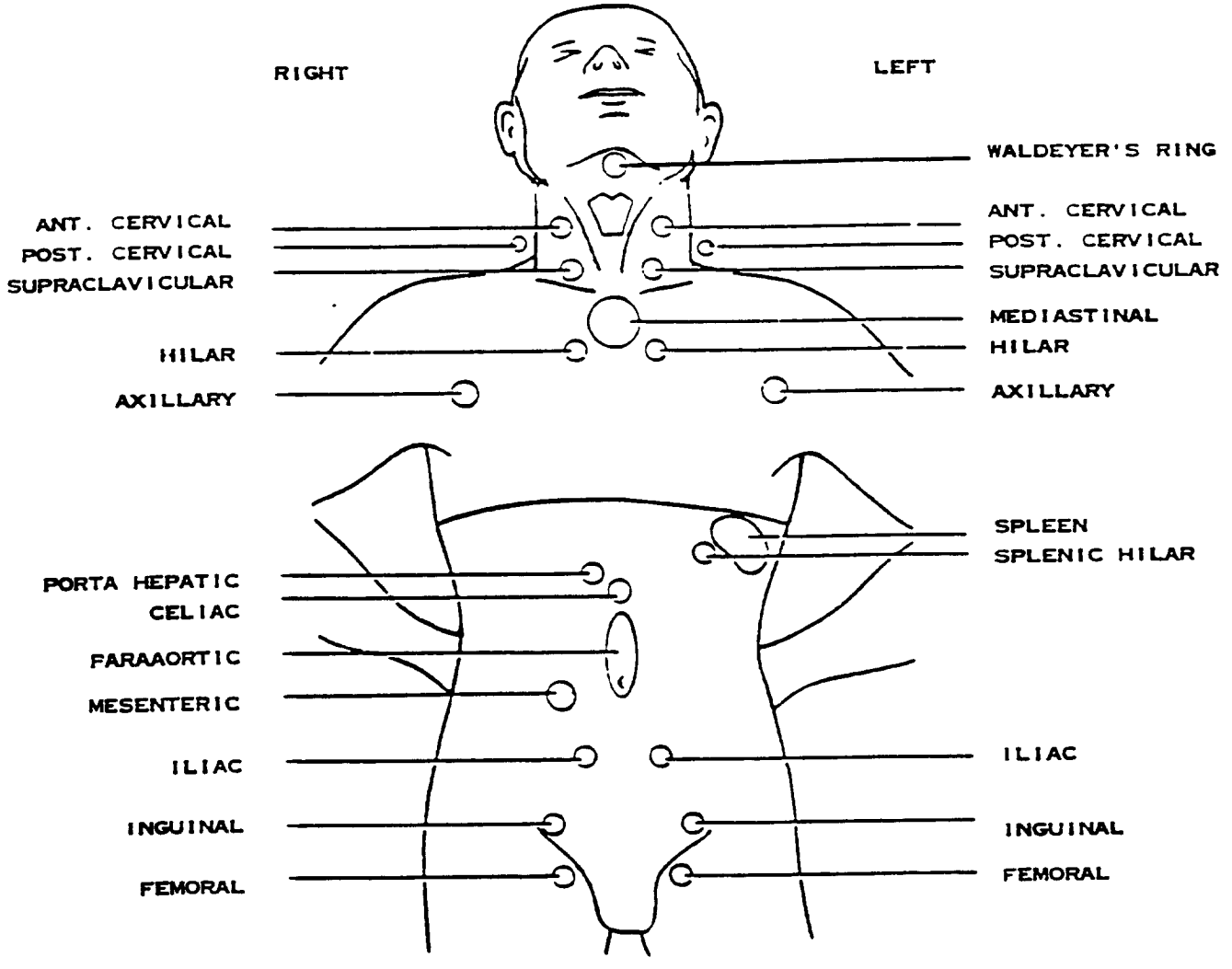
INDICATE DISEASE BY COLORING IN SCHEMATIC LYMPH NODES AND/OR SPLEEN



OTHER HEAD AND NECK _____

OTHER THORAX _____

OTHER ABDOMEN, PELVIS
LOWER TRUNK _____

OTHER, SPECIFY _____

LYMPHOMA RESTAGING

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L,F,M)

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INSTRUCTIONS: For each site, indicate disease involvement as well as how this was determined. If measurable disease is present indicate largest bidimensional size of mass.

CURRENT EXTRA-NODAL INVOLVEMENT

	---Involvement---						
		----Yes----					
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Bone Marrow	☐	☐	☐	☐	☐☐ ☐☐ ☐☐		
Lung	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Pleura	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Stomach	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Liver	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Kidney	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Bone	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
CNS/Brain	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Head and Neck	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Skin/subcutaneous	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
GI Tract	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
Additional Involved Sites:							
_____	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
_____	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	
_____	☐	☐	☐	☐	☐☐ ☐☐ ☐☐	☐☐.☐ X ☐☐.☐	

* Test codes:

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13–MRI scan
14–Radioisotope scan
15–Ultrasound
20–Histologic confirmation
21–Cytologic confirmation
99–Other

PATIENT CHARACTERISTICS

Performance status ☐

0 – Fully active
1 – Symptoms but ambulatory and able to do light work
2 – No work but self care and active > 50% of waking hours
3 – Limited self care, confined to bed or chair > 50% of waking hours
4 – Completely disabled

Is patient known to have AIDS or HIV Associated Complex or known to be HIV positive? ☐No ☐Yes

DIAGNOSTIC PROCEDURES

	No	Yes	Unknown
Bone marrow biopsy/aspiration	☐	☐	☐
Staging laparotomy	☐	☐	☐
Lymphangiogram	☐	☐	☐

Notes:

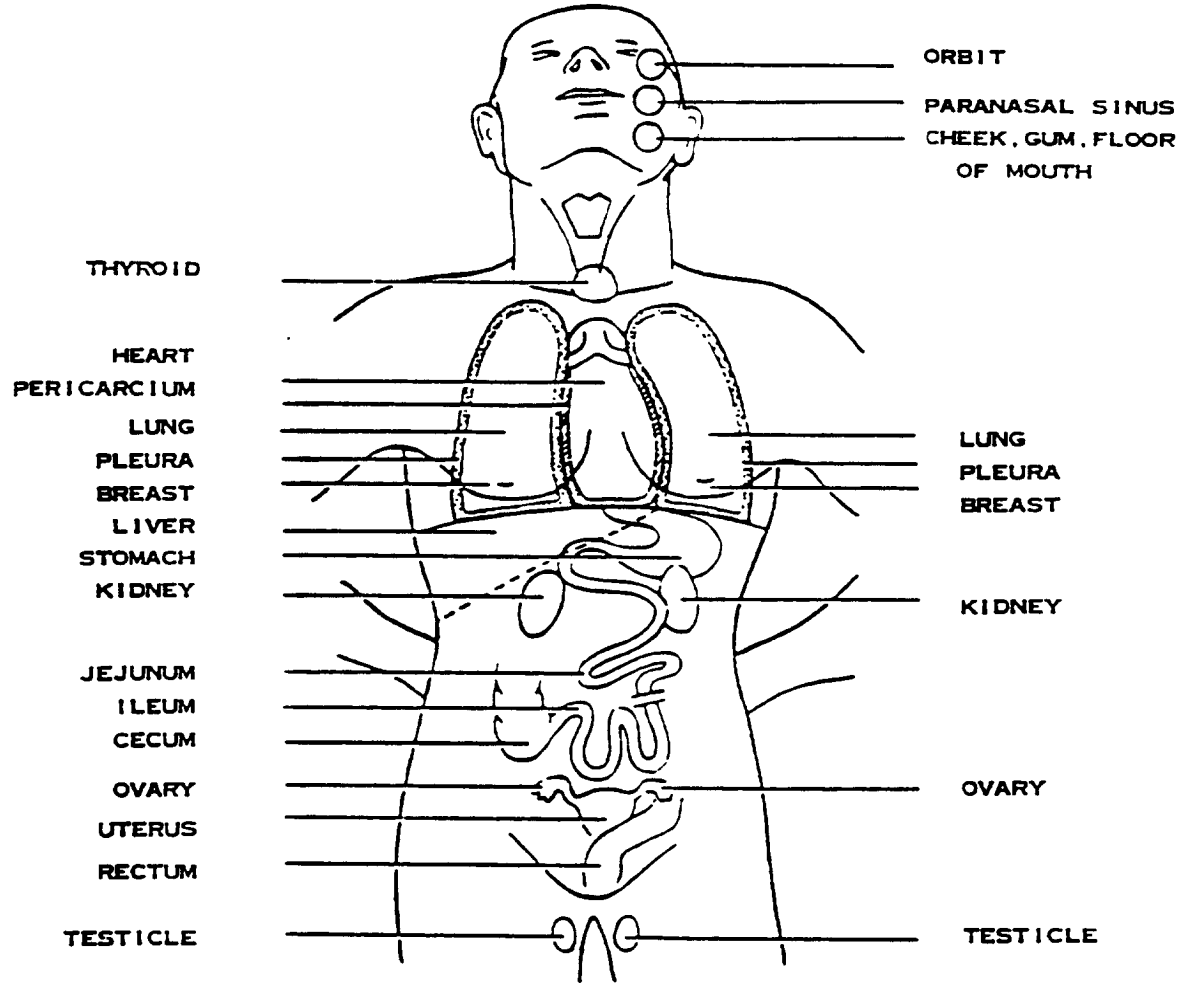
LYMPHOMA RESTAGING

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

☐ No current extranodal involvement

INDICATE DISEASE BY COLORING IN SCHEMATIC ORGANS
ON BI-SEX FIGURE



SKIN/SUBCUTANEOUS _____

BONE _____

BONE MARROW _____

BRAIN _____

OTHER, SPECIFY _____

BY: _____ DATE: _____

Southwest Oncology Group-*Operations Office*
5430 Fredericksburg Road, Suite 618
San Antonio, Texas 78229-3533
512/366-9300

Memorandum

To: All Group Data Managers

From: Charles A. Coltman, Jr., M.D., Chairman

Re: Off Treatment Notice and Notice of Death

Effective immediately for all active Southwest Oncology Group studies the attached Off Treatment Notice and Notice of Death will replace the Protocol Treatment Summary/Off Study Summary form. Please add these forms to your Master Forms Set.

OFF TREATMENT NOTICE

The purpose of this form is to notify the Study Coordinators and Statistical Center that the patient has gone off protocol specified treatment. For Southwest Oncology Group clinical studies, patients are followed until death regardless of whether they are on or off protocol treatment.

PROTOCOL STEP

A protocol step is initiated by a registrationphone call to the Statistical Center. For studies with only one registration, the Protocol Step is coded "1". For studies with multiple registrations, the first registration is coded "1"; subsequent registrations for cross-over, consolidation, or maintenance steps will have different Protocol Step codes, e.g. "2", "3", "X", "C". Leave Protocol Step blank for second and third registrations if you do not know the appropriate code.

In future protocols, Protocol Step(s) and codes will be clearly specified.

For each protocol step, submit an Off Treatment Notice to the Statistical Center within two weeks following:

successful completion of all treatment specified in protocol
or
discontinuation of protocol treatment or death.

Code the start date, stop date, and treatment description for all treatment specified for the protocol step that was administered. The Start Date is the date protocol treatment was actually started, not the date of registration; Stop Date is the last date that protocol step treatment was given, not the date of decision to discontinue treatment.

The Date Off Treatment corresponds to the reason coded under Reason Off Treatment. For example, if Reason Off Treatment is coded "2 - Toxicity, medically required, specify", code Date Off Treatment as the date the decision to discontinue treatment due to toxicity was made. If the patient has progressive disease or relapses while on protocol treatment, code Reason Off Treatment as "5 - Progression or relapse" and code the Date Off Treatment as the date of progression or relapse. If the patient continued to receive protocol treatment after progression was documented, still code the Date Off Treatment as the date of progression, but code the Stop Date as the last day protocol treatment was given.

OBSERVATION ARMS

For patients registered to Observation Arms who complete one year of observation, submit the Off Treatment Notice one year following registration to the observation arm and code Reason Off Treatment "1 - Treatment completed per protocol".
For patients who refuse to be followed, die, or have disease progression or relapse within the first year of observation, code Reason Off Treatment as the reason the patient is off the observation step and code the Date Off Treatment as the date of refusal, death, or disease progression or relapse.

NOTICE OF DEATH

Submit a Notice of Death form to the Statistical Center within four weeks of learning of the patient's death. This form is designed to more clearly define the primary and related causes of death. There should be only one square checked for each of the three causes (any cancer, toxicity..., and non-cancer...). The primary cause (Block 2) should be checked for only one of the three causes of death. The other two causes may be unrelated to the primary cause of death (Block 1), contributing to the primary cause of death (Block 3), possibly related to the cause of death (Block 4) or having an unknown relationship to the primary cause of death (Block 5). Toxicity from disease related treatment refers to any toxicities, complications, or side-effects resulting from any disease related treatment, not just protocol specified treatments. The ideal source of immediate guidance for filling out the cause of death is the treating physician.

OPERATIONAL CHANGES

Following implementation of these new data collection forms, the following modifications to data reporting are in effect:

Information on treatment response and toxicity will be reported to the Statistical Center only on flowsheets.

The old Protocol Treatment Summary/Off Study Summary will no longer be used.

Following submission of an Off Treatment Notice, patient status information must be submitted using flowsheets rather than the Protocol Treatment Summary/Off Study Summary.

CAC/mc
Enclosure

OFF TREATMENT NOTICE

Amended data: ☐ Yes, mark amended items in red

Disease Committee _____ Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient Name _____ (L,F,M)

Institution/Member _____ Physician _____

INSTRUCTIONS: For each protocol step, submit this form within 2 weeks after completion (or discontinuation) of treatment. List protocol-directed treatments that the patient received

Chemotherapy: List regimens, start and stop dates. For multidrug regimens, do not list individual drugs separately; stop date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery and in the "stop" column the date of surgery

Radiation: List sites, start and stop dates (inclusive of boosts and implants).

Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Start Date (M,D,Y)	Stop Date (M,D,Y)	REGIMEN or PROCEDURE or SITE(S)
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	

(If more room is required please continue on a separate page.)

REASON OFF TREATMENT (Check one)

- ☐ 1-Treatment completed per protocol
- ☐ 2-Toxicity, medically required, specify _____
- ☐ 3-Patient refused, due to toxicity, specify _____
- ☐ 4-Patient refused, other than toxicity, specify _____
- ☐ 5-Progression or relapse. Sites: _____
- ☐ 6-Death (attach NOTICE OF DEATH form)
- ☐ 7-Other, specify _____

DATE OFF TREATMENT

Date of completion, progression, death or decision to discontinue therapy ☐☐-☐☐-☐☐ (M,D,Y)

Will patient receive FURTHER TREATMENT?

☐ No ☐ Yes, specify: _____ ☐ Unknown

Date of LAST CONTACT (or death): ☐☐-☐☐-☐☐ (M,D,Y)

VITAL STATUS: ☐ Alive ☐ Dead (attach NOTICE OF DEATH form)

Notes:

BY: _____ DATE: _____

NOTICE OF DEATH

Amended data: ☐ Yes, mark amended items in red

Disease Committee _____ Most Recent SWOG Study No. ☐☐☐☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient Name _____ (L,F,M)

Institution/Member _____ Physician _____

INSTRUCTIONS: Submit within 4 weeks of knowledge of death.

Date of death: ☐☐-☐☐-☐☐ (M,D,Y)

Causes of Death

Any cancer (check one)

1 ☐ No 2 ☐ Primary cause 3 ☐ Contributory 4 ☐ Possible 5 ☐ Unknown

If patient has had multiple tumor types, specify those which were causes of death:

_____

_____

Toxicity from disease related treatment (check one)

1 ☐ No 2 ☐ Primary cause 3 ☐ Contributory 4 ☐ Possible 5 ☐ Unknown

If 2, 3, or 4, specify treatment and toxicity _____

_____

Non-cancer and non-treatment related causes (check one)

1 ☐ No 2 ☐ Primary cause 3 ☐ Contributory 4 ☐ Possible 5 ☐ Unknown

If 2, 3, or 4, specify _____

Autopsy done? ☐ No ☐ Yes ☐ Unknown

Death Information obtained from (check all that apply):

- ☐ Autopsy report
- ☐ Medical record / death certificate
- ☐ Physician
- ☐ Relative or friend
- ☐ Other, specify _____

Notes:

BY: _____ DATE: _____

1 [2][2][1] 4 SWOG or Other Group Patient Number [ ][ ][ ][ ][ ][ ]

Disease Type 10 [L]

Study No. 11 [ ][ ][ ][ ]

Patient Name: Last, First, Middle Init. _____

Institution _____

Hospital Unit No. _____

Trt. No. _____

Accession No. _____

Hdqts Use 15 [ ]

Radiotherapist _____

COMPLETE NEW FORM FOR EACH COURSE OF XRT

XRT FORM BEING COMPLETED AT TIME OF (Course Number)

16 [ ]
1 - 1st course
2 - 2nd course
3 - 3rd course
4 - 4th course
5 - Treatment for Progressive Disease (1st)
6 - Treatment for Progressive Disease (2nd)

DATES

	Mo	Day	Yr
Start XRT 17			
End XRT 23			

XRT MODALITY — Type

29 [ ]
1 - 60Co
2 - Megavoltage (specify equip & voltage) _____
3 - Electrons (specify equip & voltage) _____
4 - Other (specify) _____

RADIOTHERAPY TECHNIQUES
(Fill in technique for specific course)

UPPER TORSO

30 [ ][ ]
0 - Single IF field — specify site _____
1 - Parallel opposed IF fields — specify sites _____
2 - Wedge Pairs — specify _____
3 - Waldeyer's Ring Technique
4 - Shawl Technique, ant and post fields
5 - Shawl, ant field with supplementary post fields
6 - Mantle, ant and post fields
7 - Mantle, ant with supplementary post fields
8 - Other — specify _____

LOWER TORSO — LIMITED FIELDS

32 [ ][ ]
1 - Single IF field — specify site _____
2 - Parallel opposed IF fields — specify sites _____
3 - Paraaortic nodes and splenic pedicle, ant and post fields
4 - Paraaortic nodes and spleen, ant and post fields
5 - Pelvis, ant and post fields
6 - Inverted "Y", ant and post fields
7 - Inverted "Y" and splenic pedicle, ant and post fields
8 - Inverted "Y" and spleen, ant and post fields
9 - Other — specify _____

LOWER TORSO — TOTAL ABDOMEN

34 [ ][ ]
1 - Total abdomen, ant and post fields
2 - Upper 2/3 of abdomen, ant and post fields
3 - Pelvis, ant and post fields
4 - Other — specify _____

TREATMENT AREAS — TIME AND DOSAGE

		BASIC TUMOR DOSE		BOOST TUMOR DOSE	
		Dose — Rad	Time Elapsed Days	Dose — Rad	Time Elapsed Days
1 [2][2][2] 4 DUP 15	UPPER TORSO				
	1. Waldeyer's ring	36	40	43	47
	2. Right Neck	49	53	56	60
	3. Left Neck	62	66	69	73 =
	4. Right Supraclavicular	16	20	23	27
	5. Left Supraclavicular	29	33	36	40
	6. Mediastinum	42	46	49	53
	7. Right Axilla	55	59	62	66
1 [2][2][3] 4 DUP 15	8. Left Axilla	68	72	75	79 =
	9. Other — e.g. spinal cord specify _____	16	20	23	27
	LOWER TORSO				
	1. Paraaortic	29	33	36	40
	2. Pelvis	42	46	49	53
	3. Upper 2/3 Abdomen	55	59	62	66
	4. Rt iliac area	68	72	75	79 =
1 [2][2][4] 4 DUP 15	5. Lt iliac area	16	20	23	27
	6. Right Inguinal and Femoral	29	33	36	40
	7. Left Inguinal and Femoral	42	46	49	53
	8. Other — e.g. splenic pedicle specify _____	55	59	62	66 =

68 [ ] FRACTIONATION
1 - Strip
2 - Planned Split Course
3 - 3 days/wk.
4 - 4 days/wk.
5 - 5 days/wk.

69 [ ] BOOST TUMOR DOS
1 - Concurrent
2 - Sequential
3 - Not Applicable

RADIOTHERAPY HODGKIN'S & LYMPHOMA FORM PAGE 2

1 [2][2][5] 4 [DUP ——] 15

Patient Name: Last, First, Middle Init.

INTERRUPTIONS — DAYS AND REASON(S)

Days		Reasons	
16		25	
19		28	
22		31	

1 - Social
2 - Local reaction
3 - Systemic reaction
4 - Unsatisfactory WBC Count
5 - Unsatisfactory Platelet Count
6 - Other (specify) ——
9 - Unknown

Specify if Reaction is due to:

1 - Chemotherapy
2 - Radiotherapy
3 - Combination
4 - None of the above
9 - Unknown

34 [ ]

Please enclose copies of: port films, daily radiotherapy treatment record, all dose calculations and isodose curves.

Signature — Radiotherapist | Date

EVALUATION — TO BE FILLED IN BY RADIOLOGIC PHYSICS CENTER & RADIOTHERAPY STUDY COORDINATOR

	Dose Agreement within ± 5%	Dose Acceptability	Dose Rate Acceptability	RET
UPPER TORSO		[2][2][6] 1 4 [DUP ——] 15		
1. Waldeyer's ring	35	52	16	33
2. Right Neck	36	53	17	37
3. Left Neck	37	54	18	41
4. Right Supraclavicular	38	55	19	45
5. Left Supraclavicular	39	56	20	49
6. Mediastinum	40	57	21	53
7. Right Axilla	41	58	22	57
8. Left Axilla	42	59	23	61
9. Other — e.g. spinal cord specify ——	43	60	24	65
	1 - Yes 2 - No	1 - Adequate 9 - Unknown 2 - Considered Excessive 3 - Considered Inadequate 4 - Should not have been treated	1 - Adequate 9 - Unknown 2 - Too Rapid 3 - Too Slow 4 - Should not have been treated	
LOWER TORSO				
1. Paraaorta	44	61	25	69
2. Pelvis	45	62	26	73
3. Upper 2/3 Abdomen	46	63	27	77
4. Rt iliac area	47	64	28	16
5. Lt iliac area	48	65	29	20
6. Right Inguinal and Femoral	49	66	30	24
7. Left Inguinal and Femoral	50	67	31	28
8. Other — e.g. splenic pedicle specify ——	51	68	32	32

[2][2][7] 1 4 [DUP ——] 15

EVALUATION OF CURRENT COURSE

COMMENTS

38 [ ]

1 - Fully Evaluable (no deviations)
2 - Acceptable (minor deviations)
3 - Not Acceptable (major deviations)
4 - Other (specify) ——
5 - Unknown

TO BE FILLED IN AFTER LAST TREATMENT COURSE

FINAL EVALUATION OF TOTAL XRT

38 [ ]

1 - Fully Evaluable (no deviations)
2 - Acceptable (minor deviations)
3 - Not Acceptable (major deviations)
4 - Other (specify) ——
5 - Unknown

Signature — Radiotherapy Co-ordinator(s) | Date

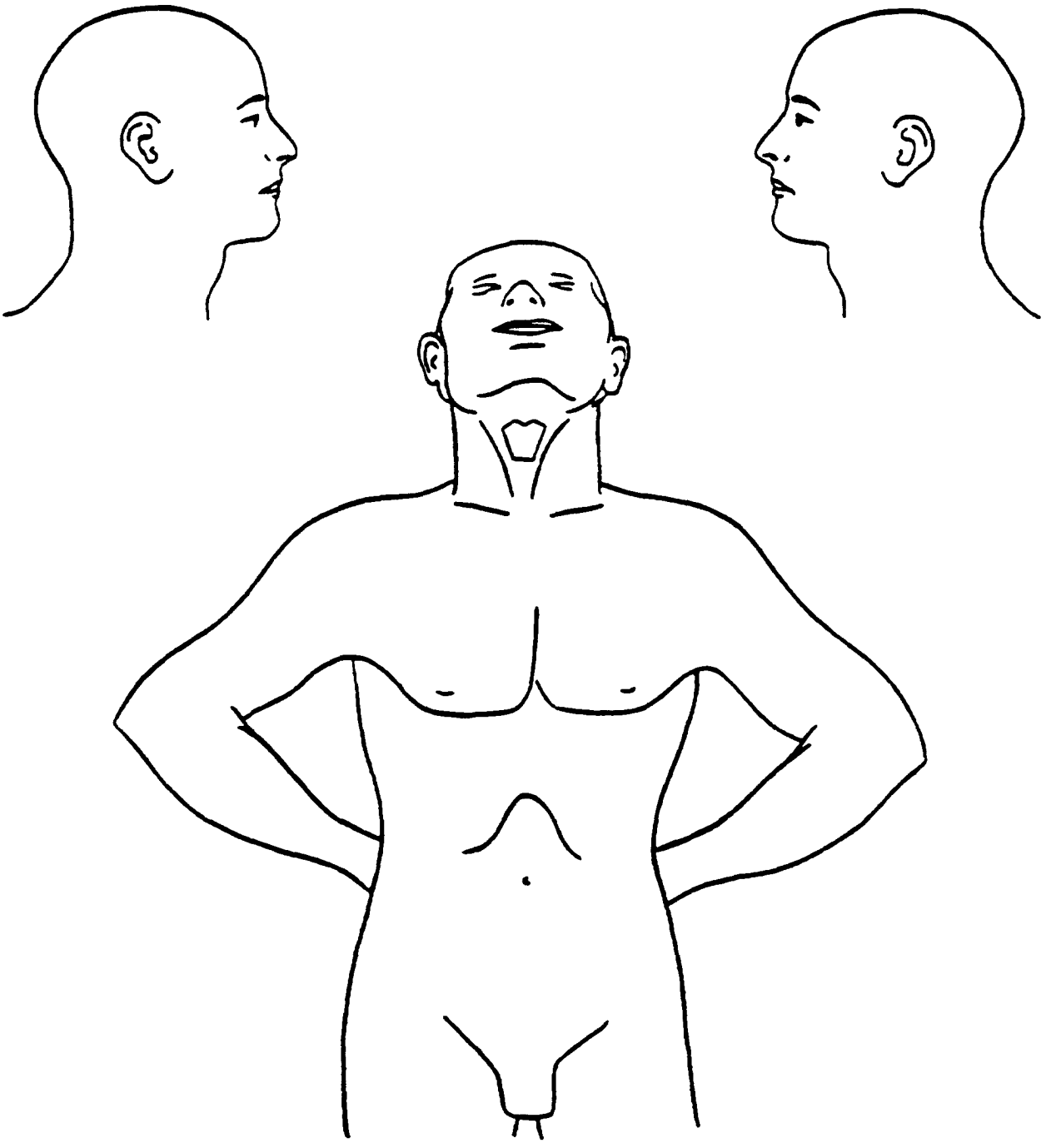
Signature — Physicist | Date

ANTERIOR FIGURE FOR RADIOTHERAPY FIELDS TO ACCOMPANY
RADIOTHERAPY LYMPHOMA FORM
(See Posterior Figure)

Patient Name _____ Pt. No. |_|_|_|_|_|_|

Investigator _____ Inst. _____

Study No. _____ Treatment No. _____ Accession No. _____



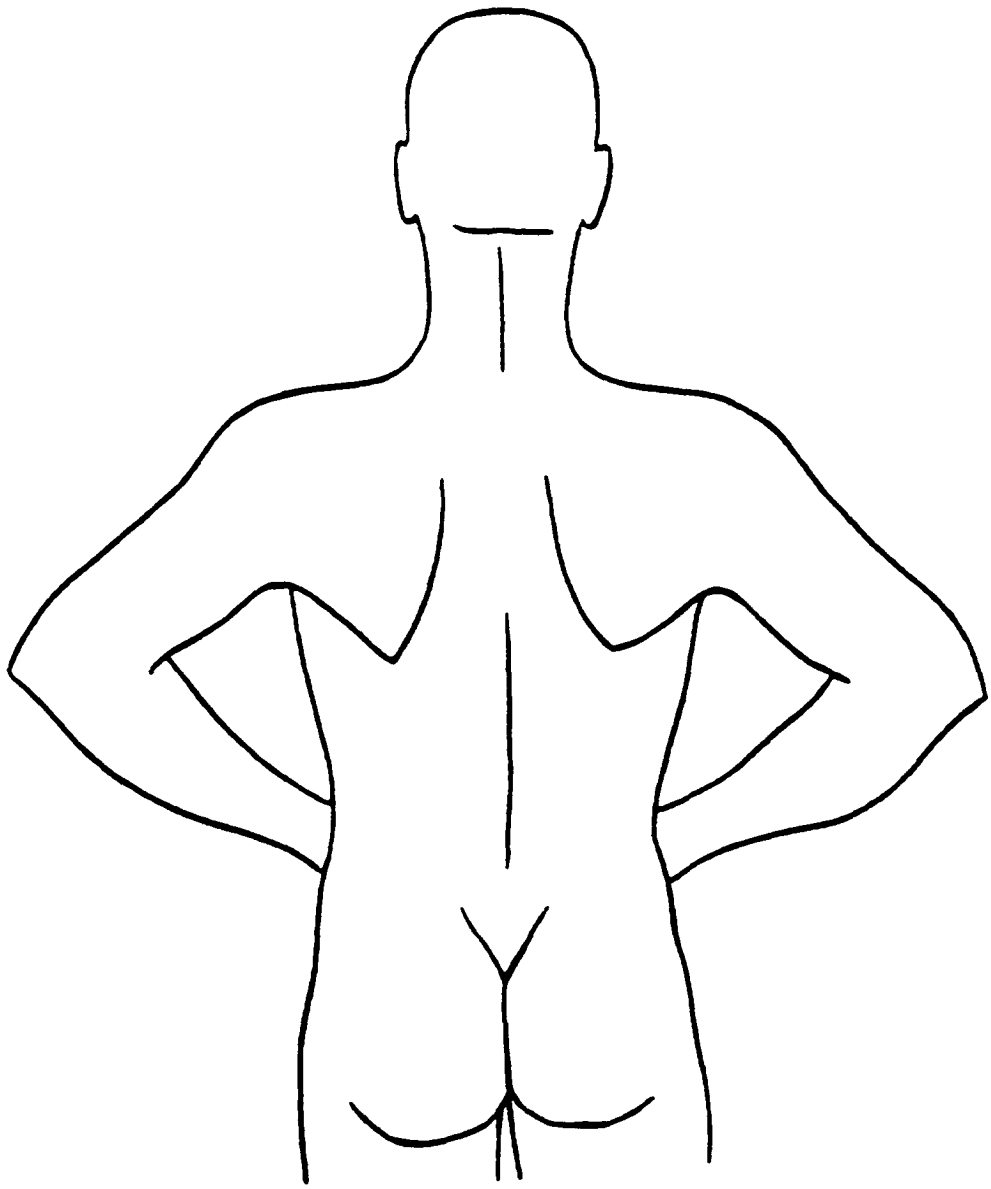
Sketch in treatment fields.

POSTERIOR FIGURE FOR RADIOTHERAPY FIELDS TO ACCOMPANY
RADIOTHERAPY LYMPHOMA FORM
(See Anterior Figure)

Patient Name _____ Pt. No. |_|_|_|_|_|_|

Investigator _____ Inst. _____

Study No. _____ Treatment No. _____ Accession No. _____



Sketch in treatment fields.

SWOG RADIOTHERAPY FORM — CHANGE IN RADIOTHERAPY PLANS

SWOG Pt. No. _____ Study No. _____ Reg. Type _____

Patient Name _____ Radiation Oncologist _____

Institution _____ Radiotherapy Facility _____

Data Management Institution _____
(If different from Institution listed above)

INSTRUCTIONS:

Use this form to report changes to the Statistical Center in the plans for a patient's radiotherapy. Complete the following sections as appropriate:

Section A if patient will ***never*** receive radiotherapy on protocol

Section B if patient received radiotherapy but at a location other than a SWOG-approved Radiotherapy Facility

Section C if patient started radiotherapy but will not complete course as described per protocol (Note -- you must still submit radiotherapy materials documenting the amount of radiotherapy that was given.)

Section D if there has been a delay in the start and/or completion of radiotherapy of 14 or more days, but radiotherapy will be given/continued

A. RADIOTHERAPY NOT GIVEN

Patient did not receive any radiotherapy on this protocol because (check one):

- ☐ patient died before radiotherapy was to begin
- ☐ patient was taken off protocol treatment by physician before receiving radiotherapy due to toxicities or surgical complications following procedures outlined in the protocol
- ☐ patient was taken off protocol treatment by physician before receiving radiotherapy due to disease progression
- ☐ patient should have received radiotherapy, protocol violation: specify

  _____
- ☐ patient refused radiotherapy: specify reason

  _____
- ☐ other: specify

  _____

B. RADIOTHERAPY NOT GIVEN AT A SWOG-APPROVED RADIOTHERAPY FACILITY.

- ☐ facility name: _____

NOTES:

SWOG RADIOTHERAPY FORM
CHANGE IN RADIOTHERAPY PLANS

SWOG Pt. No. ☐☐☐☐☐☐ Study No. ☐☐☐☐ Reg. Type ☐

C. RADIOTHERAPY TREATMENT NOT COMPLETED*

Patient started radiotherapy but will not complete radiotherapy because (check one):

- ☐ patient died before radiotherapy completed
- ☐ patient taken off radiotherapy treatment by physician due to radiotherapy toxicities
- ☐ patient taken off radiotherapy treatment by physician due to non-radiotherapy toxicities
- ☐ patient taken off radiotherapy treatment by physician due to disease progression
- ☐ patient taken off radiotherapy treatment by physician due to reasons other than toxicity and disease progression; specify reason

  _____

- ☐ patient refused further radiotherapy because of radiotherapy toxicities
- ☐ patient refused further radiotherapy because of non-radiotherapy toxicities
- ☐ patient refused further radiotherapy because of non-toxicity reasons
- ☐ other; specify_____

☐☐-☐☐-☐☐ (M, D, Y) First day radiotherapy was given

☐☐-☐☐-☐☐ (M, D, Y) Last day radiotherapy was given

Radiotherapy Summary (Note -- submit radiotherapy materials documenting the radiotherapy that was given)

	Irradiated Site	Total Rads - Target Tissue
1.	_____	_____
2.	_____	_____
3.	_____	_____

D. TREATMENT DELAY OF OVER 30 DAYS

☐☐-☐☐-☐☐ (M, D, Y) Radiotherapy starting date

☐☐-☐☐-☐☐ (M, D, Y) Estimated restart date

☐☐-☐☐-☐☐ (M, D, Y) Estimated completion date

Reason for treatment delay (check one):

- ☐ toxicities or surgical complications
- ☐ patient wishes
- ☐ other; specify_____

* If part C is submitted and the patient later continues radiotherapy, please complete and submit part D.

Name of person completing form:_____

Date: ☐☐-☐☐-☐☐ (M, D, Y)

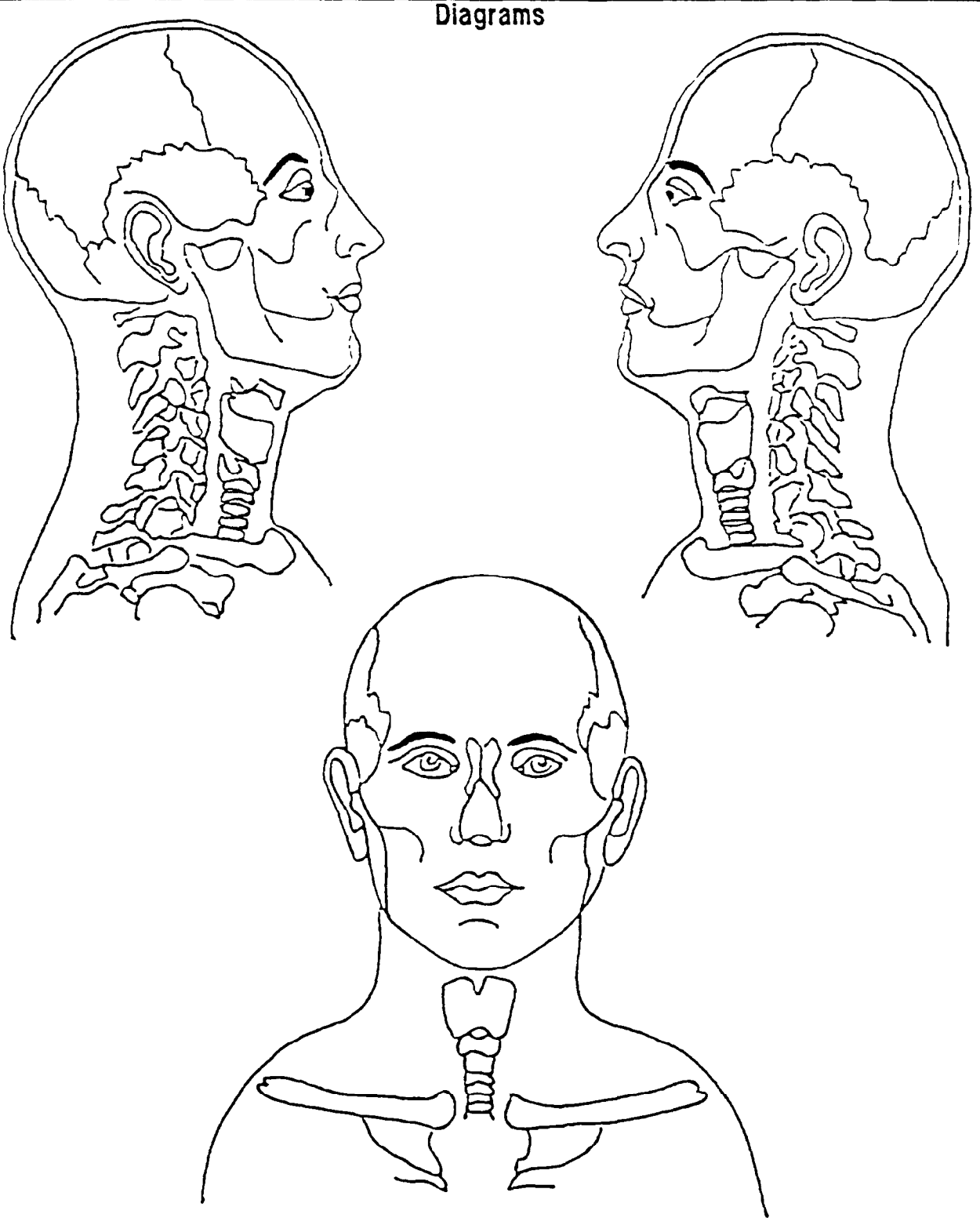
LYMPHOMA HEAD AND NECK RADIOTHERAPY FORM

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____
(L) (F) (M)

INSTRUCTIONS: Indicate proposed radiotherapy fields for sites located in Head and Neck only. Use the prestudy lymphoma diagrams for all other sites.

Diagrams



19.0 APPENDIX

19.1 This section includes Chemotherapy Toxicity Criteria (Southwest Oncology Group), Radiation Therapy Toxicity Criteria, and "Recommendations for Grading of Acute and Subacute Toxic Effects" (for reporting of ADR's), and Radiation Therapy Toxicity Criteria.

19.2 Appendix II provides examples of radiation fields.

CHEMOTHERAPY TOXICITY CRITERIA

System	0	1	2	3	4
Hematopoietic Hgb gm/dl	>2y ≥ 10.0	9.0 - 9.9	7.0 - 8.9	5.0 - 6.9	<5.0
WBC (granulocytes)u l	>4,000 (>1500)	3,000 - 3,999 (<1,500)	2,000 - 2,999 (<1,000)	1,000 - 1,999 (<500)	<1,000 (<250)
Platelets/u l	≥100,000	75,000 - 99,999	50,000 - 74,999	25,000 - 49,999	<25,000
Genitourinary					
A. Renal Creatinine Clearance	>50	40 - 50	30 - 39	20 - 29	<20
B. Bladder	Normal	Dysuria requiring no Rx and/or microscopic hematuria	Dysuria requiring therapy and/or hematuria	Hematuria + drop of Hgb. by 2 gm/dl	
Hepatic					
SGOT	<40 (normal-2xn)	41-60 (2-4.9xn)	61-200 (5-10xn)	200 (>10xn)	
SGPT	<30 (normal-2xn)	30-50 (2-4.9xn)	51-100 (5-10xn)	100 (>10xn)	
Bilirubin	<1 mg/dl	1-2 mg/dl	2.1 - 5 mg/dl	5 mg/dl	
				Clinical evidence of liver failure	
Gastrointestinal					
A. Stomatitis	Normal	Erythema	Ulcers - able to eat	Unable to eat because of ulcerations	
B. Abd. Pain	None	No Rx needed	Rx needed-helpful	Rx needed-not helpful	
C. Constipation	Daily BM	No BM <2 d	No BM x 2-4 d.	No BM >4 d.	
D. Diarrhea	<3 BM daily	3-4 liquid stools no dehydration	>4 liquid stools d. needs IV to hydrate	Blood diarrhea needs IV +/or blood	
Gastrointestinal					
E. Nausea & Vomiting	Normal	Nausea, no vomiting	Vomiting can be prevented by Rx <6 xd	Vomiting >6 xd in spite of antiemetics	
Pulmonary	Normal	No symptoms pulmonary function any parameter 10-25%<pre Rx	Pulmonary symptoms requiring Rx without need for assisted ventilation	Assisted ventilation needed	
Cardiac	Normal in all	EKG changes only or sinus tachycardia not to exceed 110 at rest	Arrhythmias except ventricular tachycardia ± EKG changes	CHF, ventricular tachycardia, pericarditis and/or effusion	
Neuromuscular					
Peripheral nerves	None	+DTR's +/or paresthesias	Absent DTR's weakness + peripheral nerve pain	Incapacity, weakness to bedridden state, paresis	
CNS	Normal	Drowsiness & nervousness	Confusion, anxiety or depression requiring therapy	Convulsions Coma Psychosis	
Skin					
Acute	Normal	Transient erythema	Vesiculation	Ulceration	
Chronic	Normal	Pigmentation, atrophy, depilation	Subepidermal fibrosis	Ulceration + necrosis	
Allergy	None	Drug fever <38° C Transient rash	Urthicaria fever >38° C, asthma	Anaphylactic reaction or anaphylactic shock	
Hypertension	Normal	<10%+	10-25%+	>25%+	

RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXIC EFFECTS

	< SEVERE (Grade 0)	< SEVERE (Grade 1)	< SEVERE (Grade 2)	SEVERE (Grade 3)	LIFE-THI (Grade 4)
Hematological (Adults)					
Hemoglobin	> 11.0 g/100 ml > 110 g/l > 6.8 mmol/l	9.5-10.9 g/100ml 95-109 g/l 5.6-6.7 mmol/l	8.0-9.4 g/100 ml 80-94 g/l 4.95-5.5 mmol/l	6.5-7.9 g/100 ml 65-79 g/l 4.0-4.9 mmol/l	< 6.5 g/100 r < 65 g/l < 4.0 mmol/l
Leukocytes ($1000/mm^3$)	> 4.0	3.0-3.9	2.0-2.9	1.0-1.9	1.0
Granulocytes ($1000/mm^3$)	> 2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
Platelets ($1000/mm^3$)	> 100	75-99	50-74	25-49	< 25
Hemorrhage	None	Petechiae	Mild blood loss	Gross blood loss	Debilitating
Gastrointestinal					
Bilirubin	< 1.25 x N[a]	1.26-2.5 x N[a]	2.6-5 x N[a]	5.1-10 x N[a]	> 10 x N[a]
Transaminases (SGOT, SGPT)	< 1.25 x N[a]	1.26-2.5 x N[a]	2.6-5 x N[a]	5.1-10 x N[a]	> 10 x N[a]
Alkaline phosphatase	< 1.25 x N[a]	1.25-2.5 x N[a]	2.6-5 x N[a]	5.1-10 x N[a]	> 10 x N[a]
Oral	No change	soreness/erythema	Erythema, ulcers; can eat solids	Ulcers; requires liquid diet only	Alimentati not possibl
Nausea/vomiting	None	Nausea	Transient	Vomiting requiring therapy	Intractable vomiting
Diarrhea	None	Transient < 2 days	Tolerable, but > 2 days	Intolerable, requiring therapy	Hemorrhag dehydratio
Renal					
Blood urea nitrogen or Blood urea creatinine	< 1.25 x N[a]	1.26-2.5 x N[a]	2.6-5 x N[a]	5-10 x N[a]	> 10 x N[a]
Proteinuria	No change	1+ < 0.3 g% < 3 g/l	2-3+ 0.3-1.0 g% 3-10 g/l	4+ > 1.0 g% > 10 g/l	Nephrotic syndrome
Hematuria	No change	Microscopic	Gross	Gross + clots	Obstructiv
Pulmonary	No change	Mild symptoms	Exertional dyspnea	Dyspnea at rest	Complete rest requir
Fever with drug	None	Fever < 38 C	Fever 38 C-40 C	Fever > 40 C	Fever with hypotensi
Allergic	No change	Edema	Bronchospasm: no parenteral therapy required	Bronchospasm; parenteral therapy required	Anaphylax
Cutaneous	No change	Erythema	Dry desquamation, vesiculation, pruritus	Moist desquamation, ulceration	Exfoliativ dermatiti requiring interventi
Hair	No change	Minimal hair loss	Moderate, patchy alopecia	Complete alopecia but reversible	Non-rever alopecia
Infection (specify site)	None	Minor infection	Moderate infection	Major infection	Major inf
Cardiac					
Rhythm	No change	Sinus tachycardia, > 110 at rest	Unifocal PVC atrial arrhythmia	Multifocal PVC	Ventricul tachycard
Function	No change	Asymptomatic, but abnormal cardiac sign	Transient symptomatic dysfunction; no therapy required	Symptomatic dysfunction responsive to therapy	Symptom function responsiv
Pericarditis	No change	Asymptomatic effusion	Symptomatic; no tap required	Tamponade; tap required	Tamponad required
Neurotoxicity					
State of communication	Alert	Transient lethargy	Somnolence < 50% of waking hours	Somnolence > 50% of waking hours	Coma
Peripheral	None	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or marked motor loss	Paralysis
Constipation[b]	None	Mild	Moderate	Abdominal distention	Distentic vomiting
Pain[c]	None	Mild	Moderate	Severe	Intractab

[a] N = upper limit of normal value of population under study.
[b] This does not include constipation resultant from narcotics.
[c] Only treatment-related pain is considered, not disease-related pain.

Examples of Radiation Fields

A. Positive mediastinum

B. Mediastinum and one or both necks

C. Both necks

D. Neck and axilla

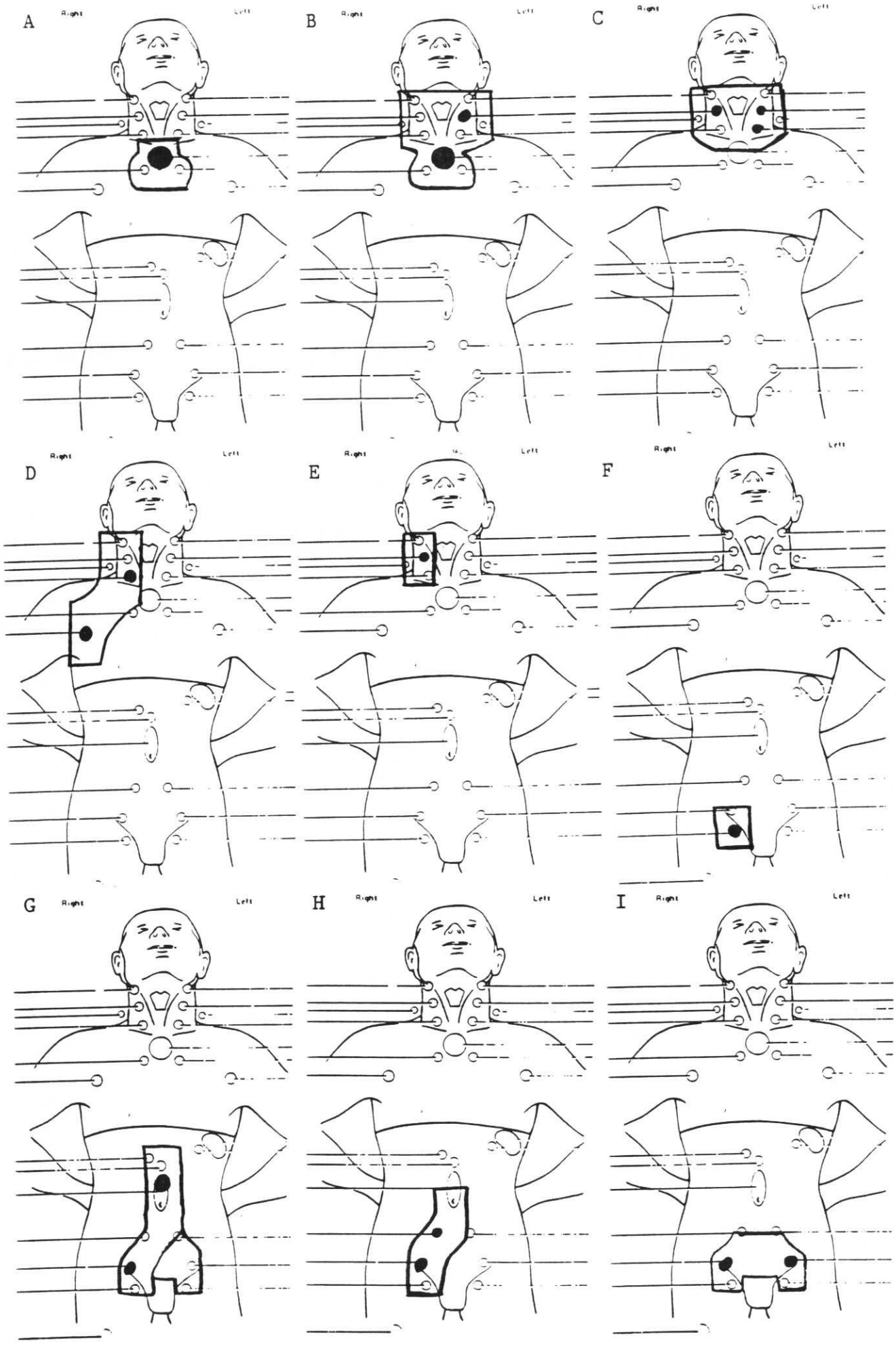
E. One neck

F. One groin

G. Inguinal and para-aortic

H. Inguinal and pelvic

I. Bilateral inguinal


A
Right
Left
B
Right
Left
C
Right
Left
D
Right
Left
E
Right
Left
F
Right
Left
G
Right
Left
H
Right
Left
I
Right
Left