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REDUCED DURATION STANFORD V CHEMOTHERAPY WITH OR WITHOUT LOW-DOSE TAILORED-FIELD RADIATION THERAPY FOR FAVORABLE RISK PEDIATRIC HODGKIN LYMPHOMA

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St. Jude Children's Research Hospital
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MEMORANDUM
Department of Oncology
Leukemia/Lymphoma Division

TO: **CPSRMC/IRB**

FROM: **Monika Metzger, MD, M.Sc.**

DATE: **June 15, 2010**

RE: **HOD08: REDUCED DURATION STANFORD V CHEMOTHERAPY WITH OR WITHOUT LOW-DOSE TAILORED-FIELD RADIATION THERAPY FOR FAVORABLE RISK PEDIATRIC HODGKIN LYMPHOMA**
Addition of Rady Children's Hospital and the University of California at San Diego (UCSD) as an alliance
Amendment 2 LOA #1

We would like to add Rady Children's Hospital and UCSD as an alliance on the HOD08 study.

St. Jude Children's Research Hospital and Rady Children's Hospital have entered into a research alliance agreement which allows Rady to collaborate on St. Jude clinical research protocols. Rady has been tasked with enrolling 25 research participants in the next year, and opening as many protocols as possible. Dr. Raul Ribeiro is the St. Jude liaison for Rady.

Rady has expressed an interest in participating in the HOD08 study. Catherine Madigan, MD will be the PI; however the radiation therapy will be done at UCSD. Rady plans to enroll 1-2 participants per year.

Thank you for your consideration.

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Protocol Summary

HOD08, REDUCED DURATION STANFORD V CHEMOTHERAPY WITH LOW-DOSE TAILORED-FIELD RADIATION THERAPY FOR FAVORABLE RISK PEDIATRIC HODGKIN LYMPHOMA

Principal Investigator: Jamie Flerlage, MD

IND holder: This is a non-IND study.

Brief overview: This is a phase II clinical trial using risk-adapted, multi-modality therapy. The goals of this study are to 1) Increase the proportion of patients that will be in complete remission at the end of 8 weeks of chemotherapy and therefore will not require radiation therapy; 2) maintain treatment outcomes by using a combined-modality approach with an abbreviated dose-intensive chemotherapy regimen with limited-volume, conformal radiotherapy for patients that are not in CR at the end of chemotherapy; and 3) reduce acute and long-term treatment sequelae by a) minimizing the cumulative doses of anthracyclines, bleomycin, and alkylating agents, b) increasing the number of complete responders, thus decreasing the number of patients requiring radiation, and c) tailoring the volume of radiation to initially involved nodal sites.

Intervention: Combined-modality therapy with abbreviated dose-intensive chemotherapy regimen (STANFORD V) with limited-volume, conformal radiotherapy for participants who are not in complete remission at the end of chemotherapy.

Brief outline of treatment plan: Patients will be treated with 8 weeks of Stanford V chemotherapy. Radiation therapy will be omitted for patients achieving a complete response after 8 weeks of chemotherapy. Patients who achieve less than a complete response after 8 weeks of chemotherapy will receive 25.5 Gy to individual nodal sites (tailored fields) starting 2-3 weeks following completion of all chemotherapy and recovery of ANC to at least 1000.

Objectives:

Primary objectives

- To increase the complete response rate after 8 weeks Stanford V by at least 20% compared to patients on HOD 99 after 8 weeks VAMP.

Secondary objectives:

- To estimate the disease failure rate within the radiation fields.
- To examine patterns of treatment failure for children treated with low dose tailored field radiation therapy.
- To describe acute hematologic and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.
- To compare the survival distributions (event free, overall and local failure) and toxicities of favorable risk patients treated with 8 weeks of Stanford V chemotherapy and low-dose tailored-field radiation to those on the favorable risk group of the HOD99.
- To compare the survival distributions between patients that will not be prescribed radiotherapy after 8 weeks Stanford V and those patients on HOD99 that did not receive radiotherapy after VAMP.
- To estimate the event-free survival distributions of favorable risk patients treated with Stanford V chemotherapy alone and patients treated with Stanford V chemotherapy plus low dose tailored field radiation.

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Hypotheses/estimates: With the success of current chemotherapy for Hodgkin lymphoma, the primary goal of this protocol is to increase the proportion of favorable risk Hodgkin lymphoma patients treated with 8 weeks Stanford V chemotherapy alone that will not require any radiotherapy by at least 20% compared to favorable risk patients treated with VAMP on HOD99. In HOD99 44% (27/62) of favorable risk patients (excluding stage I nodular lymphocyte predominant histology) achieved a complete response (CR) at 8 weeks after two cycles of VAMP chemotherapy, and thus required no radiotherapy. A historical control design is used to test the hypothesis of a 20% increase (from 44% to 64%) in the proportion of patients not requiring radiotherapy.

Criteria for evaluation: At the end of all prescribed chemotherapy, response will be determined for each individual nodal group. The response evaluation will be based on the multidisciplinary (oncologist, radiotherapist, and radiologist) interpretation of physical examination, laboratory and diagnostic imaging and response criteria listed in Section 7.1 of the protocol. Toxicity and performance reporting will be according to CTCAE Version 3.0.

Study design: Multicenter, phase II study utilizing risk adapted multi-modality therapy.

Study population: Participants with previously untreated Hodgkin lymphoma with localized disease designated as "favorable" comprise those with asymptomatic non-bulky stage I/II disease involving less than 3 nodal regions.

Sample size: 80 evaluable participants (stage IA nodular lymphocyte predominant histology patients are excluded from the primary objective.

Randomization: N/A

Data analyses:

Primary aims

- To increase the proportion of patients that will not require any radiotherapy by at least 20% compared to the favorable risk arm in HOD99. The hypothesis test will be performed for the proportion of patients not requiring any radiotherapy (which is equivalent to the complete response (CR) rate) compared with the historical control for HOD99 which was 27/62 (44%) by using an exact binominal test. A 95% confidence interval of the complete response (CR) rate will be provided.

Secondary aims

- To estimate the disease failure rate within the radiation fields. Disease failure within the radiation field is defined as disease that recurs in the initially involved nodal region within the field of irradiation. The disease failure rate within the radiation field will be estimated with a 95% confidence interval using appropriate methods (e.g., estimate cumulative incidence in the presence of competing risks).
- To examine patterns of treatment failure for children treated with tailored field radiation therapy. In relapsed patients, nodal sites of disease, as well as extra-nodal sites of disease, will be evaluated for treatment failure. A local failure is classified as disease that recurs in the initially involved nodal region within the field of irradiation; otherwise it will be classified as a distant failure. If both failures (local and distant) are observed, it will be treated as a local failure. Bone marrow failure

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will always be classified as a distant site of failure. Descriptive statistics related to local/distant failure will be produced. The cumulative incidence of local failure will be estimated and effects of prognostic factors will be examined. Effect of competing risks (distant failure, second malignancy and death) will be taken into account. Relapse rate within the radiation fields will be estimated and confidence interval will also be calculated.

- To describe acute hematologic and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The acute hematologic and infectious toxicities will be summarized by descriptive statistics.
- To compare the survival distributions (event-free, overall and local failure) and toxicities of favorable risk patients treated with this reduced Stanford V chemotherapy and low-dose tailored-field radiation to those on the favorable risk group of the HOD99 that received VAMP and low-dose involved-field radiation. Log-rank and Gray's tests will be used to compare outcome (event-free survival and overall survival distributions and cumulative incidence of local failure) of favorable risk patients treated on this protocol vs. patients treated on HOD99 and distributions between patients that will not be prescribed radiotherapy after 8 weeks Stanford V and those patients on HOD99 treated with VAMP and did not receive radiotherapy. In the presence of competing risks, Gray's test will be used to compare outcome distributions (e.g., cumulative incidence of local failure).

Anticipated primary completion date: July 2017

Anticipated study completion date: Anticipated July 2017

Timeframe for primary outcome measure: 8.5 years

Data management: Provided by St. Jude Children's Research Hospital, Comprehensive Cancer Center research personnel, Leukemia/Lymphoma Division.

Human subjects: The risks to participants will be related to the toxicity of multi-modality chemotherapy and radiation. There is also the risk that reducing therapy will increase the risk of relapse. Participants will be informed of this and other potential side effects during informed consent. Adverse events will be monitored and reported and treated appropriately.

1.0 OBJECTIVES

1.1 Primary objective

(Applied to non-stage IA non-LP favorable risk patients only)

1.1.1 To increase the complete response rate of favorable risk patients (excluding all patients with stage IA nodular lymphocyte predominant Hodgkin lymphoma) after 8 weeks Stanford V by at least 20% compared to favorable risk patients on HOD 99 after 8 weeks VAMP.

1.2 Secondary objectives

(Applied to all favorable risk patients)

1.2.1 To estimate the disease failure rate within the radiation fields.

1.2.2 To examine patterns of treatment failure for children treated with low dose tailored field radiation therapy.

1.2.3 To describe acute hematologic and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

1.2.4 To compare the survival distributions (event-free and overall) and cumulative incidence of local failure and toxicities of favorable risk patients treated with 8 weeks of Stanford V chemotherapy and low-dose tailored-field radiation to those on the favorable risk group of the HOD99 study that received VAMP and low-dose involved-field radiation.

1.2.5 To compare the survival distributions between patients that will not be prescribed radiotherapy after 8 weeks Stanford V and those patients on HOD99 that did not receive radiotherapy after VAMP.

1.2.6 To estimate the event-free survival distributions of favorable risk patients treated with Stanford V chemotherapy alone and patients treated with Stanford V chemotherapy plus low dose tailored field radiation.

2.0 BACKGROUND AND RATIONALE

2.1 Introduction

Cure rates for pediatric Hodgkin lymphoma have improved dramatically over the past 30 years. Currently 90% - 100% of patients with localized disease and 70% - 90% of patients with advanced stage disease achieve long-term disease-free survival. [1-3,3-17] With improved survival in pediatric Hodgkin lymphoma, treatment and management decisions have become more complex because of considerations regarding acute and late effects of therapy, as well as quality of life.

2.2 Evolution of Pediatric Hodgkin Lymphoma Therapy

In early stage Hodgkin lymphoma standard-dose (35-44 Gy) extended-volume radiotherapy (RT) alone achieves excellent long-term disease-free survival, but results in growth abnormalities such as intraclavicular narrowing, shortened sitting height, decreased mandibular growth and neck size, and atrophy of soft tissues and muscle development that can severely affect quality of life.[18-20] Concern for these effects led to pediatric trials implemented in the 1970s which modified treatment strategies to address the specific needs of children.[6,21-26] These studies determined that multi-agent chemotherapy could be used to treat subclinical disease and reduce the required dose of radiation at involved sites.

In the 1980s, with long-term follow-up demonstrating feasibility and efficacy of combination chemotherapy in pediatric Hodgkin lymphoma, study objectives were modified to improve cure rates for advanced stage patients and reduce the MOPP (mechlorethamine, vincristine, procarbazine, prednisone)-related sequelae of infertility and secondary leukemia. During this era, treatment with standard-dose radiation therapy alone was restricted to adolescents with localized disease who had achieved skeletal maturity. In combined modality regimens, radiation was reduced in dose (15-25.5 Gy) and volume (involved fields rather than extended fields). By the end of the era, six treatment cycles of non-cross-resistant combination chemotherapy plus low-dose, involved field RT evolved as the standard. As a result of these changes, follow-up of patients treated in the 1980s had indicated improvement in disease-free survival with a reduced incidence of cardiopulmonary, gonadal, and neoplastic complications.[2,3,7-10]

The goal of therapy in the 1990s focused on further reducing therapy among patients with favorable disease presentations to minimize acute and late complications, without compromising disease control. These objectives resulted from long-term follow-up studies of Hodgkin lymphoma survivors that showed that the decline in event-free survival for patients followed more than 10 years from diagnosis resulted from late toxicity of therapy rather than from Hodgkin lymphoma itself.[27-30] These late events resulted in early mortality, most commonly from the development of second malignant neoplasms (SMN) or non-neoplastic treatment complications and could be attributed to specific treatment modalities (e.g., anthracycline chemotherapy, radiation therapy).

Treatment programs throughout the 1990s have attempted to reduce or eliminate agents or modalities associated with unacceptable cancer-related morbidity and mortality. However, reductions in therapy intensity must be made cautiously, since they may compromise disease-control.

The desire to avoid radiation-related SMN in long-term Hodgkin survivors has been a major objective of pediatric investigations evaluating regimens prescribing chemotherapy alone. Results from the Late Effects Study Group indicate a standardized incidence ratio (SIR) of 11.8 (95% CI, 8.7-15.4) for developing a SMN following treatment for Hodgkin's disease.[31] The most common solid tumors observed in the cohort were breast (SIR 75.3, CI 44.9-118.4), thyroid (SIR 32.7, CI 15.3-55.3), bone (SIR 24.6, CI 6.4-54.5), brain (SIR 10.5, CI 2.7-23.4), colorectal (SIR 38.9, CI 7.3-95.3), and gastric cancer (SIR 12.3, CI 11.4-145.2). Other pediatric investigators have similarly reported excess risks of second solid tumors in survivors of pediatric Hodgkin lymphoma.[32-36] SMN were the second most frequent cause of death (after Hodgkin lymphoma) in patients treated on St. Jude Hodgkin lymphoma trials from 1962 to 1990 [28] a fact that emphasizes the need for further refinements in pediatric Hodgkin lymphoma therapy.

Several investigators have demonstrated disease-free survival rates in children treated with chemotherapy alone which are comparable to those observed after combined modality therapy.[37-45] However, these studies have predominantly been reported with brief follow-up, from non-industrialized countries, or have used supplemental radiation therapy in select patients. Chemotherapy-alone protocols offer advantages for children treated at centers in developing countries where radiation facilities and trained personnel may be lacking and precise clinical staging difficult to perform. The use of chemotherapy-alone regimens also avoids the long-term growth and neoplastic complications associated with higher doses of radiation therapy. The potential disadvantages of chemotherapy alone regimens include 1) a higher cumulative alkylating drug exposure (compared to those prescribed in combined modality therapy regimens) and 2) increased morbidity from myelosuppression, gonadal toxicity, and secondary leukemia.

2.3 Summary of Combined Modality Therapy Results

The development of the four drug combination of MOPP [46] in the 1960s, and the appreciation of the adverse effects of high-dose radiation therapy on musculoskeletal development in growing children provided the background for the first combined modality therapy investigations in pediatric patients with Hodgkin lymphoma.[11] The major toxicity of MOPP, given for 6 cycles, has been an associated risk of acute leukemia,[46-49] sterility in males and a risk of sterility in females that increases with advancing age.[50] ABVD (doxorubicine, bleomycin, vinblastine and dacarbazine)[51] has also been used as first line therapy with results similar to MOPP,[52] but without the same risk of second malignancy and sterility.[53] The primary adverse side effects of ABVD are pulmonary toxicity related to bleomycin and cardiovascular side effects secondary to doxorubicin. These effects are even more evident when mediastinal or mantle irradiation is used in conjunction with ABVD, and are dose-related.[54,55]

The development of ABVD and the desire to avoid MOPP sequelae of infertility and secondary leukemia resulted in the use of alternating multiagent chemotherapy regimens.[52,56] The prototype MOPP/ABVD regimen has the theoretical advantage of enhanced antineoplastic activity, reduced MOPP-related sequelae because of the lower cumulative exposure to alkylating agent chemotherapy, and reduced ABVD-related sequelae because of the limited doses of doxorubicin and bleomycin.[3,22,24,52] Pediatric trials of alternating multiagent drug combinations with MOPP/ABVD or similar hybrid therapies have been uniformly efficacious and have led to subsequent pediatric studies in which radiation doses and volumes have been further reduced.[2,3,7-10,25]

2.4 Rationale for Risk-Adapted Therapy

Pediatric trials in the early 1990s established that excellent outcomes could be achieved in early-stage patients with "favorable" presentations with fewer cycles of multi-agent chemotherapy and lower radiation doses and volumes in clinically staged patients. "Favorable" localized disease was characterized by the absence of bulk of mediastinal and peripheral lymphadenopathy. The designation of bulky mediastinal lymphadenopathy was assigned if the ratio of mediastinal lymphadenopathy to the maximal trans-thoracic dimension was 33% or more, a clinical presentation previously reported to have an improved outcome with combined modality therapy.[25] The prognostic implications of peripheral nodal bulk have not been consistently considered in earlier pediatric Hodgkin trials. The definition of "bulky" has varied in recent clinical trials from 4 to 6 and even 10 cm, and its prognostic implication is felt to be analogous to bulky mediastinal lymphadenopathy, although this has not been prospectively evaluated.

Combined modality programs currently under study emphasize chemotherapy regimens that limit the cumulative doses of alkylating agents, anthracyclines, and bleomycin and use low-dose, involved-field radiation therapy to reduce the frequency and severity of treatment sequelae.[57] Some modifications of therapy, particularly those attempting to limit alkylating agent chemotherapy,[25,58,59] have been associated with inferior disease control and emphasize the need for investigators to proceed with caution in their attempts to reduce late treatment effects.

2.4.1 Summary of risk-adapted therapy trials

Many multi-institutional trials have shown that children with favorable stage (IA and IIA, non-bulky) Hodgkin lymphoma can be cured with abbreviated chemotherapy followed by 15 to 25 Gy involved field radiotherapy (Table 1):[60]

Table 1: Selected Trials of Combined Modality Therapy in Favorable-Risk Pediatric Hodgkin Lymphoma

Study Group/Trial	Sample Size	Treatment	Event-Free or Disease-Free Survival	Overall Survival	Follow-up (Years)
Stanford	44 (CS/PSI-III)	3 MOPP/3 ABVD + 15-25.5 Gy IFRT	100	100	10
French Society of Pediatric Oncology	65	4 ABVD + 20-40 Gy IFRT	90		4
	67	2 MOPP/2 ABVD + 20-40 Gy IFRT	87		4
St. Judes Children's Research Hospital	28 (CSII)	5 COP(P)/4 ABVD + 20 Gy IFRT	96	96	5
French Society of Pediatric Oncology MDH-90	202	4 VBVP + 20 Gy IFRT (good responders)	91	97.5 (all)	5
		4 VBVP + 1-2 OPPA + 20-40 Gy IFRT (poor responders)	78		5
Stanford/St. Jude/Dana Farber	110	4 VAMP + 15-25.5 Gy IFRT	93	99	5
U.S. Children's Cancer Group	294	4 COPP/ABV + 21 Gy IFRT	100 (IFRT)	100 (IFRT)	3
German Multicenter HD-90	267	2 OPPA/OEPA + 20-35 Gy IFRT	94	99.6	5
German Multicenter HD-95	281	2 OPPA/OEPA + 20-35 Gy IFRT	94	NA	5
U.S. Pediatric Oncology Group	46	4 DBVE + 25.5 Gy IFRT	91	98	6

Table cited from Hodgson, et al[60]. References for the individual trials: [2,3,7,12-16,61]

The major focus of these trials is to reduce treatment-related toxicity while maintaining high rates of cure.

2.4.2 Results of Pediatric Hodgkin's Group Collaborative Trials

Study design for favorable risk patients

In 1990, investigators from Stanford, Dana Farber, and St. Jude initiated studies with objectives of reducing cardiopulmonary, gonadal, and neoplastic treatment sequelae with the use of combination chemotherapy regimens that eliminated or reduced exposure to alkylating agents, anthracyclines and bleomycin. Patients with favorable (peripheral nodal disease < 6 cm or mediastinal mass to thoracic cavity ratio < 33% by chest radiograph) localized disease received 4 cycles of vinblastine, Adriamycin, methotrexate, and prednisone (VAMP) chemotherapy. Patients with localized, unfavorable bulky presentations and advanced disease received 6 cycles of vinblastine, etoposide, prednisone, and adriamycin (VEPA) chemotherapy. All patients received involved-field radiation with the prescribed dose based on disease response after 2 cycles of

chemotherapy. Patients with a complete response received 15 Gy; those with a partial response or bulky disease at presentation received 25.5 Gy.

Outcome and toxicity of VAMP plus RT

Mature results of the VAMP plus radiotherapy regimen among 110 patients show a 5- and 10-year overall survival of 99% (SE,1.0%) and 96%, (SE, 2.6%) respectively, and 5- and 10-year event-free survival (EFS) were 93% (SE, 2.5%) and 89% (SE, 4.2%) with a median follow up of 9.6 years (range, 1.7 to 15 years).[11,61] The regimen is very well tolerated and acute toxicity is easily managed in the outpatient setting. Blood product transfusions and admissions for neutropenic fever are rare. In regard to long term toxicity, the most frequently observed endocrine abnormality was subclinical hypothyroidism (42%) after neck radiation. Thyroid nodules were detected in three children, 8 years after diagnosis. Soft tissue hypoplasia was recorded in three children. Osteopenia and/or osteoporosis occurred in 13 children, which may represent an underestimate since bone density studies were not routinely preformed. Weight gain and/or obesity were noted in 16 children, with body mass index values of 26.4 to 41.2. Mild asymptomatic changes in pulmonary volumes, diffusion, or both were recorded in 34% of tested patients. One girl had a decline in left ventricular fractional shortening, which dropped to less than 25% 3 years after diagnosis with symptomatic cardiac failure during pregnancy. Fertility is believed to have been maintained in all girls, since all girls of pubertal age had normal menses. One boy was found to be azoospermic after receiving 25 Gy pelvic/15 Gy para-aortic/splenic RT. Two patients developed a second malignancy. One patient was diagnosed with follicular thyroid cancer, 8 years after 25.5 Gy to a field that included the thyroid gland, presumably radiation induced. This patient is disease free and believed cured after subtotal thyroidectomy and [I^{131}] thyroid ablation. The second patient developed Ewing sarcoma 4 years after treatment for his Hodgkin lymphoma, outside his prior radiation field of 25.5 Gy to the high cervical nodal chain. He died of refractory metastatic sarcoma. Four girls, routinely screened for breast disease, have undergone breast biopsies; all revealed a benign tumor.

Outcome of VEPA plus RT

Accrual to the VEPA plus radiotherapy regimen was closed in 1993 because of the inferior event-free survival experienced by advanced and unfavorable patients.[58] Mature results of this trial suggest that disease control in patients with advanced stage Hodgkin lymphoma is compromised when patients are treated with regimens that do not contain alkylating agent chemotherapy. The 5-year event-free survival for this cohort was 68%±6% and overall survival was 81%±5%, survival rates below the range typically observed for pediatric patients with advanced stage disease treated with combined modality therapy.

Outcome of VAMP/COP plus RT

The subsequent study for unfavorable and advanced disease prescribed alternating cycles of VAMP and COP chemotherapy with low-dose involved-field radiation therapy and started in 1993.[62] The dose of radiation was the same as that given on the earlier study: 15 Gy for patients achieving a complete response after the first 2 cycles, and 25.5 Gy for patients with a partial response and to all sites of bulky lymphadenopathy. Between 1993 and 2000, 159 children were enrolled on the VAMP/COP + RT arm. The 5-year event-free survival for the entire VAMP/COP + RT cohort was 76% ± 4% and 5-year overall survival was 93%±2.5%. Event-free survival was somewhat higher for the 77 patients with localized unfavorable stage I/II disease than for the 88 patients with advanced stage III/IV disease though the difference was not statistically significant (5-year estimates: 82% ± 5% versus 68% ± 6.5%, p=0.09).

Overall, treatment outcomes following the VAMP/COP + RT regimen are no better than other regimens used for unfavorable and advanced stage pediatric Hodgkin lymphoma. Follow-up is ongoing to determine whether regimen-related long-term toxicity will be significantly less than that observed after combined modality treatment protocols including higher doses of alkylating agents, higher radiation doses, and larger RT volumes.

2.5 Proposed Study and Definition of Prognostic Groups

The HOD 2008 study for low risk pediatric Hodgkin lymphoma patients aims to: 1) increase the proportion of patients that will be in complete remission at the end of 8 weeks of chemotherapy and therefore will not require radiation therapy, 2) maintain excellent treatment outcomes by using a combination of an abbreviated dose-intensive chemotherapy regimen plus limited-volume, conformal radiotherapy for patients that are not in CR at the end of chemotherapy; and 3) reduce acute and long-term treatment sequelae by a) minimizing cumulative exposure to anthracyclines, bleomycin, and alkylating agents, b) increasing the number of complete responders thus decreasing the number of patients requiring radiation and c) tailoring the volume of radiation to initially involved nodal sites.

Patients with localized disease designated as “favorable” comprise those with asymptomatic non-bulky stage I/II disease involving less than 3 nodal regions. The treatment will comprise 8 weeks of Stanford V chemotherapy. Patients with less than a complete response at the end of chemotherapy will proceed to receive low-dose, 25.5 Gy tailored-field radiation therapy.

2.5.1 Rationale for testing 8 weeks of Stanford V chemotherapy with or without low-dose tailored-field radiation therapy in favorable-risk pediatric Hodgkin lymphoma

Stanford V experience

The Stanford V regimen is an abbreviated, multi-agent, dose-intensive regimen that utilizes many of the most active chemotherapy agents for Hodgkin lymphoma:

vinblastine, doxorubicin, vincristine, bleomycin, mechlorethamine, etoposide, and prednisone. The regimen features increased dose-intensity of individual drugs, reduction in the cumulative doses of bleomycin and doxorubicin compared with ABVD or hybrid regimens, and substantial reduction of mechlorethamine with omission of procarbazine (see Tables 1, 2). It has been used in the adult Hodgkin lymphoma population with promising results. In a series of 142 patients, 12 weeks of Stanford V and 36 Gy of radiation therapy to all initially bulky sites and macroscopic splenic disease were given to all stage III/IV patients and stage I/II patients with bulky mediastinal adenopathy.[63] The 5-year freedom from progression rate was 89% (95% CI, 83% to 94%) with 97% freedom from progression in the 32% of patients with unfavorable stage I/II disease and 85% in the stage III/IV patients. A reduced Stanford V version (8 weeks) for favorable risk stage I/II patients in adults is underway at Stanford. Although results of the entire study have not yet been published, patients who had a negative PET scan at the end of chemotherapy had superior EFS.[64]

HOD99 and HOD05 experience with Stanford V

There is accumulating data and experience with other dose-intensive chemotherapy regimens in pediatrics that suggest such an approach is safe and effective. The Children Oncology Group has been studying a relatively dose-intensive regimen, DBVE-PC (doxorubicin, bleomycin, vincristine, etoposide – prednisone and cyclophosphamide) for intermediate risk patients and AV-PC (doxorubicin, vincristine, prednisone, cyclophosphamide) for favorable risk patients. Our own group has been using Stanford V chemotherapy with response-based, low dose, involved-field radiotherapy in the unfavorable-risk patients since 2002 (HOD 99) and the same regimen with tailored field radiation in intermediate risk patients (HOD 05) since 2006. To date, we have enrolled 125 patients with stage IB, II (bulky mediastinum, “E” lesion, or > 2 nodal sites), III, and IV disease to treatment with 12 weeks of Stanford V chemotherapy and 15 to 25.5 Gy involved-field (tailored-field in the intermediate risk protocol) radiation. Early response is assessed at week 8 and the radiation dose determined on the basis of this response. There has been no treatment-related mortality, the regimen has been easy to administer and well tolerated. Grade III/IV neutropenia has been the most commonly observed toxicity, but the rate of hospitalizations for febrile neutropenia has been extremely low.

Historical control for HOD08

Our current trial treats favorable risk patients with four cycles of the efficacious and well-tolerated VAMP regimen. Based on the promising experience of other groups in omitting radiation therapy in favorable risk patients, we have been prospectively evaluating this approach since 1999 (in the HOD 99 study). Patients who have a rapid early response to the first two cycles of VAMP, defined as at least 75% reduction in the product of all lesions in conjunction with a negative positive emission tomography (PET) scan are not receiving radiation therapy, whereas patients with a partial early response receive low-dose (25.5 Gy) involved-field radiotherapy. On this arm there have been 5 events, and to date, the 2-year EFS (SE) is 95.0% (3.0%) and 3-year EFS rate is 90.8% (4.4%) (April, 2008 DSMB report) with so far a 100% overall-survival. Of these patients 58% did not

receive radiation therapy. However if we discount all stage IA nLP HL 27 of 62 patients (44%) achieved a complete response (CR) at 8 weeks and did not require radiation. When looking at intermediate risk patients treated on HOD 05 with Stanford V, the early response evaluation data at 8 weeks suggests that it is reasonable to assume that at least 20% more favorable risk patients will achieve a CR after 8 weeks of Stanford V and therefore avoid radiotherapy.

Our interest in further testing the Stanford V regimen in pediatric favorable risk patients is generated by its tolerability, its relatively low cumulative doses of agents with potentially significant acute and long-term sequelae compared to other standard regimens for favorable-risk disease, and the desire to further increase the proportion of patients that will not require radiation therapy. Table 2 shows the dose-intensity of Stanford V and other pediatric regimens. Table 3 shows the cumulative doses of the important agents that are associated with adverse acute and long-term sequelae, where 8 weeks of Stanford V compares favorably in all respects. While some of the other pediatric regimens have shown excellent efficacy in controlling disease, there are still significant acute and late effects associated with their use. Many of the currently open national and international trials also require hospitalization for the administration of the chemotherapy. Further, the German pediatric regimens have utilized higher doses of radiation with its attendant risks of growth abnormalities and second malignancies, and have documented gonadal toxicity in both males and females.[16] Our own previous VAMP experience has been excellent with a 5- and 10-year overall survival of 99% (SE,1.0%) and 96% (SE,2.6%), respectively, and a 5-and 10-year event-free survival (EFS) of 93% (SE,2.5%) and 89% (SE,4.2%) at a median follow-up of 9.6 years (range, 1.7 to 15).[11] These patients also were cured without an alkylating agent, bleomycin, etoposide, or high-dose, extended-field radiotherapy, however they all received involved field radiation (15 Gy if they had a CR at early response evaluation or 25.5 Gy for less than a CR). Treating our favorable risk patients with 8 weeks of Stanford V and limiting the radiation to those patients that exhibit less than a complete response at the end of therapy will make the therapy easier to administer, even more tolerable, and will allow us to learn more about the efficacy of this regimen in pediatric patients.

Table 2: Dose Intensities of Pediatric Hodgkin lymphoma Regimens (mg/m^2/week)

	Stanford V	**4 VAMP**	**2 OPPA**	**2 OEPA**	**4 ABVD**	**3 AV-PC**	**4 COPP/ABV (CCG5942)**	**2 (4) DBVE**	**4 VBVP**
Anthracyclines									
Doxorubicin	**12.5**	12.5	20	20	12.5	16.7	8.75	12.5	
Alkylators									
Cyclophosphamide						400	150		
Procarbazine			375				175		
Dacarbazine					187.5				
Mustargen	**1.5**								
Vinca alkaloids									
Vincristine	**0.7**		1.125	1.125		0.93	0.35	0.75	
Vinblastine	**3**	3			3		1.5		4
Epipodophyllotoxins									
Etoposide	**30**			125				125	167
Other									
Prednisone	**140**	140	210	210		93	140		107
Methotrexate		10							
Bleomycin	**2.5**				5		2.5	5	3.3

Table 3: Cumulative Doses of Agents Associated with Long-Term Sequelae in Pediatric Hodgkin Lymphoma Regimens (mg/m^2)

	8 week Stanford V	**4 VAMP**	**2 OPPA**	**2 OEPA**	**4 ABVD**	**3 AV-PC**	**4 COPP/ABV (CCG 5942)**	**2 (4) DBVE**	**4 VBVP**
Radiation [IFRT] (Gy)	+/- 25	+/- 25	+ 20-35	+ 20-35	+ 20–40	+ 21	+ 21	+ 25.5	+ 20
Anthracyclines									
Doxorubicine	100	200	160	160	200	150	140	100 (200)	
Alkylators									
Cyclophosphamide						3600	2400		
Procarbazine			3000				2800		
Dacarbazine					3000				
Mustargen	12								
Vinca alkaloids									
Vincristine	5.6		9	9		8.4	5.6	6 (12)	
Vinblastine	24	48			48		24		48
Epipodophyllotoxins									
Etoposide	240			1000				1000 (2000)	2000
Other									
Prednisone	1120	2240	1680	1680		840	2240		1280
Methotrexate		160							
Bleomycin	20				80		40	40 (80)	40

Limited volume conformal radiation therapy will be utilized in this study to treat patients with less than a CR following Stanford V.8 systemic therapy. This limited volume approach is based on the findings that infield recurrences in our previous collaborative studies (HOD90, HOD94 and HOD99) occurred primarily at sites of initial nodal involvement.[65] Involved field irradiation delivered in these clinical trials included entire nodal region even when only a limited number of lymph nodes within the region were involved. Resulting lymphatic regions were treated with anterior and posterior oriented portals that would encompass the lymphatics at risk and adjacent normal tissue (thyroid, lung, heart, breast, kidney and bowel). Though doses to the normal structures were low this exposure still carries a long term risk that is well documented in studies of long term survivors of pediatric HL[31,54,66,67]. The dose of radiation and subsequent risk to normal tissue is most simply reduced by avoidance during planning, an approach more easily accomplished with techniques such as conformal or intensity modulated radiation therapy. This has been carried out uniformly in several large pediatric studies in children with brain tumors and sarcomas.[68,69] The evolution towards this approach in pediatric HL was initiated in several German pediatric Hodgkin lymphoma studies utilizing a more conformed radiation therapy approach delivering limited volume treatment to involved lymphatics rather than traditional nodal regions.[15,70] In patients that received no radiation therapy all failures were in initially involved lymphatics; patients that did receive radiation experienced only a 7% risk of recurrence of which 65% had a component of failure in an initially involved lymph node. The ongoing HOD05 trial builds on this experience delivering tailored field radiation to the initially involved lymph nodes with a 2 cm treatment margin. In this trial the entire lymphatic region is not necessarily targeted and the dose of radiation is prescribed based on each lymph node's individual response at 8 weeks of therapy (CR – 15 Gy, PR – 25.5 Gy). This study's primary objective is to reduce the exposure of children with early stage HL to significant radiation by inducing early complete remission. As a corollary to this objective we will also limit the exposure of normal tissue to radiation in the cohort that achieves a less than complete response by delivering RT to tailored fields with less volume than involved fields treated on prior protocols. Limited volume conformal radiation therapy will be used in this trial treating at risk lymphatics with a small margin. It is hoped that further reductions in treatment volume, even if minor, may result in reductions in long term musculoskeletal, pulmonary, cardiac, endocrine and genitourinary toxicity and a lower risk of second cancer.

~~2.5.2 Substitution of nitrogen mustard by cyclophosphamide~~

~~In times of national shortage and unavailability of nitrogen mustard, an equi-effective drug needs to be identified. For the last several decades, this substitution has been done with cyclophosphamide. The dose substitution from nitrogen mustard is the one used in the changes from MOPP to COPP and are the "alkylator equivalent" doses also used by the adult groups in Stanford. 72-74 There is no reason to believe that there is any difference in efficacy and therefore we do not feel that there is a need in changing the objectives or statistics of the study. This substitution can be viewed as the equivalent substitution of E. coli to Erwinia asparaginase in ALL or etophos for patients allergic to etoposide. The greatest risk in this substitution relates to kidney and bladder toxicity. Therefore, patients receiving cyclophosphamide will require having post hydration intravenous fluids for 4 hours after~~

~~chemotherapy administration in order to protect these organs.~~

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

3.1.1 Histologically confirmed, previously untreated Hodgkin lymphoma.

3.1.2 Age: Participants must be 21 years of age or younger

3.1.3 Stage must be classified as one of the following:

Ann Arbor stage IA or IIA with:

a. Non-bulky mediastinal disease (< 33% mediastinal to thoracic ratio on CXR)
b. < 3 nodal regions involved on the same side of the diaphragm
c. No "E" lesion

3.1.4 Female patients who are post-menarchal must have a negative pregnancy test. Patients of reproductive potential must agree to use an effective contraceptive method.

3.1.5 Signed informed consent.

3.1.6 If re-evaluation of a patient's disease shows unfavorable risk features or intermediate risk features, the patient will be removed from the HOD08 study and consented to the HOD99 or the HOD05 study.

3.2 Exclusion Criteria

3.2.1 Intermediate or High risk disease, defined as Stage IB, IIIA, any IV or IA/IIA with "E" lesion(s), 3 or more nodal sites involved, or bulky mediastinal adenopathy

3.3 Research Participant Recruitment and Screening

Research participants will be recruited by study investigators at St. Jude and collaborating sites through regular clinical practice.

3.4 Enrollment on Study at St. Jude

Register all research participants with the Protocol office and notify the Leukemia/Lymphoma Clinical Research Office. A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the 'Participant Eligibility Checklist'. The study team will enter the eligibility checklist information into the St. Jude Clinical Trials Management

System (CTMS). Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The complete signed consent/assent form(s) must be faxed or emailed to the CPDMO at [redacted] to complete the enrollment process.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member from the Milli helpline is on call Saturday, Sunday, and holidays from 8:00 am to 6:00 pm. If you have a therapeutic research enrollment and need assistance releasing your consent, please call the Milli helpline [redacted] on call number.

3.5 Enrollment Instructions for Collaborating Sites

Collaborating Sites must register a potential research participant to receive a "Research Identification Number" (RIN), this is an eight digit automated number beginning with an "R", before screening and/or enrolling the participant. The RIN request form will be sent to St. Jude. Once form received, St. Jude will register the research participant and then email the RIN to email address provided on the registration form. This will register the participant only, it will not enroll the participant on the study.

St Jude should be notified within 24 hours of enrollment and confirmation of eligibility at the site. The completed Eligibility Checklist should be faxed to [redacted]. Call [redacted] if confirmation of the enrollment information is needed. The Protocol Eligibility Coordinator will then record the screening and/or enrollment into St. Jude's centralized enrollment system.

4.0 TREATMENT PLAN

4.1 Chemotherapy Doses and Schedule

(See also appendix 1I):

Drug/Agent	*Dose*	*Route*	*Schedule (days)*	*Max Dose*
Adriamycin	25 mg/m^2	IV	Day 1 of weeks 1, 3, 5, 7	
Vinblastine	6 mg/m^2	IV	Day 1 of weeks 1, 3, 5, 7	
*Mechlorethamine	6 mg/m^2	IV	Day 1 of weeks 1, 5	
Vincristine	1.4 mg/m^2	IV	Day 1 of weeks 2, 4, 6, 8	2 mg
Bleomycin	5 units/m^2	IV	Day 1 of weeks 2, 4, 6, 8	
Etoposide	120 mg/m^2	IV	Day 1 of weeks 3, 7	
Prednisone	40 mg/m^2/day divided in 3 doses	PO	Every other day of weeks 1-8	20 mg three times daily given every other day

~~*Given the current shortage of Mechlorethamine and the lack of it for the foreseeable future, cyclophosphamide will be used as a substitution as follows:~~
~~Cyclophosphamide 650mg/ m2 IV Day 1 of weeks 1 and 5.~~

4.2 Therapy Sequence

Patients will be treated with 8 weeks of Stanford V chemotherapy in the schedule outlined above. Radiation therapy will be omitted for patients achieving a complete response after 8 weeks of chemotherapy. Patients who achieve less than a complete response after 8 weeks of chemotherapy will receive 25.5 Gy to individual nodal sites (tailored fields) starting 2-3 weeks following completion of all chemotherapy and recovery of ANC to at least 1000.

4.3 Chemotherapy Administration Guidelines and Supportive Medical Care

These guidelines are provided to help physicians caring for patients treated on this protocol. They are guidelines not protocol requirements. Nothing in these guidelines is intended to supplant the judgment of the treating physician regarding patient management. Institutional policy and custom may dictate other approaches to the management of the areas discussed in this section.

4.3.1 Deliver full dose (100%). Delay drug at weeks 3, 5, and 7 if necessary, to give full dose.

4.3.2 Administer chemotherapy at weeks 3, 5, and 7 when ANC $\geq$ 500/mm^3, and platelets $\geq$ 100,000/mm^3.

4.3.3 Chemotherapy will not be delayed at weeks 2, 4, or 6 due to low counts.

4.3.4 No dose modifications will be made in obese patients with the exception of prednisone that will be capped at a total dose of 60 mg per day and vincristine at 2 mg.

4.3.5 Administer *Pneumocystis carinii* prophylaxis as follows or as recommended by institutional guidelines: Trimethoprim-sulfamethoxazole 150 mg TMP/m^2:750 mg SMX/m^2 for 3 consecutive days per week at the onset of therapy and continue for 6 weeks after chemotherapy or radiotherapy is completed.

4.3.6 G-CSF (5 mcg/kg) should only be used if needed for severe infection during a period of neutropenia or to shorten treatment delays due to myelosuppression at weeks 3, 5, and 7. It should be discontinued if the ANC is $\geq$ 2,000/mm^3 on any one measurement or $\geq$ 1000/mm^3 two days in a row.

4.3.7 It is recommended that Bleomycin be withheld if the DLCO drops below 70% at the discretion of the treating physician.

4.4 Radiotherapy

4.4.1 Timing of initiation of tailored-field radiation therapy

Radiation therapy will be initiated approximately 2-3 weeks after completion of the last chemotherapy week or as soon as counts have recovered to ANC $\geq$ 1000/mm^3, and platelets $\geq$ 100,000/mm^3 and radiation treatment planning is complete.

4.4.2 Dose:

4.4.2.1 In patients who experience a mixed response, defined as a CR at one Ann Arbor nodal site (e.g. neck) and a PR at another (e.g. mediastinum), no radiation will be given to the site with complete response and 25.5 Gy will be given to the site with partial response..

4.4.2.2 The dose will be 25.5 Gy in 150 cGy fractions administered five times per week for 17 days to nodal volumes that do not achieve a CR after 8 weeks of Stanford V chemotherapy.

4.4.3 Volume of treatment for limited volume conformal radiation therapy

General: Patients will receive radiation therapy to the sites of initial nodal involvement. The classic entire nodal regions do not need to be treated when only a portion of the nodal region is involved (e.g. for low cervical nodal involvement the high cervical lymph nodes will not be treated). Contoured target volumes are required for treatment on this study.

ICRU 50 and ICRU 62 volume guidelines are used in defining volumes for this study. The gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) as well as adjacent normal tissue structures including thyroid, heart, lungs, kidneys, liver, bladder and other adjacent normal tissues as appropriate will be delineated for each tumor site on the treatment planning CT prior to undergoing treatment.

Volume definitions:

GTV – Sites of initial lymphatic involvement that do not achieve a CR after 8 weeks of systemic therapy will be contoured as the GTV. The volume of the GTV will be drawn on the post-systemic therapy simulation CT study. Administration of intravenous contrast is encouraged to differentiate lymphatics from adjacent normal tissues. Adjustments to the GTV should be made to

account for reductions in the size of the involved node following systemic therapy. Multiple GTVs may be necessary as a larger conglomerate of lymphatics resolves into distinct lymph nodes following systemic therapy.

CTV – A 1 cm anatomically constrained margin incorporating the adjacent lymphatic region will be added to the GTV(s). These volumes do not have to be contiguous (e.g. neck and mediastinal volumes may not necessarily touch).

PTV – a planning target volume will be added to account for set-up uncertainty and target motion. This will be determined by the treating radiation therapist, who will account for local institutional practices and adequacy of patient immobilization.

Normal tissue volumes

The following normal tissues should be delineated based on the location of the lymphatics requiring radiation. Delineation of other normal tissues is at the discretion of the radiation oncologist:

Neck	Thyroid
Chest	Heart Lungs
Abdomen	Liver Kidneys
Pelvis	Bladder

4.4.4 Target dose

Prescription point – The prescription point is to a point within the PTV with the goal of coverage of the PTV with the 95% isodose volume

Prescribed total dose

PTV-1 – A total dose of 25.5 Gy delivered at 1.5 Gy per fraction. Lymphatic tumors that achieve a CR following chemotherapy will not be targeted or radiated

Treatment fraction size and fractionation - The daily radiation fraction size will be 150 cGy prescribed once daily.

Tissue heterogeneity - Dose corrections are encouraged for tissue heterogeneity but are not required.

Dose heterogeneity - Treatment plans must have no more than 10% of the

combined GTV, CTV and PTV volume exceed 110% of the prescribed dose.
Dose limitations – Normal tissues should be maximally shielded as allowed by the target volume. Portions of the target volume may be partially shielded if necessitated by normal tissue tolerance. The following are recommended guidelines for normal tissue tolerances but individual patient and tumor circumstances may require deviation from these normal tissue limits.

Heart: The whole heart may not receive more that 20 Gy and 50% of the heart may not receive more than 25 Gy.

Lung: The volume of the total lung receiving more than 20 Gy should be limited to less than 40% (V20Gy<40%)

Liver: The entire liver should not receive more than 15 Gy

Kidney: Maximum of 15 Gy to the entire kidney volume bilaterally.

Treatment interruptions – Treatment interruptions should be kept to a minimum, but may be necessary for significant events such as infection, neutropenia or thrombocytopenia.

4.4.5 Equipment

Energy: Megavoltage linear accelerators utilizing 6MV - 18MV photons or 6 MeV through 18 MeV electrons

Field Shaping: Multileaf collimator or cerrobend block shaped fields.

Immobilization: Immobilization devices are encouraged for daily positioning for treatment.

4.4.6 Techniques

Only external beam radiotherapy techniques are allowed on this study. Techniques may range from *en face* and parallel-opposed treatment techniques to multiple static non-coplanar beam arrangements using conformal techniques with single (3-D conformal) or multiple (intensity modulated) field segments. Intensity-modulated radiation therapy using dynamic multileaf collimation will be allowed. Regardless of the chosen technique, 3-dimensional imaging will be required for treatment planning and target and normal tissue definitions. All treatment fields will be irradiated daily and weekly portal imaging is required. The treating radiation oncologist may choose to perform portal imaging more frequently depending on the requirements of treatment for a specific case.

4.4.7 Urgent radiotherapy

Urgent radiotherapy at the time of presentation and prior to chemotherapy will be given for those presenting with life threatening conditions such as airway compromise, spinal cord compression, or disease interfering with optimal and timely work-up of the patient.

4.4.8 Oophoropexy

Oophoropexy should be offered prior to pelvic radiotherapy in all females who require pelvic radiotherapy. A testicular shield should be used for male patients requiring radiation therapy to the pelvic region during that course of therapy when feasible.

4.4 Participation of St. Jude Affiliates in the Treatment Plan (St. Jude participants only)

Participants may receive standard chemotherapy, as well as laboratory/tests to monitor for toxicity at St. Jude affiliates and local physicians' offices, as recommended by treating investigator. Radiotherapy and all protocol required response assessments will be done at St. Jude.

5.0 DRUG INFORMATION

5.1 Bleomycin (Blenoxane®)

Source and pharmacology: Bleomycin is an antitumor antibiotic produced by the fermentation of *Streptomyces verticillus.* It is thought to act by inhibiting the incorporation of thymidine into DNA, thus inhibiting DNA synthesis. Bleomycin also appears to labilize the DNA structures causing both double and single strand DNA breaks. It exerts its major effects in the G2 and M1 phases of the cell cycle. It is poorly absorbed via the GI tract and must be given via the parenteral route. Approximately 50-70% of a dose is excreted as unchanged drug by the kidneys, with the remainder being hydrolyzed by intracellular aminopeptidase, found in most tissues. Bleomycin has an elimination half-life of 3-5 hours for patients with "normal" kidney function. The dosage of bleomycin should be reduced for patients with renal dysfunction.

Formulation and stability: Bleomycin is available in vials containing 15 units and 30 units of bleomycin sulfate as a white or yellowish lyophilized powder. Intact vials should be stored under refrigeration. The contents of each vial should be diluted with 1 to 5 ml or 2-10 ml of 0.9% NaCl respectively, resulting in final concentrations of 15 to 3 units/ml. It may be further diluted in 0.9% NaCl but should not be diluted in D5W due to a loss in potency. Diluted solutions (in sodium chloride) are stable for 24 hours at room temperature

Supplier: Commercially available from Mead Johnson.

Toxicity: Toxicities include mild nausea and vomiting, anorexia, alopecia and skin rash, hyperpigmentation and tenderness. Less common reactions include renal toxicity, hepatotoxicity, MI, and myelosuppression. Anaphylactic reactions are rare but potentially life threatening and can be characterized by severe fever, chills, hypotension and wheezing. Pneumonitis can occur and may progress to pulmonary fibrosis. This occurs most commonly with cumulative dosages of > 400 units (200 units/m^2) in adults. Oxygen inhalation therapy accentuates pulmonary toxicity and should be used with caution. It is recommended that follow-up pulmonary function tests be done during the course of therapy and for 1 year following completion of therapy.

~~**5.2 Cyclophosphamide**~~

~~Source and pharmacology: Cyclophosphamide is a nitrogen mustard derivative. It acts as an alkylating agent that causes cross-linking of DNA strands by binding with nucleic acids and other intracellular structures, thus interfering with the normal function of DNA. Cyclophosphamide is cell-cycle, phase non-specific. Cyclophosphamide is well absorbed from the GI tract with a bioavailability of > 75%. Cyclophosphamide is a prodrug that requires activation. It is metabolized by mixed-function oxidases in the liver to 4-hydroxycyclophosphamide, which is in equilibrium with aldofosfamide. Aldofosfamide spontaneously splits into cyclophosphamide mustard, which is considered to be the major active metabolite, and acrolein. In addition, 4-hydroxycyclophosphamide may be enzymatically metabolized to 4-ketocyclophosphamide and aldofosfamide may be enzymatically metabolized to carboxyphosphamide which are generally considered to be inactive. Cyclophosphamide and its metabolites are excreted mainly in the urine. Dosage adjustments should be made in patients with a creatinine clearance of < 50 ml/min.~~

~~Formulation and stability: Cyclophosphamide is available in 25 and 50 mg tablets. Cyclophosphamide is also available in vials containing 100, 200, 500, 1000 and 2000mg of lyophilized drug and 75 mg mannitol per 100 mg of cyclophosphamide. Both forms of the drug can be stored at room temperature. The vials are reconstituted with 5, 10, 25, 50 or 100 ml of sterile water for injection respectively to yield a final concentration of 20 mg/ml. Reconstituted solutions may be further diluted in either 5% dextrose or 0.9% NaCl containing solutions. Diluted solutions are physically stable for 24 hours at room temperature and 6 days if refrigerated, but contain no preservative, so it is recommended that they be used within 24 hours of preparation.~~

~~Supplier: Commercially available~~

~~Toxicity: Dose limiting toxicities of cyclophosphamide are bone marrow suppression and cardiac toxicity. Cardiac toxicity is typically manifested as~~

~~congestive heart failure, cardiac necrosis or hemorrhagic myocarditis and can be fatal. Hemorrhagic cystitis may occur and necessitates withholding therapy. The incidence of hemorrhagic cystitis is related to cyclophosphamide dose and duration of therapy. Forced fluid intake and/or the administration of mesna decrease the incidence and severity of hemorrhagic cystitis. Other toxicities reported commonly include nausea and vomiting (may be mild to severe depending on dosage), diarrhea, anorexia, alopecia, immunosuppression and sterility. Pulmonary fibrosis, SIADH, anaphylaxis and secondary neoplasms have been reported rarely.~~

5.3 Doxorubicin (Adriamycin®)

Source and pharmacology: Doxorubicin is an anthracycline antibiotic produced by *Streptomyces peucetius*. Doxorubicin exerts its anti-tumor effects in several different ways. Doxorubicin intercalates between base pairs of DNA causing steric obstruction, disruption of DNA function and inhibition of RNA synthesis. In addition, doxorubicin inhibits topoisomerase II, an enzyme responsible for allowing strands of DNA to pass through one another as they unwind. Lastly, doxorubicin undergoes enzymatic electron reduction to generate highly reactive species, including the hydroxyl free radical, which is thought to be responsible for the drug's cardiac toxicity, but may play a role in its anti-tumor activity as well. Doxorubicin is cell-cycle, phase non-specific. Doxorubicin is widely distributed in the tissues and plasma, but does not cross the blood brain barrier to an appreciable extent. It is metabolized to doxorubicinol, which is thought to be the major active metabolite, and aglycones. Doxorubicin and its metabolites are excreted mainly in the bile and feces (≈80%). The remainder is excreted in the urine. Dosage should be reduced in patients with liver dysfunction (bilirubin > 1.2 mg/dl) or renal dysfunction (creatinine > 3 mg/dl).

Formulation and stability: Doxorubicin is available in vials containing 10 mg, 20 mg, 50 mg and 200 mg as a 2mg/ml red-orange solution. It is also available in vials containing 10 mg, 20 mg, 50 mg, 100 mg and 150 mg of doxorubicin as a red-orange lyophilized powder. Intact vials of doxorubicin solution should be stored under refrigeration while the lyophilized product should be stored at room temperature. Both products should be protected from light. Lyophilized doxorubicin can be reconstituted by adding 5, 10, 25, 50 or 75 ml of 0.9% NaCl respectively to the 10, 20, 50, 100 and 150 mg vials to produce a final concentration of 2 mg/ml. Bacteriostatic diluents are not recommended. After reconstitution, the resultant solution should be protected from light and is stable for 7 days at room temperature and 15 days if refrigerated.

Supplier: Commercially available

Toxicity: Dose-limiting toxicities include myelosuppression and cardiotoxicity. Two forms of cardiac toxicity can occur. Acute toxicity may take the form of arrhythmias, heart block or pericarditis and may be fatal. The chronic form of

cardiotoxicity is related to total cumulative dose and is characterized by heart failure. Mediastinal radiotherapy and/or other cardiotoxic drugs may increase the risk of cardiotoxicity. In general, total lifetime dosages of 450-550mg/m^2 should not be exceeded. Other toxicities include nausea and vomiting, mucositis, alopecia, diarrhea and red discoloration of the urine and other body fluids. Severe tissue damage and necrosis can occur upon extravasation. Radiation recall reactions can occur and can be severe. Rarely, allergic reactions have occurred. Typhilitis can occur when combined with cytarabine.

5.4 Etoposide (VP-16) (Vepesid®)

Source and pharmacology: Etoposide is an epipodophyllotoxin derived from *Podophyllum pelatatum.* It is thought to act mainly by inhibiting topoisomerase II, causing double and single strand DNA breaks. Etoposide is cell cycle, phase-specific, with activity in the G2 and S phases. Absorption of etoposide is approximately 30-40% and is highly variable and somewhat dose-dependent. It is extensively bound to serum proteins and is metabolized in the liver, including cytochrome P450 3A metabolism to several moieties that include a reactive oxidized species. Etoposide and its metabolites are excreted mainly in the urine with a smaller amount excreted in the feces. Dosage adjustments should be considered in patients with liver dysfunction, kidney dysfunction or hypoalbuminemia.

Formulation and stability: Etoposide is available in multi-dose vials containing 100mg, 150mg, 500mg and 1000mg of etoposide as a 20mg/ml solution and 30% alcohol. Etoposide is also available as a 50 mg capsule. The intact vials of etoposide solution should be stored at room temperature. The capsules should be stored under refrigeration. Etoposide solution should be diluted in D5W or 0.9% NaCl prior to administration. Solutions with a final concentration of 0.2 and 0.4 mg/ml are stable at room temperature for 96 hours and 24 hours respectively.

Supplier: Commercially available

Toxicity: Dose limiting toxicity is myelosuppression. Nausea and vomiting (usually of low to moderate severity), diarrhea, mucositis (particularly with high doses), alopecia and anorexia are fairly common. Hypotension can occur with rapid infusions. Other side effects reported less commonly include hepatitis, fever and chills, anaphylaxis and peripheral neuropathy. Secondary leukemia has been reported.

5.5 Mechlorethamine Hydrochloride (Nitrogen Mustard, Mustargen®)

Source and pharmacology: Mechlorethamine hydrochloride is a nitrogen analog of sulfur mustard. It is a bifunctional alkylating agent that interferes with DNA replication and transcription of RNA, resulting in disruption of nucleic acid function. Mechlorethamine possesses weak immunosuppressive activity.

Mechlorethamine by intracavity administration results in sclerosing caused by an inflammatory reaction on serous membranes adherence of serosal surfaces. Mechlorethamine is absorbed orally, but should not be given by this route as it is extremely irritating to tissues. When administered by the intravenous route, mechlorethamine is rapidly transformed, with less than 0.01% being excreted unchanged in the urine. Within minutes of an IV dose, unchanged mechlorethamine is undetectable in the blood.

Formulation and stability: Mechlorethamine hydrochloride is supplied in vials containing 10 mg of light yellow brown crystalline powder that is very soluble in water. The vials of powder should be stored at room temperature protected from light. Each vial should be reconstituted with sterile water for injection or normal saline to a concentration of 1 mg/ml immediately prior to administration. The colorless mechlorethamine solution is highly unstable and undergoes rapid chemical transformation. Mechlorethamine is a highly toxic drug and caution should be used in admixture and administration of this agent.

Toxicity: Major and dose limiting toxicities of mechlorethamine include hematologic toxicities, nausea and vomiting. Anorexia, diarrhea, severe hematemesis, and peptic ulcers have been reported after intravenous administration. Immediate and delayed neurotoxicity (sometimes severe) have been reported in patients receiving high doses or intra-arterial and regional perfusion administration. CNS adverse effects reported following IV administration include weakness, headache, drowsiness, vertigo, light-headedness, convulsions, progressive muscle paralysis, paresthesia, cerebral degeneration, coma, and death. Neurotoxicity appears to increase with age and dose administered. It also occurs more frequently in patients who receive procarbazine or cyclophosphamide. Hyperuricemia has been reported following administration of mechlorethamine, especially in lymphoma patients. Rare adverse effects reported include alopecia, jaundice, tinnitus, diminished hearing, fever, and metallic taste. Mechlorethamine is a powerful vesicant, and great care should be taken to avoid contact with skin or mucous membranes. If eye contact occurs, the eye(s) should immediately be irrigated with copious amounts of normal saline or ophthalmic irrigation solution followed by an ophthalmologic examination. If skin contact occurs, the affected area should be irrigated with copious amounts of water for at least 15 minutes, followed by 2% sodium thiosulfate solution. Extravasation of even small amounts of mechlorethamine will result in painful inflammation and induration. In severe reactions, sloughing may occur. If extravasation occurs, as much infiltrated drug as possible should be removed by aspiration. The local reaction may be minimized by promptly infiltrating the area with isotonic sodium thiosulfate injection and applying cold compresses for 6 – 12 hours. Thrombosis and thrombophlebitis may result from direct vein contact or as a result of insufficient dilution.

Supplier: Commercially available.

5.6 Prednisone

Source and pharmacology: Prednisone is a synthetic congener of hydrocortisone, the natural adrenal hormone. Prednisone is a white or yellowish crystalline powder. It binds with steroid receptors on nuclear membranes, impairs cellular mitosis and inhibits protein synthesis. Prednisone also has potent anti-inflammatory effects and suppresses the immune system. Prednisone is well absorbed orally. It is converted to prednisolone, the pharmacologically active metabolite, in the liver. Prednisolone is further metabolized to inactive compounds in the liver. The metabolites are excreted mainly in the urine.

Formulation and stability: Prednisone is available as various strength tablets and oral solution from multiple manufacturers. All dosage forms can be stored at room temperature. At St. Jude Children's Research Hospital, prednisolone oral solution may be substituted for prednisone liquid at equal doses due to its superior palatability.

Supplier: commercially available

Toxicity: Side effects of prednisone vary depending on the duration of its use. Side effects that can occur with short term use include sodium and water retention with associated hypertension, peptic ulcer with possible perforation and hemorrhage, increased susceptibility to infections, emotional instability, insomnia, increased appetite, weight gain, acne and hyperglycemia. Side effects more commonly associated with prolonged use include cataracts, increased intraocular pressure and associated glaucoma, development of a "cushingoid" state, compression fractures, menstrual irregularities, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness particularly in times of stress as in trauma, surgery or illness, osteoporosis and muscle wasting.

5.7 Vinblastine (Velban®)

Source and pharmacology: Vinblastine is an alkaloid extracted from the periwinkle plant *(Vinca Rosea)*. It reversibly binds to microtubule and spindle proteins causing metaphase arrest. It may also block cellular utilization of glutamic acid, thereby inhibiting purine synthesis and urea formation via the citric acid cycle. Vinblastine is highly protein bound and poorly penetrates the CSF. Metabolism in the liver is extensive with one metabolite, deacetyl vinblastine, being more active than the parent drug. The major route of elimination is via the bile. Dosages should be adjusted for patients with impaired liver function (bilirubin > 3 mg/dl).

Formulation and stability: Vinblastine is available in 10 ml vials containing 1mg/ml of vinblastine in solution. Intact vials of vinblastine solution and lyophilized vinblastine should be stored under refrigeration.

Supplier: Commercially available

Toxicity: The dose limiting toxicity is myelosuppression. Other toxicities reported commonly include alopecia, mild nausea and vomiting and constipation. Vinblastine is a vesicant and may cause severe tissue damage if extravasation occurs. Vinblastine rarely produces neurotoxicity characterized by peripheral neuropathy, loss of deep tendon reflexes, weakness, jaw pain and "foot drop". This toxicity is much less common than with vincristine. Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids.

5.8 Vincristine (Oncovin®)

Source and pharmacology: Vincristine is an alkaloid obtained from the periwinkle *(Vinca rosea)* plant. It reversibly binds to microtubule and spindle proteins causing metaphase arrest. Vincristine has poor penetration into the CSF. It is approximately 75% protein bound. Extensive metabolism occurs in the liver. Excretion is primarily in the bile. A dosage decrease is recommended in patients with a bilirubin > 3 mg/dl.

Formulation and stability: Vincristine is supplied in multiple-dose 1 mg/ml vials containing 1 ml, 2 ml and 5 ml. The intact vials should be stored under refrigeration and protected from light.

Supplier: Commercially available

Toxicity: Dose limiting toxicity is neurotoxicity. This can be characterized by constipation and/or paralytic ileus, ptosis, vocal chord paralysis, weakness, jaw pain, abdominal pain, peripheral neuropathies, loss of deep tendon reflexes and "foot drop". Peripheral neuropathy is often the first sign of neurotoxicity and is initially reversible. Other toxicities reported include alopecia, mild nausea and vomiting, SIADH, myelosuppression, orthostatic hypotension, optic atrophy, transient cortical blindness, and auditory damage. Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. Myelosuppression is rare at usual doses. Vincristine is a vesicant and may cause severe tissue damage if extravasation occurs. NOTE: dose reduction may be necessary in patients < 1 year of age. Dosing on a per kg (rather than per m^2) basis has been advocated for infants in order to decrease toxicity.

5.9 Filgrastim (G-CSF, Neupogen®)

Source and pharmacology: G-CSF (granulocytic colony stimulating factor), is a biosynthetic hematopoietic agent that is made using recombinant DNA technology in cultures of *Escherichia coli.* G-CSF stimulates production, maturation and activation of neutrophils. In addition, endogenous G-CSF enhances certain functions of mature neutrophils, including phagocytosis, chemotaxis and antibody--dependent cellular cytotoxicity.

Formulation and stability: G-CSF is supplied in vials containing 300 mcg and 480 mcg of G-CSF at a concentration of 300 mcg/ml. The intact vials should be stored under refrigeration. The vials can be left out of refrigeration for 24 hours, but should be discarded if left at room temperature for longer periods of time. G-CSF can be drawn up into tuberculin syringes for administration and stored under refrigeration for up to 7 days prior to usage. G-CSF can be further diluted for IV infusion in 5% dextrose. Do not dilute in saline---precipitate may form. If the final concentration of this product is < 15 mcg/ml, it is recommended that albumin be added to a final concentration of 2mg/ml (0.2%) to minimize adsorption of the drug to infusion containers and equipment.

Supplier: Commercially available

Toxicity: G-CSF causes marked leukocytosis. Adverse reactions reported commonly include bone pain, thrombocytopenia, diarrhea, nausea, rash, alopecia, fever, anorexia and pain or bruising at the injection site. Allergic reactions, MI, atrial fibrillation, and splenomegaly have been reported rarely. G-CSF is contraindicated in patients with allergy to E. coli derived products.

6.0 EVALUATIONS, TESTS, AND OBSERVATIONS

6.1 Required Clinical Staging Evaluation

(See also Appendix III):

- History and physical exam
- Complete blood count with differential
- C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)
- LDH, alkaline phosphatase and albumin
- Urine pregnancy test for female patients after menarche.
- Chest x-ray (mediastinal adenopathy must be expressed as 33% or greater of the maximum intrathoracic diameter, less than 33% of the maximum intrathoracic diameter, or no mediastinal involvement)
- CT scan of the neck and chest with contrast
- CT scan or MRI of the abdomen and pelvis with contrast
- PET scan

Surgical staging

Staging laparotomy with splenectomy is not required; however, untreated patients who have been surgically staged when referred are eligible.

Initial staging

Initial staging will be based on the primary physician's interpretation of physical examination, laboratory and diagnostic imaging evaluations.

6.2 Other Pre-therapy Evaluations

These studies are recommended for good clinical care or as clinically indicated:

- Blood chemistry profile including electrolytes, BUN, creatinine, bilirubin, SGOT, and SGPT.
- Urinalysis
- Echocardiogram and EKG
- Pulmonary function studies
- Panorex and dental evaluation

6.3 Recommended and Required Schedule of On-Therapy Evaluations

The recommended and required schedule of evaluations during chemotherapy is outlined in Appendix III.

All patients will be evaluated for chemotherapy response after finishing all 8 weeks of chemotherapy. Required response evaluation will comprise a history and physical exam, CT scan or MRI of areas of nodal involvement and PET scan (if previously positive). For patients not requiring radiotherapy (because they are in CR) this will be considered their end of therapy evaluation.

6.4 Off Therapy Evaluations

6.4.1 Required Off Therapy (Post-RT) Evaluation

Required end of therapy evaluation for patients receiving radiotherapy should be performed approximately 4-8 weeks after completion of all radiation, and will comprise of a CT scan or MRI of areas of initial nodal involvement and PET (only if previously positive), as well as physical examination, CBC with differential, and ESR/CRP.

Pulmonary function studies should be obtained at response evaluation or off therapy.

Note that patients with residual imaging abnormalities may be designated to be in complete remission unconfirmed based on the definition outlined in section 7.1.5.1.

Required 1-year and 2-year off-therapy evaluations should include a physical examination, ESR or CRP and diagnostic imaging studies and CT scan. PET is optional. See section 6.4.3 and appendix V for specific late effects testing required at the 1-, 2-, 5- and 10-year off-therapy anniversary evaluations.

A schedule of off-therapy studies to be obtained is listed in tabular form in Appendix IV. If there is a suspicion of recurrent disease by signs or symptoms, specific exams should be performed as indicated. All patients with suspected relapse or progressive disease should undergo biopsy of the most accessible site of recurrence or progression whenever possible.

6.4.2 Recommended schedule of off-therapy evaluations

After confirmation of disease status at the first off-therapy evaluation, study patients should have regular follow-up with a recommended schedule of every 3 months for 1 year, every 4 months for the next 2 years, every 6 months for the 4th year, and annually thereafter. Follow-up studies are recommended as clinically indicated for patients with abnormal baseline and to monitor organ dysfunction related to the toxic effects of chemotherapy and include a physical examination, CBC with differential and ESR or CRP. Chest radiograph is recommended as clinically indicated during follow-up for patients with mediastinal disease (see appendix IV and V for specific guidelines).

6.4.3 Recommended late effects evaluations

Specific late effects testing should follow the Children's Oncology Group *Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* http://www.survivorshipguidelines.org.

Recommended late effects testing should include evaluation of the following organ systems as outlined in Appendix V:

- Heart: echocardiogram, electrocardiogram at 1, 2, 5 and 10 years.
- Lung: pulmonary function studies at 1, 2, 5 and 10 years
- Growth: physical examination with attention to growth abnormalities of soft tissues and bones with every physical exam.
- Dental: panorex and dental evaluation at 5 years.
- Thyroid: Free T_4 and TSH yearly if patient received radiation possibly encompassing the thyroid, but need to be captured only at 1, 2, 5, and 10 years.
- Document initiation date for thyroid hormone replacement therapy, if applicable.

- Fertility: Record menstrual cycle and pregnancy information. Referral of men for semen analysis or measurement of testosterone levels is optional and should be performed when appropriate.
- Obtain pathology of second tumors for histological review.

Patients in first CR will be followed for at least 10 years after completion of therapy. A HOD08 Follow-Up Form for Patients in First Remission should be submitted every year.

A Late Effects Follow-Up Form for Patients in First Remission should be submitted at years 1, 2, 5 and 10.

Evaluations at 1, 2, 5, and 10 years should be performed within 6 months of the Off-Therapy anniversary date. We recognize, however, that patients may be monitored more frequently and that off therapy evaluations and diagnosis of treatment-related toxicity may not adhere exactly to 1, 2, 5, or 10 years after completion of therapy. For patients in first remission, whose off therapy evaluations are performed beyond the 6 month anniversary date, a HOD08 Late Organ Function Screening Form For Patients in First Remission and a HOD08 Late Effects Follow-Up Form can be submitted as part of good clinical practice.

A HOD08 Follow-Up After Relapse Form should be submitted on an annual basis on patients with a history of progressive disease or relapse for as long as the study is open for follow-up.

7.0 EVALUATION CRITERIA

7.1 Response Criteria

At the end of all prescribed chemotherapy, response will be determined for each individual nodal group. The response evaluation will be based on the multidisciplinary (oncologist, radiotherapist, and radiologist) interpretation of physical examination, laboratory and diagnostic imaging and the following criteria:

7.1.1 Complete response (CR):

Disappearance of all measurable or evaluable disease, signs, symptoms and biochemical changes related to the tumor. Biopsy confirmation is not mandatory. Residual PET-negative CT scan abnormalities representing $\geq$ 75% reduction (as measured by the product of 2 perpendicular diameters of lesions by CT or MR imaging) in the original tumor volume will be considered scar tissue without active tumor.

7.1.1.1 Complete response unconfirmed (CRu):

Persistent radiographic abnormalities (PET negative) at a site of previous disease not thought to represent active disease as long as residual abnormalities are stable or improved when compared to previous evaluations. Biopsy is not required to confirm a complete remission status.

7.1.2 Partial response (PR):

Reduction of 50% to 75% in the original tumor volume of any measurable lesion by CT scan regardless of PET avidity. Persistence of PET avidity in residual nodal masses that shrunk ≥ 75% (as measured by the product of 2 perpendicular diameters of lesions by CT or MR imaging) from original tumor volume.

7.1.3 Stable disease (SD):

Neither sufficient shrinkage (<50%) to qualify for partial response, nor sufficient increase (<25%) or appearance of new lesions to qualify for progressive disease.

7.1.4 Progressive disease (PD):

An increase in the product of two perpendicular diameters of any measured lesion by >25% over the size present at entry on study or the appearance of new areas of biopsy proven disease.

7.1.5 Remission evaluation after completion of therapy

Patients that did not achieve a complete response after 8 weeks of chemotherapy and went on to receive radiation therapy will undergo a complete disease evaluation 4 to 6 weeks after completing all prescribed radiotherapy. Patients will be designated to be in complete remission after the completion of all of the protocol-prescribed chemotherapy and radiotherapy as long as off therapy evaluations do not reveal new abnormalities suggestive of disease progression.

7.1.5.1 Complete response unconfirmed (CRu):

Persistent radiographic abnormalities (PET negative) at a site of previous disease not thought to represent active disease as long as residual abnormalities are stable or improved when compared to previous evaluations. Biopsy is not required to confirm a complete remission status.

7.1.6 Evaluation of progressive disease or relapse

Biopsy is required (whenever possible) for confirmation of progression during planned therapy, or for relapse following completion of therapy.

Patients with progressive disease on therapy will be taken off treatment. All patients will be followed for survival and remain on study. Patients will receive salvage therapy according to investigator preference. When progression or relapse occurs, a protocol outcomes event form and off-treatment form should be submitted.

7.2 Toxicity Evaluation Criteria

This study will utilize the CTCAE Version 3.0 for toxicity and performance reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The toxicities are to be reported on the appropriate data collection forms.

8.0 CRITERIA FOR OFF THERAPY AND OFF-STUDY

8.1 Off-Therapy Criteria:

- Therapy completed
- Progressive disease
- Development of unacceptable toxicities or if protocol therapy or testing become detrimental to the patient's health (with the concurrence of the principal investigator).
- Participant/family decision to withdraw consent for protocol treatment at any time for any reason. Patients who withdraw consent for therapy remain on study unless they also withdraw consent for study participation.

8.2 Off-Study Criteria:

- Death
- Ineligible for study
- Loss to follow-up (with the concurrence of the principal investigator)
- Participant/family decision to withdraw consent from protocol and follow up at any time for any reason.
- Noncompliance (with the concurrence of the principal investigator)
- Completion of 10 year follow-up

If re-evaluation of a patient's disease shows unfavorable risk features or intermediate risk features, the patient will be removed from the HOD08 study and consented to the HOD99 study or the HOD05 study. The HOD99 study is for the treatment of patients with unfavorable risk features and the HOD05 study is for

the treatment of patients with intermediate risk features. Chemotherapy treatment for the HOD99 unfavorable risk group, HOD08 favorable risk group and HOD05 intermediate risk group is the same. Radiation therapy will be given based on the patient's response to treatment and according to protocol.

9.0 ADVERSE EVENT REPORTING AND GRADING

9.1 Recording and Reporting Adverse Events

This study will utilize the CTCAE Version 3.0 for toxicity and performance reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). Additionally, the toxicities are to be reported on the appropriate data collection forms. The following procedures will be followed:

1. Identify the event using the protocol-defined criteria ((as delineated in CTCAE v3);
2. Determine if the AE is unexpected or expected (refer to protocol, consent, investigator's brochures, package insert and/or product labeling);
3. Assign grade of the event using the CTCAE criteria;
4. Determine attribution (i.e., if the AE is related to the medical intervention).
5. Identify whether the AE requires expedited reporting

Adverse events will be collected and recorded in the protocol-specific research database for the study, and reviewed by treating investigators and study PI.

9.2 Reporting Unanticipated Problems to the St. Jude IRB

Adverse events that are considered "**unanticipated problems**" will be reported in an expedited manner according to the guidelines outlined below. Unanticipated problems include those events which (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized. Specifically, adverse events that fall into the following categories will be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5):

1. Adverse events determined to be **serious, unexpected, and related or possibly related** to participation in research.

2. Serious adverse events that are expected in some subjects, but are determined to be occurring at a **significantly higher frequency or severity** than expected.

3. Other unexpected adverse events, regardless of severity, that may **alter the IRBs analysis of the risk versus potential benefit of the research**, and, as a result, warrant consideration of **substantive changes in the research protocol or informed consent process/document**.

Adverse events meeting any of the above categories for participants enrolled on St. Jude trials (both at St. Jude and at collaborating sites) will be reported to the St. Jude IRB, and to all collaborating sites' IRBs (if applicable) using expedited procedures.

FURTHER GUIDELINES FOR REPORTING ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

To determine whether an adverse event is an unanticipated problem, and therefore requires expedited reporting under 45 CFR part 46, the PI will take into account the following:

1. The description of known or foreseeable adverse events and risks in the IRB-approved research protocol, any applicable investigator brochure, the current IRB-approved informed consent document, and other relevant sources of information, such as scientific literature, product labeling, and package inserts.
2. Any underlying diseases or conditions of the subject experiencing the adverse event.
3. A careful assessment of whether the adverse event is related or possibly related to the subject's participation in the research study.

Particular AEs and SAEs require more prompt reporting to the various governing regulatory authorities. The key to whether a SAE should be reported expeditiously or not to the St. Jude IRB is based on its expectedness of the event. Is this SAE an expected or unexpected event? Expeditious reporting to the various Federal governing regulatory authorities is based on the relationship of the unexpected event to the protocol treatment and the seriousness of the event.

Serious adverse events that are identified by the PI or designated sub-investigator as <u>expected</u>, regardless of causality are not subject to expedited reporting. All expected SAEs will be reported to the St. Jude IRB and St. Jude Office of Regulatory Affairs in a summary type format on an annual or semi-annual basis or more frequently if requested by the IRB, FDA, or PI.

All **<u>unexpected</u> SAEs that are at least possibly related to the protocol treatment** need to be reported to the IRB's at all participating sites (and FDA for IND studies) expeditiously. The nature and severity of the event will dictate the exact time frame for expeditious reporting (24 – 48 hours vs. 10 days).

Expeditious Adverse Event Reporting Requirements to the St. Jude IRB

- All deaths **that occur while participants are on active therapy or within 30 days of protocol therapy OR deaths that are deemed unexpected and at least possibly related to study treatment will be reported to the St. Jude IRB immediately (within 24-48 hours of notification) using the electronic *TRACKS system***. Immediate reporting is required even if few event specific facts are available at the time of the initial report. In this case, a complete follow-up report detailing the event should be submitted to the IRB within 10 days of the event.

- All life threatening SAEs that are deemed **unexpected and at least possibly related** to study treatment will be reported to the St. Jude IRB as soon as possible using the electronic TRACKS system but no later then 24 - 48 hours and followed up in with a complete report within 10 working days of the occurrence of the event.

- All other **unexpected** SAEs (not fatal or life threatening) determined to be **at least possibly related** to study treatment will need to be reported to the St. Jude IRB within 10 working days of the occurrence.

Follow-up reports

Follow-up reports for the expedited adverse event reports submitted to the St. Jude IRB are required for those that are checked as "unresolved" at the time of the report. Typically, follow-up reports should be submitted when the investigator becomes aware of significant new information regarding the initial event or subsequent patient status, or when the event has completely resolved and any sequelae have been identified and/or resolved.

10.0 DATA COLLECTION, MONITORING AND CONFIDENTIALITY

Data Management will be supervised by the Director of Clinical Trials Management, and Manager of Clinical Research Operations for the Leukemia/Lymphoma Division, working with Dr. Flerlage or her designee. All protocol-specific data and all grade 3-5 adverse events will be recorded by the clinical research associates into the CRIS database, ideally within 1-2 weeks of completion of study phase (chemotherapy or radiation therapy). All questions will be directed to the attending physician and/or PI and reviewed at regularly-scheduled working meetings. The attending physicians (or their designees) are responsible for keeping up-to-date roadmaps in the patient's primary medical chart.

Regular (at least monthly) summaries of toxicity and protocol events will be generated for the PI and study team to review.

For collaborating sites, data collection forms will be sent to Jamie Flerlage, M.D., St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN, 38105-3678; [redacted] (see Appendix II). Data will be entered into the HOD08 database, by a Clinical Research Associate (CRA), within 1-2 weeks of receiving the information. For participants seen at St. Jude, data will be entered within 7 days of the clinical encounter, laboratory test and/or radiological exam.

10.1 On-Study Forms

At the time of patient entry, a HOD08 Registration Form and HOD08 Registration Sites of Involvement Form.

10.2 During Treatment

After 8 weeks of chemotherapy, a HOD08 Response Assessment Form will be completed; after completion of all chemotherapy and radiation therapy, a HOD08 Off-Therapy Response Assessment Form will be completed. *For patients in CR after 8 weeks of chemotherapy the Response Evaluation form will serve as the Off-Therapy Response form.*

10.3 After Treatment

- After completion of all chemotherapy, a HOD08 Treatment Schema, HOD08 Toxicity Screening Form and HOD08 Grade III/IV Adverse Event/Toxicity/Blood Product Administration Form, if applicable.

- After completion of radiation therapy, a HOD08 Radiation Therapy Form and Radiation Dose to Site of Involvement Form.

- At years 1-10 after completion of therapy, a HOD08 Follow-Up Form for Patients in First Remission or Follow-Up after Relapse Form.

- At the time of relapse, death or second tumor, a HOD08 Protocol Outcomes Event Form.

- At the time a patient is taken off treatment or off study, a HOD08 Off-Treatment/Off-Study Form.

- At year 1, year 2, year 5 and year 10 after completion of therapy, a HOD08 Late Organ Function Screening Form For Patients In First Remission and a HOD08 Late Effects Follow-Up Form for Patients in First Remission. These evaluations should be performed within 6 months of the 1-, 2-, 5- and 10-year Off-Therapy (Post-RT) anniversary date if the patient remains on study. The forms can also be used to provide information for patients in first remission, whose off therapy evaluations

are performed beyond the 6 month anniversary date as part of good clinical care.

10.4 Study Monitoring

This study is considered moderate risk for monitoring purposes. Protocol and regulatory compliance, including essential regulatory documentation, will be assessed as well as the accuracy and completeness of data points related to the primary study objective semi- annually. If the study design has strata, accrual will be tracked continuously. The first two enrollees and then 10% of participants will be monitored semi-annually.

The PI and study team are responsible for protocol and regulatory compliance, and for data accuracy and completeness. The study team will meet at appropriate intervals to review case histories or quality summaries on participants and retain copies of the minutes which are signed by the PI.

The Eligibility Coordinators in the Central Protocol and Data Monitoring Office (CPDMO) will verify informed consent documentation of and eligibility status for 50% of the St. Jude participants within 5 working days of enrollment completion. During semi-annual routine monitoring events, the Monitor will verify informed consent documentation and eligibility status for 50% of non-St. Jude participants as well as perform consent and eligibility verification on selected St. Jude enrollments. Overall study conduct, compliance with primary objectives, age of majority consenting, safety assessments and reporting, and the timeliness and accuracy of database entries are monitored routinely.

Study documents routinely monitored on selected participants include medical records, database entries, study worksheets, and case report forms. Study documents are monitored for participant status, demographics, staging, subgroup assignment, treatments, investigational drug accountability, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in a separate study-specific monitoring plan. The study-specific monitoring plan may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended).

The recording and reporting of Adverse Events, Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) to include type, grade, attribution, duration, timeliness and appropriateness will be reviewed by the Monitor/ CRM. The CRM will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Continuing reviews by the Internal Review Board (IRB) and Scientific Review Committee (CT-SRC) will occur at least annually. In addition, unanticipated problems are reviewed in a timely manner by the IRB.

St. Jude affiliates and domestic collaborating study sites will be monitored on-site by a representative of St. Jude as needed. International collaborators will be monitored by a Contract Research Organization (CRO), or other mechanism according to the study specific monitoring plan.

10.5 Confidentiality

All data will be maintained in a secure, password-protected database accessible only by study personnel.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size

With the success of current chemotherapy for Hodgkin lymphoma, one of the goals of this protocol is to increase the proportion of favorable risk Hodgkin lymphoma patients treated with Stanford V alone that will not require any radiotherapy by at least 20% compared to favorable risk patients treated with VAMP on HOD99. In HOD 99, 44% (27/62) of favorable risk patients achieved a complete response (CR) at 8 weeks after two cycles of VAMP chemotherapy, and thus required no radiotherapy. A patient is considered to have achieved complete response if all nodal regions of this patient achieve complete responses. A historical control design is used to test the hypothesis of a 20% increase (from 44% to 64%) in the proportion of patients not requiring radiotherapy. The sample size was calculated based on a two-sample binomial test with historical control group (Makuch and Simon, 1980, implemented in DSTPlan; one-sided test). A total of 64 evaluable patients (stage IA nodular lymphocyte predominant histology subjects are excluded from the analysis) will be needed for the trial to have 80% power with a 5% type I error to detect a 20% increase compared with data from the historical HOD99 trial.

Update 3/14/2013: Given the recently published data on the impact of mechlorethamine drug shortage on children with Hodgkin lymphoma (Metzger et al. NEJM 2012), as evaluated on patients treated with a modified Stanford V regimen with cyclophosphamide on HOD99 and HOD05, we will substitute all participants on HOD08 treated with cyclophosphamide.

In order to be able to properly prove the primary objective on HOD08 (to increase the number of patients in CR after 8 weeks of Stanford V and therefore reducing the number of patients requiring radiotherapy, as well as to have an accurate EFS estimate), participants treated with cyclophosphamide will need to be excluded from the analysis.

11.2 Accrual

As of October 2008 (the most recent DSMB report) 72 eligible favorable risk patients (excluding stage IA nLP patients) were enrolled on HOD99 over an eight-year period (see Table S1) with an average of 8 patients per year. Based on this data, we estimate that the annual accrual rate will be 8 favorable risk patients per year and the study will need approximately 8 years to finish accrual. The study PI anticipates a yearly accrual of 10 favorable risk patients (see statement below) and with such an accrual rate, the duration of the study would be approximately 6.5 years.

Update 5/31/13: By adding the additional 16 participants for the primary objective to replace participants treated with cyclophosphamide, the duration of the study will be approximately 8.5 years.

Statement regarding accrual from Dr. Jamie Flerlage: Given the short therapy and anticipated low toxicity, we believe that we can attract at least 2 patients per year specifically for this protocol.

Table S1: Annual accrual rate for favorable risk patients after excluding stage IA nLP patients enrolled on HOD99

2000	2001	2002	2003	2004	2005	2006	2007	2008
5	6	7	11	11	6	7	12	7

11.3 Statistical Methods & Analysis

Primary Objective

Objective 1.1.1: To increase the proportion of patients that will not require any radiotherapy by at least 20% compared to the favorable risk arm in HOD99

The hypothesis test will be performed for the proportion of patients not requiring any radiotherapy (which is equivalent to the complete response (CR) rate) compared with the historical control for HOD99 which was 27/62 (44%) by using an exact two-sample binominal test. A 95% confidence interval of the complete response (CR) rate also will be provided.

Note: patients with stage IA nodular lymphocyte predominant Hodgkin disease do not contribute to the primary objective.

Interim analysis for response rate:

The CR rate will be monitored by a two-stage historical control design[71]. It gives early evidence of the efficacy of the treatment plan.

This design provides a 5% significance level for testing that the 8-week Stanford V chemotherapy regimen achieves at most a 44% CR rate, and 80% power against the alternative that Stanford V achieves at least a 64% CR rate. The sample size for this study is 64 patients. The study is to be monitored by a group sequential approach (Xiong et al.[73]) with one interim analysis following evaluation of the first group of 32 patients (Table S2). If 13 or fewer of these patients have CR after 8 weeks of chemotherapy, then consideration will be given to closing the study to accrual. If 14 or more of the first group of patients have CR after 8 weeks, patient accrual will continue until 64 patients have been evaluated for response unless the stopping rule of 37 patients not achieving CR is met.

To make the interim analysis sufficiently flexible to facilitate reporting at DSMB meetings, the time frame for interim analysis may be adjusted to the date of the DSMB meeting.

The interim analyses results will be masked to the PI and reported only to the DSMB to facilitate their decision making for continuation of patient accrual.

Table S2: Eight-week Stanford V chemotherapy feasibility: two-stage monitoring rule based on Xiong's SCPRT.

Group number	Group size	Total size	Lower bound (# of patients who do not achieve CR)
1	32	32	13
2	32	64	37

Secondary objectives

Note: patients with stage IA nodular lymphocyte predominant Hodgkin disease will contribute to all secondary objectives.

Objective 1.2.1: To estimate the disease failure rate within the radiation fields.

Disease failure within the radiation fields is defined as disease that recurs in the initially involved nodal region within the field of irradiation. The disease failure rate within the radiation fields will be estimated with a 95% confidence interval using appropriate methods (e.g., estimate cumulative incidence in the presence of competing risks)

Objective 1.2.2: To examine patterns of treatment failure for children treated with tailored field radiation therapy.

In relapsed patients, nodal sites of disease, as well as extra-nodal sites of disease, will be evaluated for treatment failure. A local failure is classified as disease that recurs in the initially involved nodal region within the field of irradiation; otherwise it will be classified as a distant failure. If both failures (local and

distant) are observed, it will be treated as a local failure. Bone marrow failure will always be classified as a distant site of failure. Descriptive statistics related to local/distant failure will be produced. The cumulative incidence of local failure will be estimated and effects of prognostic factors will be examined. Effect of competing risks (distant failure, second malignancy and death) will be taken into account. Relapse rate within the radiation fields will be estimated and confidence interval will also be calculated.

Objective 1.2.3: To describe acute hematologic and infectious toxicities as they relate to transfusion requirements, growth factor support, episodes of febrile neutropenia and hospitalizations, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

The acute hematologic and infectious toxicities will be summarized descriptively.

Objectives 1.2.4 and 1.2.5: To compare the outcome (event-free and overall survival distributions and cumulative incidence of local failure) and toxicities of favorable risk patients treated with this reduced Stanford V chemotherapy and low-dose tailored-field radiation to outcome and toxicities in the favorable risk group of HOD99. To compare the event-free survival distributions between patients that will not be prescribed radiotherapy after 8 weeks Stanford V and those patients on HOD99 that received VAMP without radiotherapy.

Log-rank tests will be used to compare event-free survival and overall survival. Event-free survival will be defined as the time interval from the date of study enrollment to the date of first event (relapsed or progressive disease, second malignancy, or death from any cause) or to the date of last follow-up for patients without events. Survival will be defined as the time interval from study enrollment to date of death from any cause or to date of last follow-up. Gray's test will be used to compare the cumulative incidence of local failure between favorable risk patients treated on this protocol vs. patients treated on HOD99 and other regimens.

Update 3/14/2013*:* A stratified log-rank test will be used to compare the event-free survival and overall survival distribution by stratifying patients who received cyclophosphamide versus mechlorethamine.

Objective 1.2.6-1.2.7: To estimate the event-free survival distributions of favorable risk patients treated with Stanford V chemotherapy alone and patients treated with Stanford V chemotherapy plus low dose tailored field radiation.

Event-free survival distributions of favorable risk patients treated with Stanford V chemotherapy alone and patients treated with Stanford V chemotherapy plus low dose tailored field radiation will be estimated by the Kaplan-Meier method.

11.4 Data Safety Monitoring Board

This study has been referred to the St. Jude Data and Safety Monitoring Board (DSMB) for regular monitoring, and will be sent to the DSMB upon approval by the St. Jude CPSRMC and IRB. The DSMB is charged with advising the Director and other senior leaders of St. Jude Children's Research Hospital (SJCRH) on the safety of clinical protocols being conducted by SJCRH investigators and on their continuing scientific validity. Refer to the DSMB Charge and Criteria for Protocol Referral for more information regarding DSMB review.

12.0 OBTAINING INFORMED CONSENT

The process of obtaining informed consent will follow the institutional guidelines. Informed consent will be obtained by the attending physician or his/her designee in the presence of at least one witness. At the time of initial examination, consent will be sought for banking of tissue specimens (currently TBANK at St Jude). After the diagnosis is confirmed and the research participant is deemed eligible, we will seek consent from the parents or guardians to enroll the research participant on HOD08 protocol.

Verbal assent will be obtained from research participants 7 to 14 years old and written assent from research participants 14 to 18 years old. Patients 18 years old and older will sign for themselves.

12.1 Consent at the Age of Majority

Research participants must be consented at the next clinic visit after reaching age of majority. In the state of TN, this is 18 years old. At affiliate and collaborating sites, research participants must be consented at the age of majority according to local laws.

12.2 Consent When English is Not the Primary Language

When English is not the participant, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information will be documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information.

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APPENDIX I: ANN ARBOR STAGING CLASSIFICATION FOR HODGKIN'S DISEASE

Definition

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

The absence or presence of fever >38°C (100.4°F) for three consecutive days, night sweats, and/or unexplained loss of 10% of more of body weight in the six months preceding admission are to be denoted in all cases by the suffix letters A or B, respectively.

E = extranodal extension

Appendix II: HOD 08 FAVORABLE RISK TREATMENT with Nitrogen mustard

SCHEMA HT _____cm WT _____kg BSA _____

Week	Date given	Agent	Dose	Agent	Dose	Agent	Dose	Agent	Dose
1	_____	Prednisone* _____ (40 mg/m²/day divided in 3 doses, 60 mg max dose [20 mg three times daily given every other day] x 8 weeks) **Indicate yes/no if prednisone received.	_____	**Mustard (6mg/m²)**	_____	**Adriamycin (25mg/m²)**	_____	**Velban (6mg/m²)**	_____
2	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		
3	_____		_____	**VP-16 (120 mg/m²)**	_____	**Adriamycin (25 mg/m²)**	_____	**Velban (6mg/m²)**	_____
4	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		
5	_____		_____	**Mustard (6mg/m²)**	_____	**Adriamycin (25mg/m²)**	_____	**Velban (6mg/m²)**	_____
6	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		
7	_____		_____	**VP-16 (120 mg/m²)**	_____	**Adriamycin (25 mg/m²)**	_____	**Velban (6mg/m²)**	_____
8	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		

*Prednisone 60 mg/day max dose *Vincristine 2 mg max dose

**Explain reasons Prednisone not given during each cycle, if applicable. Include dates.

Signature of Primary Attending:_____ **Date: _____**

Appendix HA: HOD 08 FAVORABLE RISK TREATMENT with Cyclophosphamide

SCHEMA HT _____cm WT _____kg BSA _____

Week	Date given	Agent	Dose	Agent	Dose	Agent	Dose	Agent	Dose
1	_____	Prednisone* _____ (40 mg/m²/day divided in 3 doses, 60 mg max dose [20 mg three times daily given every other day] x 8 weeks) **Indicate yes/no if prednisone received.	_____	**Cyclophosphamide (650mg/m²)**	_____	**Adriamycin (25mg/m²)**	_____	**Velban (6mg/m²)**	_____
2	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		
3	_____		_____	**VP-16 (120 mg/m²)**	_____	**Adriamycin (25 mg/m²)**	_____	**Velban (6mg/m²)**	_____
4	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		
5	_____		_____	**Cyclophosphamide (650mg/m²)**	_____	**Adriamycin (25mg/m²)**	_____	**Velban (6mg/m²)**	_____
6	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		
7	_____		_____	**VP-16 (120 mg/m²)**	_____	**Adriamycin (25 mg/m²)**	_____	**Velban (6mg/m²)**	_____
8	_____		_____	***Vincristine (1.4mg/m²)**	_____	**Bleomycin (5u/m²)**	_____		

*Prednisone 60 mg/day max dose *Vincristine 2 mg max dose
**Explain reasons Prednisone not given during each cycle, if applicable. Include dates.

Signature of Primary Attending: _____ **Date:** _____

Appendix III: SCHEDULE OF ON AND OFF THERAPY EVALUATION

	H&P	CBC[1]	ESR or CRP	Chest XR	Urine Pregnancy	UA	Chemistry Profile	PFT	ECHO/ EKG	CT neck & chest	CT or MRI abdomen & pelvis	PET	Panorex and dental assessment
Pre-therapy	X	X	X	X	**X**	O	X[3]	O	O	X	X	X	O
Week 1	X	X											
Week 2	O	O											
Week 3	X	X											
Week 4	O	O											
Week 5	X	X											
Week 6	O	O											
Week 7	X	X											
Week 8 Evaluate Response[6]	X	X	X			O	**X**	X[7]		X[2]	X[2]	X[4]	
Post-RT/Off Therapy	X	X	X	X[9]		O	O	X[7]	X[8]	X[5]	X[5]	X[5]	
1 and 2 year evaluation	X		X					X	X	X[5]	X[5]	O	

X = Required study evaluations **O = Evaluations suggested for good patient care.**

[1]CBC obtained pre-therapy during staging does not need to be repeated prior to week 1 of chemotherapy and is else only required prior to weeks 3, 5, 7, and response evaluations

[2]Repeat imaging studies of involved areas.

[3]LDH, alkaline phosphatase and albumin are required as part of the clinical staging evaluation.

[4]PET only needs to be repeated if previously positive.

[5]Post-RT restaging will include diagnostic imaging studies previously positive.

[6]For patients achieving a CR at the end 8 weeks of chemotherapy this evaluation will be considered their off therapy evaluation.

[7]Obtain PFTs at response evaluation *or* off therapy.

[8] Echocardiogram and EKG *as clinically indicated*

[9]Chest radiograph *as clinically indicated* during therapy and Post-RT for patients with mediastinal disease.

Appendix IV: RECOMMENDED SCHEDULE OF OFF THERAPY FOLLOW-UP FOR DISEASE STATUS

Time since End of Therapy	H&P	CBC	ESR or CRP	CXR[1]	CT[3] neck/ chest	CT or MRI[3] abdomen/pelvis	PET[2] Scan
3 months	X	X					
6 months	X	X					
9 months	X	X					
1-year-off therapy evaluation	X	X	X	X	X	X	O
16 months	X	X					
20 months	X	X					
2-year off therapy evaluation	X	X	X	X	X	X	O
28 months	X	X					
32 months	X	X					
3 years	X	X					
3 ½ years	X	X					
4 years	X	X					
4 ½ years	X	X					
5 years and yearly thereafter	X	X					

[1] Chest radiograph is recommended *as clinically indicated* during follow-up for patients with mediastinal disease
[2] Optional
[3] 1 and 2 year off therapy CT or MRI, only re-image sites that are positive at diagnosis

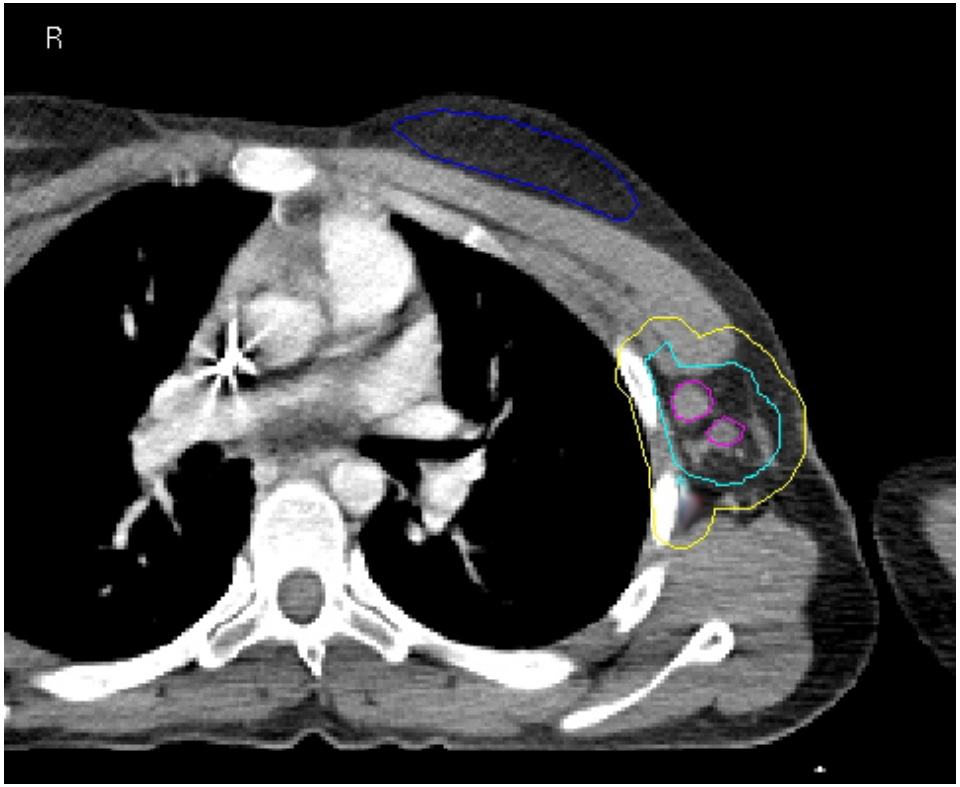
Appendix V: RECOMMENDED OFF THERAPY FOLLOW-UP FOR LATE ORGAN TOXICITY

Off Therapy Follow-Up for Late Organ Toxicity	Physical Exam[1] (includes growth and fertility information)	Dental[2]	ECHO/ EKG	T_4/TSH[3]	PFT
Annually	**X**			**X**	
1-year evaluation			**X**	**X**	**X**
2-year evaluation			**X**	**X**	**X**
5-year evaluation		**X**	**X**	**X**	**X**
10 -year evaluation			**X**	**X**	**X**

Specific late effects testing should include evaluation of the following organ systems:
[1]**Growth:** physical examination with attention to growth abnormalities of soft tissues and bones.
[1]**Fertility:** Record menstrual cycle and pregnancy information. Refer men for semen analysis when appropriate.
[2]**Dental:** A panorex and dental evaluation at 5 years off therapy is recommended for good clinical practice.
[3]**Thyroid:** Free T_4 and TSH annually for patients treated with cervical and upper mediastinal irradiation should be followed annually for good clinical practice, but are required only at 1, 2, 5, and 10 years.
Document initiation date for Thyroid hormone replacement therapy, if applicable.
Obtain pathology of second tumors for histological review

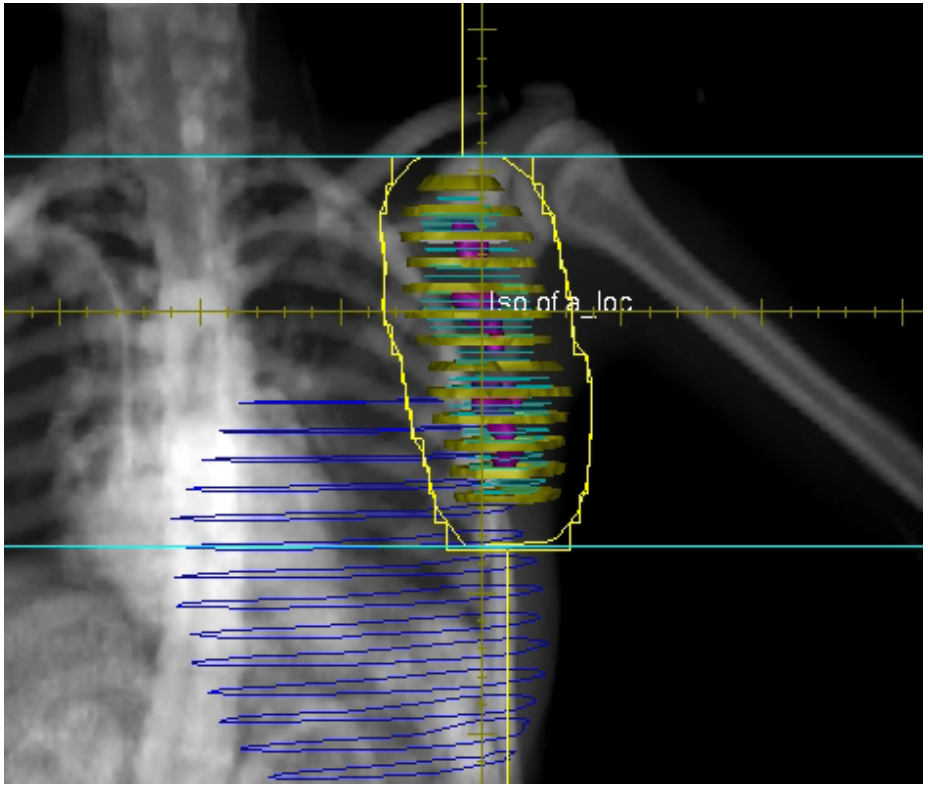
Appendix VI: EXAMPLE TAILORED RADIATION THERAPY TREATMENT FIELDS

(case 1) - Patient with clinical stage IA Hodgkin lymphoma with a PR following 8 weeks of chemotherapy. Contoured target volumes are shown based on the post-chemotherapy residual in the left axilla. Treatment fields are shaped in 3-dimensions



Dose: 25.5Gy / 1.5Gy fxn

Volume: Initial nodal sites with a 1 cm margin



APPENDIX VII: TESTS PERFORMED FOR GOOD CLINICAL CARE

- History & Physical Exams
- Complete Blood Counts
- Chest X-ray
- Urine pregnancy test
- Blood chemistry profile including electrolytes, BUN, creatinine, bilirubin, alkaline phosphatase, SGOT, and SGPT
- C-Reactive Protein (CRP) or erythrocyte sedimentation rate (ESR)
- Urinalysis
- Thyroid Function Tests
- Pulmonary Function Tests
- Echocardiogram
- EKG
- CT neck and chest with contrast
- CT or MRI abdomen & pelvis with contrast
- PET scan
- Referral for sperm cryopreservation for male patients.