Long-Term Results of CCG 5942: A Randomized Comparison of Chemotherapy With and Without Radiotherapy for Children With Hodgkin's Lymphoma—A Report From the Children's Oncology Group

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ABSTRACT

Purpose

In 1995, the Children's Cancer Group (CCG) opened a trial for patients with Hodgkin's lymphoma evaluating whether low-dose involved-field radiation therapy (IFRT) improved event-free survival (EFS) for patients achieving a complete response after chemotherapy. We present the long-term study outcome using final data through March 2007.

Patients and Methods

Between January 1995 and December 1998, 826 eligible patients were enrolled onto CCG 5942. Four hundred ninety-eight patients achieving an initial complete response to chemotherapy were randomly assigned to receive IFRT or no further therapy. EFS and overall survival (OS) were assessed from the date of study entry or random assignment, as appropriate.

Results

Ten-year EFS and OS rates for the entire cohort were 83.5% and 92.5%, respectively. In an as-treated analysis for randomly assigned patients, the 10-year EFS and OS rates were 91.2% and 97.1%, respectively, for IFRT and 82.9% and 95.9%, respectively, for no further therapy. For EFS and OS comparisons, $P = .004$ and $P = .50$, respectively. Bulk disease, "B" symptoms, and nodular sclerosis histology were risk factors for inferior EFS.

Conclusion

With a median follow-up of 7.7 years, IFRT produced a statistically significant improvement in EFS but no improvement in OS. For individual patients, the relative risks of relapse versus late effects of IFRT must be considered. Patient and disease characteristics and early response assessment will aid in deciding which patients are most likely to benefit from IFRT.

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INTRODUCTION

Approximately 95% of children and young adults with early-stage Hodgkin's lymphoma and 85% of patients with advanced-stage disease are cured with chemotherapy and involved-field radiation therapy (IFRT).¹⁻⁶ Late effects such as second tumors arising in radiated fields and cardiopulmonary toxicity are of particular concern for children who receive combined-modality therapy.^{7,8} Lower doses and smaller radiotherapy (RT) fields will reduce the risk of cardiac toxicity.⁹ However, one recent study indicated that a reduction in RT dose from 36 to 44 Gy to 15 to 25 Gy may not significantly decrease the risk of second tumors.¹⁰

In an effort to reduce late effects of therapy for children and adolescents with Hodgkin's lymphoma, the Children's Cancer Group (CCG) opened a randomized trial in January 1995 comparing IFRT with no further therapy for patients achieving a complete response to initial chemotherapy.⁶

The initial report of this trial, based on data through February 2001, showed that patients receiving IFRT had a significant event-free survival (EFS) advantage compared with patients receiving chemotherapy alone.⁶ No definite conclusion could be drawn concerning the impact of IFRT for overall survival (OS) because of the relatively short median follow-up. We now update the results using final data through March 2007.

Fig 1. CONSORT diagram.

PATIENTS AND METHODS

Details of the protocol and the chemotherapy regimens used have been previously reported (Fig 1).⁶ The study design is shown in Figure 2, and definitions of clinical groups are listed in Table 1. Briefly, all patients underwent clinical staging with computed tomography and gallium scans and were assigned to risk-adapted initial chemotherapy based on stage, presence or absence of “B” symptoms, presence or absence of bulk disease, hilar adenopathy, and the number of involved nodal sites. In this protocol, bulk disease was defined as a mediastinal mass ratio greater than or equal to one third or a nodal aggregate greater than 10 cm.

Patients received four or six cycles of cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine or six cycles of intensified chemotherapy including high-dose cytarabine and etoposide. Response was assessed at the end of chemotherapy. A complete response to initial chemotherapy was defined as the resolution of all disease or at least 70% mass reduction in tumor volume in conjunction with a change from positive to negative on gallium scan; such patients were eligible for random assignment to receive IFRT or no further therapy. Patients showing a partial response were assigned to IFRT.

RT was scheduled to begin 3 weeks after completion of chemotherapy. A dose of 21 Gy was delivered in once-daily fractions of 1.75 Gy to involved fields using anteroposterior/posteroanterior techniques. The definition of involved

Fig 2. Study schema. COPP/ABV, cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine; CR, complete response; LD-IFRT, low-dose involved-field radiation therapy; PR, partial response. Data adapted.⁶

Table 1. Definitions of Clinical Groups

Clinical Group
Group 1
Stage I patients without adverse disease features*
Stage II patients without adverse disease features and without clinical B symptoms†
Group 2
Stage I patients with adverse disease features*
Stage II patients with adverse disease features and/or without clinical B symptoms†
Stage III patients
Group 3
Stage IV patients

NOTE. Data adapted.⁶

*Adverse disease features comprise one or more of the following: hilar adenopathy, involvement of four or more nodal regions, mediastinal tumor with diameter greater than or equal to one third of the chest diameter, and node or nodal aggregate with a diameter greater than 10 cm.

†Clinical B symptoms comprise one or more of the following: unexplained loss of more than 10% of body weight, unexplained recurrent fever greater than 38°C, and drenching night sweats.

Fig 3. Event-free survival (EFS) and overall survival (OS) from the time of study entry for all patients. Ten-year EFS is 83.5% (SE, 1.3%), and 10-year OS is 92.5% (SE, 1.0%).

field at the time of this protocol was more extensive than the contemporary standard of care. The bilateral neck was treated any time there was unilateral neck or mediastinal involvement. The mediastinal field always included the hila and extended inferiorly to the diaphragm. Axillary disease called for treatment of a full mantle. Any disease below the diaphragm mandated treatment of all para-aortic nodes, spleen, and porta hepatis. Stage IV patients with pulmonary metastases received 10.5 Gy of whole-lung RT with partial transmission blocks. Patients with biopsy-proven residual disease at the completion of chemotherapy received a boost dose of 14 Gy to the residual disease for a total dose of 35 Gy. Post-treatment review of RT compliance was performed, but on-treatment reviews were not done.

The initial study design planned for 650 randomly assigned patients, which would give adequate (> 80%) power for detecting a 1.5-fold or higher increase in event rate as a result of elimination of IFRT. At one planned interim analysis, the prespecified monitoring boundary was crossed, and the study accrual was suspended. The data from the reduced sample size had provided sufficient evidence rejecting the null hypothesis that the event rate was the same among patients randomly assigned to no further therapy compared with those assigned to RT.

Survival estimates were based on the Kaplan-Meier estimator, and comparisons between survival curves were based on the log-rank test, with the overall comparison between IFRT and no further therapy among randomly assigned patients stratified for clinical group. The study was not designed to have adequate power in each of the clinical groups to detect a treatment effect that is the same size as that for the overall comparison. The subset analyses by clinical groups were exploratory analyses. SEs are reported with the estimates of EFS and OS.

RESULTS

Patients

Eight hundred twenty-six eligible patients were enrolled between 1995 and 1998. At that time, the study was closed to accrual, and random assignment was terminated because interim data analysis showed a significant excess of relapses in patients randomly assigned to no RT. Among the 826 patients enrolled, 16 had progressive disease and were removed from study. Among the remaining patients, 30 patients were not assessable for response to initial chemotherapy. Among the 780 patients who completed initial chemotherapy and had response assessed, 144 patients had a partial response and were supposed to be assigned to receive IFRT. Of these, 132 patients received RT and 10 patients did not; for two patients, the treatment was un-

known. Six hundred thirty-six patients achieved a complete response to initial chemotherapy. Four hundred ninety-eight patients were randomly assigned to receive either IFRT ($n = 249$) or no further therapy ($n = 249$). Twenty-three patients randomly assigned to receive IFRT received no further therapy, whereas seven patients randomly assigned to no further therapy received IFRT. Thus, 265 initially randomly assigned patients received no further treatment, and 233 patients received IFRT. One hundred thirty-eight patients were not randomly assigned (69 patients while the random assignment was ongoing and 69 patients after the random assignment was terminated). Of these patients, 85 patients received no further therapy, and 47 patients received IFRT; for six patients, the subsequent treatment was not known.

Overall Outcome

The 10-year EFS and OS rates from study entry for the entire cohort were 83.5% (SE, 1.3%) and 92.5% (SE, 1.0%), respectively (Fig 3). One hundred twenty-nine patients experienced a qualifying event for EFS, which included disease progression, relapse, second malignancy (other than thyroid cancer), or death from any cause. Progressive disease occurred in 16 patients, and relapse occurred in 108 patients. Two patients died during initial chemotherapy (one from fungal sepsis and one from pulmonary embolism), and three patients developed a nonthyroid second malignancy (acute myeloid leukemia, $n = 2$; large-cell lymphoma, $n = 1$). No secondary breast cancers were seen at this point in follow-up.

Until the data cutoff, there were 54 deaths in study patients. As previously indicated, two patients died while receiving initial chemotherapy, and two patients developed secondary leukemia from which they died. One patient died in an accident while in second remission. For the remaining 49 patients, death resulted from either progressive disease or toxicity related to treatment for relapse.

Outcome in Randomly Assigned Patients

The 10-year EFS rates from random assignment for patients assigned to IFRT or to no further therapy were 89.7% (SE, 2.0%) and 83.8% (SE, 2.4%), respectively ($P = .048$). In an as-treated analysis, the 10-year EFS rates for patients treated with IFRT or with no further therapy were 91.2% (SE, 2.0%) and 82.9% (SE, 2.4%), respectively

Fig 4. As-treated event-free survival analysis for randomly assigned patients. Ten-year event-free survival rates with involved-field radiation therapy (IFRT) and no radiation therapy (RT) are 91.2% (SE, 2.0%) and 82.9% (SE, 2.4%), respectively ($P = .004$).

($P = .004$; Fig 4). Sixty-two randomly assigned patients experienced at least one EFS event (43 patients receiving no further therapy and 19 patients receiving IFRT). In an as-treated analysis, the 10-year OS rates from random assignment for patients receiving IFRT or no further therapy were 97.1% (SE, 1.2%) and 95.9% (SE, 1.3%), respectively ($P = .50$; Fig 5).

Nineteen patients treated initially with chemotherapy and IFRT experienced at least one event. One patient had a secondary large-cell lymphoma and then experienced a relapse of the lymphoma but remains alive. Eighteen patients experienced relapse. The median time to relapse was 20 months (range, 1 to 70 months) from random assignment. One patient had no follow-up data available beyond relapse. Seven patients are alive in second remission with a median follow-up of 64 months since relapse (range, 1 to 77 months). The remaining 10 patients had a subsequent event; six patients are dead of disease, and four patients are alive (three in third remissions from 44 to 70 months and one in fourth remission 4 months from last relapse).

Forty-three patients treated initially with chemotherapy alone experienced relapse as the first event. One patient also developed secondary acute myeloid leukemia 9.4 years after relapse, and no additional follow-up is available. The median time to relapse was 8.5

months (range, 1 to 76 months). Twenty-seven patients remain in second remission from 0.5 to 132 months from relapse with a median follow-up of 61 months. One patient died in an accident while in second remission. Five patients are alive after a second relapse, and one patient has no follow-up after second relapse. Eight patients died after a first or second relapse.

Table 2 lists the as-treated, exploratory results for the patients who received no further therapy or IFRT based on clinical group as defined in the protocol. In group 1 patients who received four cycles of initial chemotherapy, there was a statistically significant difference in EFS with the addition of IFRT ($P = .001$). For the more unfavorable group 2 and 3 patients who received augmented chemotherapy, the trend for improved EFS with IFRT did not reach statistical significance. Of the 109 group 1 patients who did not receive IFRT and had a reported baseline erythrocyte sedimentation rate (ESR), 59 patients had an ESR less than 20 mm/h and 50 had an ESR ≥ 20 mm/h. Three relapses occurred in the 59 patients with an ESR less than 20 mm/h compared with eight relapses in the 50 patients with ESR ≥ 20 mm/h ($P = .07$). Group 1 patients with nodular sclerosis histology and an ESR less than 20 mm/h who received no IFRT had a 10-year EFS rate of $90.4\% \pm 6.5\%$.

Fig 5. As-treated overall survival analysis for randomly assigned patients. Ten-year overall survival rates with involved-field radiation therapy (IFRT) and no radiation therapy (RT) are 97.1% (SE, 1.2%) and 95.9% (SE, 1.3%), respectively ($P = .50$).

Table 2. EFS for Patients Randomly Assigned to Low-Dose IFRT or No Further Therapy

Group	IFRT			No Further Therapy			<i>P</i>
	No. of Patients	EFS (%)	SE (%)	No. of Patients	EFS (%)	SE (%)	
All patients	233	91.2	2.0	265	82.9	2.4	.004
Clinical group 1	94	100	—	113	89.1	3.0	.001
Clinical group 2	103	84.0	3.8	122	78.0	3.9	NS
Clinical group 3	36	88.5	5.4	30	79.9	7.4	NS
Nodular sclerosis	113	88.7	3.1	130	78.9	3.7	.04
Mixed cellularity and lymphocyte predominant	35	95.8	4.1	52	96.2	2.7	NS

Abbreviations: EFS, event-free survival; IFRT, involved-field radiation therapy; NS, not significant.

Among all 826 enrolled patients, B symptoms and bulk disease were independent predictors of relapse. The 210 patients with B symptoms at diagnosis had a 10-year EFS of 71.7% (SE, 3.2%) compared with 87.5% (SE, 1.4%) for patients with no B symptoms ($P < .001$). For 261 patients with bulk disease, 10-year EFS was 75.6% (SE, 2.7%) compared with 87.2% (SE, 1.5%) for patients without bulk disease ($P < .001$).

Three hundred thirty randomly assigned patients had a central pathology review performed. Two hundred forty-three patients had nodular sclerosis histology, 53 patients had mixed cellularity histology, and 34 patients had lymphocyte-predominant histology. Table 2 lists EFS rates for patients with nodular sclerosis histology compared with patients with either mixed cellularity or lymphocyte-predominant histology stratified by whether they received IFRT or no further therapy. For patients receiving no RT, 26 of 130 patients with nodular sclerosis histology experienced events compared with only two of 52 patients in the combined mixed cellularity and lymphocyte-predominant group ($P = .01$). Ten-year EFS was 78.9% (SE, 3.7%) for patients with nodular sclerosing histology compared with 96.2% (SE, 2.7%) for patients with either mixed cellularity or lymphocyte-predominant histology.

DISCUSSION

CCG 5942 was the first study in children and young adults with Hodgkin's lymphoma to evaluate the impact of IFRT on EFS and OS in patients achieving a complete response to initial chemotherapy in a randomized clinical trial. In the planning of the CCG 5942 study, discussions took place concerning the appropriate end point to assess the safety of eliminating RT for patients achieving a complete response to initial chemotherapy. Although it was recognized that patients with relapsed Hodgkin's lymphoma have relatively high rates of survival after salvage therapy, the short-term toxicity and late effects of salvage therapy are especially significant.^{7,11} Because Hodgkin's lymphoma often remains responsive to third- and fourth-line therapies, mortality from multiply relapsing disease typically occurs many years after initial diagnosis. Therefore, to protect patients, we chose EFS as the appropriate end point for our trial. Approximately 4 years into the study, a significant EFS difference favoring RT was found, and the random assignment was terminated. At that time, we could make no

statements concerning any difference in survival because of the short follow-up for patients who experienced a relapse.

We have now updated the study results using final data through March 2007. In the as-treated analysis, the 10-year EFS for patients achieving a complete response to initial chemotherapy was 91.2% for the IFRT group versus 82.9% for the no further therapy group ($P = .004$). The vast majority of relapses in both arms occurred within 4 years of random assignment (15 of 19 relapses for IFRT; 41 of 43 relapses for no further therapy). Approximately 90% of relapses in the no further therapy arm occurred in sites of original disease, suggesting that many may have been prevented with IFRT.

We were able to determine relapse treatment for the majority of patients. Patients who experienced relapse after chemotherapy alone generally received chemotherapy and RT if the relapse was limited (stage I or II) and asymptomatic. Patients with more advanced disease at relapse and patients who initially received IFRT generally received stem-cell transplantation. In an as-treated analysis, the 4-year postrelapse survival was 69.7% (SE, 11.4%) among the 19 randomly assigned patients who experienced relapse after chemotherapy and RT (one of the patients has no follow-up data beyond relapse) and 82.5% (SE, 6.1%) for 43 patients who experienced relapse after chemotherapy alone ($P = .33$). The OS for patients treated with chemotherapy alone versus chemotherapy and IFRT was not significantly different.

There are a number of ways in which these results could be interpreted. It seems that, for every 100 patients who achieve a complete response to initial therapy, treatment with IFRT will prevent nine relapses. If the toxicity of IFRT is minimal, then all patients should receive RT. However, when the risk of late effects from RT is high, the risk-benefit ratio of IFRT must be reconsidered. As a result of tremendous efforts to quantify late risks of RT by institutions and cooperative groups such as the Children's Cancer Group and the Childhood Cancer Survivor Study, our ability to predict risk for individual patients is improving.¹²⁻¹⁴ The risks associated with IFRT will vary dramatically depending on the age and sex of the patient as well as the individual RT fields. The risk of breast cancer is only a concern for female patients. Smaller fields that do not include significant volumes of critical tissues such as breast and heart will have much less risk than a traditional mantle field.

The choice of chemotherapy may also dictate the need for RT. It has been shown that a more aggressive chemotherapy regimen may offset the potential benefit of the addition of RT.^{5,15} This may explain why it was more difficult to show a statistical improvement in EFS with IFRT in clinical group 2 and 3 patients in this study who received more intensive chemotherapy. Also, small numbers may not yield adequate power to detect a true difference, especially for group 3. The dilemma is how to determine which treatment will yield the lowest toxicity because additional chemotherapy and low-dose RT are both associated with risk. These decisions will also be influenced by individual patient characteristics such as age, sex, and distribution of disease. Since the time of this study, progress has been made in development of dose-intense regimens with lower cumulative amounts of alkylating agents and improved late toxicity profiles. Likewise, RT techniques have become much more precise and targeted.

A German Pediatric Oncology Group trial (GPO-HD 95) conducted between 1995 and 2001 used risk-adapted chemotherapy and assigned all patients achieving a complete anatomic response to receive no further therapy.⁴ Other patients received 20 to

35 Gy of RT to involved fields. Among low-risk patients, only 22% achieved complete response and avoided RT and 3% experienced progressive disease while on chemotherapy, leaving 75% of the patients receiving combined-modality therapy. Unlike the results we report, there was no EFS benefit for IFRT in low-risk (group 1) patients, but patients with intermediate- and high-risk disease (groups 2 to 3) had a statistically significantly higher relapse rate if they received chemotherapy alone. The different findings most likely are a result of smaller cohorts of patients in subgroup analyses. It is also plausible that the difference may have to do with the choice of chemotherapy or with the definition of complete response, because the German study required a more than 95% reduction in tumor volume for complete response, unlike the 70% reduction used in this trial. Although there has been no difference in OS, the GPO-HD 95 study concluded that there was improved outcome with chemotherapy plus RT versus chemotherapy alone.

Hodgkin's lymphoma is a heterogeneous disease, and therefore, some types of Hodgkin's lymphoma may show a greater or lesser benefit from the addition of IFRT to chemotherapy. In an analysis restricted to randomly assigned patients who achieved a complete response, patients with the nodular sclerosis subtype had a significantly higher relapse rate when treated with chemotherapy alone compared with patients with mixed cellularity or lymphocyte-predominant histology. Patients with either mixed cellularity or lymphocyte-predominant histology who achieved a complete response with chemotherapy alone had a 10-year EFS of 96%. This contrasts with a recent report concerning adult patients with lymphocyte-predominant histology in which six of seven patients treated with chemotherapy alone experienced relapse.¹⁶

Early response to chemotherapy has been shown to be an important prognostic factor in many cancers, including Hodgkin's lymphoma.^{17,18} Volumetric and/or fluorodeoxyglucose-positron emission tomography (FDG-PET) scan response after one to two cycles of chemotherapy may predict outcome and may identify patients less likely to relapse after chemotherapy alone. In the recently concluded CCG intermediate-risk study AHOD0031, a standard treatment approach of four cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide chemotherapy followed by IFRT was compared with an early response-directed treatment plan. In the response-directed arm, patients with a rapid

early response to two cycles of chemotherapy, who also achieved a complete response with no disease by functional imaging (FDG-PET or gallium) after four cycles, received no RT. Early results showed no significant difference in EFS.¹⁹

In our study, IFRT as consolidation therapy for patients achieving a complete response to chemotherapy produced a statistically significant reduction in relapse rate but no survival benefit. To perform an informed risk-benefit analysis, it remains important to identify patients who are most likely to be cured with the least amount of therapy. In this trial, patients with either mixed cellularity or lymphocyte-predominant histology and clinical group 1 patients with nodular sclerosis histology and an initial ESR less than 20 mm/h who achieved a complete response after chemotherapy were more likely to be cured with chemotherapy alone. Going forward, we expect that early response to chemotherapy determined by anatomic and functional (FDG-PET) imaging will identify patients in whom therapy may be reduced. Additional long-term data on the late effects of current chemotherapy regimens as well as IFRT are needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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