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CLINICAL INVESTIGATION **Lymphoma**

DECLINING USE OF RADIOTHERAPY IN STAGE I AND II HODGKIN'S DISEASE AND ITS EFFECT ON SURVIVAL AND SECONDARY MALIGNANCIES

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Purpose: Concerns regarding long-term toxicities have led some to withhold radiotherapy (RT) for the treatment of Stage I and II Hodgkin's disease (HD). The present study was undertaken to assess the use of RT for HD and its effect on overall survival and the development of secondary malignancies.

Methods and Materials: The present study included data from the Surveillance, Epidemiology, and End Results database from patients aged ≥20 years who had been diagnosed with Stage I or II HD between 1988 and 2006. Overall survival was estimated using the Kaplan-Meier method, and the Cox multivariate regression model was used to analyze trends.

Results: A total of 12,247 patients were selected, and 51.5% had received RT. The median follow-up for the present cohort was 4.9 years, with 21% of the cohort having >10 years of follow-up. Between 1988 and 1991, 62.9% had undergone RT, but between 2004 and 2006, only 43.7% had undergone RT ($p < .001$). The 5-year overall survival rate was 76% for patients who had not received RT and 87% for those who had ($p < .001$). The hazard ratio adjusted for other variables in the regression model showed that patients who had not undergone RT (hazard ratio, 1.72; 95% confidence interval, 1.72–2.02) was associated with significantly worse survival compared with patients who had received RT. The actuarial rate of developing a second malignancy was 14.6% vs. 15.0% at 15 years for those who had and had not undergone RT, respectively ($p = .089$).

Conclusions: The present study is one of the largest studies to examine the role of RT for Stage I and II HD. Our results revealed a survival benefit with the addition of RT with no increase in the development of secondary malignancies compared with patients who had not received RT. Furthermore, the present nationwide study revealed a >20% absolute decrease in the use of RT from 1988 to 2006.

Hodgkin's disease, Radiotherapy, Second malignancy.

INTRODUCTION

The treatment of early-stage Hodgkin's disease (HD) has been a success story in oncology, when an incurable disease became curable in the 1960s with the use of external beam radiotherapy (RT). Since then, chemotherapy has similarly demonstrated significant improvements in the outcomes of patients with advanced disease, as well as those with early stages. The results have been so impressive that cooperative groups changed the treatment paradigm from improving survival to maintaining the same survival and reducing the morbidity by seeking to minimize the use of RT and chemotherapy. In the early 1990s, several publications revealed significant long-term complications associated with a combined modality approach involving full-dose chemotherapy and extended-field RT (1–4).

This led to the investigation of two treatment strategies. First, the use of combined modality therapy but with a reduction in the irradiated volume, radiation dose, number of chemotherapy cycles, and number of chemotherapy agents; and second, the use of chemotherapy alone with additional cycles and the elimination of RT from the treatment paradigm. The proponents of the chemotherapy-alone strategies believed improved overall survival (OS) would be seen owing to the reduction in late radiation-related mortality. Furthermore, any increase in relapses seen with chemotherapy-alone strategies would not affect survival, because these patients could be salvaged with additional chemotherapy and stem cell transplantation (5).

These two approaches were then tested in several prospective Phase III trials (6–10). All 5 trials showed a significant improvement in disease control with the addition of RT; however, this did not translate into a benefit in OS for

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those with Stage I and II HD. These trials were limited by the low patient numbers and limited follow-up that might have precluded them from demonstrating any significant survival benefit or any detriment from delayed radiation morbidity.

We undertook the present study to determine in a large population-based cohort whether RT would be associated with a survival benefit for those with Stage I and II HD. Furthermore, we examined the overall trends in the use of RT in early-stage HD and the effect of RT on the second malignancy rate compared with patients who had not undergone RT.

METHODS AND MATERIALS

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute covers 26% of the U.S. population and collects incidence and survival data from 17 population-based cancer registries. The database contains information on primary tumor site, age, gender, histologic type, stage at diagnosis, first course of treatment, follow-up, and cause of death.

Data and study population

The eligible patients had histologically confirmed HD. Those with lymphocyte-predominant Hodgkin's lymphoma were excluded from the present analysis. We restricted the analysis to patients aged ≥20 years who had been diagnosed between 1988 and 2006. The patients with extent of disease codes that corresponded to the current American Joint Committee on Cancer Stage I and II were included. Patient who presented with Stage III or IV or an unknown stage were excluded. The patients were classified into two groups according to whether they had undergone RT as a part of their initial treatment. The final sample size included 12,467 patients.

Overall survival was the primary study endpoint. OS was defined as the interval from diagnosis to the date of death from any cause. Cause-specific survival (CSS) was also estimated and defined from the point of diagnosis to the date of death from HD. The exposure variables included categorical variables for the type of treatment received. The plausible risk factors included in the statistical analysis were age, gender, RT, histologic type, year of diagnosis, stage (I vs. II), extranodal involvement, B symptoms, and city population. Information regarding the use of chemotherapy, local control, performance status, and specific RT technique (*i.e.,* dose, fractionation, beam energy) was not available from the SEER database.

Statistical analysis

The estimates of OS and CSS were calculated using the Kaplan-Meier method. The log–rank test was used to estimate whether differences were present in OS and CSS among these patients. All statistical tests were two-sided and done at the .05 significance level.

The multivariate Cox regression model was used to determine whether the variables were independent predictors of OS and CSS. Hazard ratios and the corresponding 95% confidence intervals were constructed in models adjusted for all listed covariates of interest. The data were analyzed using Statistical Analysis Systems, version 9.3 (SAS Institute, Cary, NC).

RESULTS

The median follow-up for the present cohort was 4.9 years, with 21% of the cohort having >10 years of follow-up. Of the 12,447 patients included in the present study, 51.5% underwent RT as a primary component of their treatment. The categorical variables of age, gender, SEER registry, year of diagnosis, stage, extranodal involvement, B symptoms, histologic type, and city population were significant predictors of the administration of RT (Table 1). Patients with Stage II disease, extranodal involvement, B symptoms, and lymphocyte-rich or nodular sclerosis histologic features were more likely to receive RT.

When examining the year of diagnosis, a significant change was found in the use of RT during the study period. Between 1988 and 1991, 62.9% of the cohort had undergone RT and between 2004 and 2006, only 43.7% had undergone RT ($p < .001$; Fig. 1).

Univariate analysis

Of the patients with Stage I and II HD, the 5-year OS rate was 76% for those who had not undergone RT and 87% for those who had undergone RT ($p < .001$; Fig. 2). For the patients with Stage I and II HD, the 5-year CSS rate was 88% for patients who had not undergone receive RT and 94% for those who had ($p < .001$; Fig. 3). To control for any bias that would have precluded patients from undergoing any therapy, we also examined those patients who had survived a minimum of 1 year. In that cohort, the 5-year OS rate was 85% for those who had not undergone RT and 90% for those who had ($p < .001$).

Multivariate analysis

Of all the patients, RT was associated with significantly improved OS, even after adjustment for patient and tumor characteristics (Table 2). Other variables adversely affecting survival on multivariate analysis included older age, female gender, earlier year of diagnosis, no extranodal involvement, B symptoms, and lymphocyte-depleted histologic features. Patients with Stage I and II tumors, when analyzed separately, were both found to benefit from the addition of RT, after adjustment for the known patient and tumor characteristics.

Secondary malignancies

Of the entire cohort, 5.3% of patients developed a second malignancy at a median of 4.3 years of follow-up. The patients who had undergone RT were more likely to develop secondary solid malignancies, and those who had not undergone RT were more likely to develop secondary leukemia. The actuarial rate of developing any second malignancy was 14.6% vs. 15.0% at 15 years for those who had and had not undergone RT (Fig. 4). To control for advancements in therapy that might have significantly changed the second malignancy rate in the present cohort, we also examined the rate of developing a second malignancy by treatment era. When examined by treatment era, the actuarial rate of developing a second malignancy was 6.9% at 8 years if treated between 1998 and 2007 and 7.3% at 8 years if treated between 1988 and 1997 ($p = .18$).