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IMRT inb Hodgkin Lymphoma

Association of intensity-modulated radiation therapy on overall survival for patients with Hodgkin lymphoma

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ABSTRACT

Purpose: The purpose of this study was to compare outcomes with Hodgkin lymphoma (HL) patients receiving IMRT (intensity-modulated radiation therapy), versus those receiving 2D/3D-CRT (3-dimensional conformal RT) in a large observational cohort.

Patients and methods: We evaluated patients diagnosed with stage I–IV HL from 1998 to 2011 from the National Cancer Database (NCDB). The association between IMRT use vs. 2D/3D-CRT, co-variables, and outcome was assessed in a Cox proportional hazards model. Propensity score (PS) matching was performed to balance known confounding factors. Survival was estimated using the Kaplan–Meier method.

Results: Of the 76,672 patients with HL within the NCDB, 12,393 patients with stage I-IV HL received RT (median dose = 30.6 Gy) and were eligible for this study, and 6013 patients analyzed for overall survival. The cohort had a median follow-up of 6.2 years and median age of 37 years (range: 18–90). The RT modalities used were: 2D/3D-CRT (n = 11,491, 92.7%) or IMRT (n = 902, 7.3%). Patients were more likely to receive IMRT if they were of male gender, early stage, no "B" symptoms, and treated at comprehensive cancer programs (all $p < 0.05$). During this time period, there was a significant decrease in use of 2D/3D-CRT from 100% to 81.5%, with a subsequent increase in IMRT utilization from 0% to 18.5%. Five-year overall survival for patients receiving 2D/3D-CRT (n = 5844) was 89.9% versus 95.2% for those receiving IMRT (n = 169; HR = 0.45; 95% CI, 0.23–0.91, p = 0.02). After PS-matching based on clinicopathologic characteristics, IMRT use remained associated with improved overall survival (HR = 0.40; 95% CI, 0.16–0.97, p = 0.04).

Conclusions: Our study reveals that HL patients receiving modern RT techniques were associated with an improvement in overall survival. This may have been related to patient selection, access to improved staging and management, or improvements in treatment technology. This represents the only study examining survival outcomes of advanced RT modalities, which may be considered on a case-by-case basis for highly selected patients with HL.

There will be an estimated 9050 new cases of Hodgkin lymphoma (HL) in the U.S. in 2015, with an estimated 1150 new deaths in 2015 [1]. Historically, excellent survival rates for HL were attributed to the efficacy of definitive extended-field RT (EFRT) [2,3], but with concerning treatment-related morbidity. In fact, Kaplan et al. found dramatic improvements in overall survival (OS) in patients with HL with the advent of megavoltage linear accelerator and advances in treatment planning capabilities [4]. Combining safer chemotherapy with reduced field and dose, modern conformal RT led to further improvements in disease control [5,6].

There are few disease sites in which advanced radiotherapy modalities, such as IMRT (intensity-modulated RT), have been associated with improvements in outcome when compared to historical techniques such as 2D or 3D-CRT (conformal radiation therapy). For example, IMRT has also demonstrated improvements in disease control and quality of life in head and neck cancer and prostate cancer patients [7]. Cancer patients that require escalation of RT dose may require IMRT to prevent high doses of irradiated volume to nearby organs at risk and provide maximal cure rates [8–11]. For HL patients treated in the era of in the era of dose de-intensification, early dosimetric studies have demonstrated improved sparing of vital structures with IMRT, when compared to optimized 3D-CRT plans [12]. Paradoxically, despite the need for dose de-escalation, these advanced RT modalities may be helpful to decrease death from late-term morbidity.

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Despite evidence of improved event-free survival with the addition of consolidation RT [6], many centers continue to omit RT in the treatment of lymphoma because of concern for late radiation side effects and effectiveness of salvage therapy. To minimize late-term toxicity while maintaining high cure rates, radiation oncologists have found ways to deliver RT by effectively reducing the radiation dose needed to control lymphoma to 20–30 Gy [13]; by further reducing the treatment field from EFRT to IFRT to involved-site RT (ISRT) techniques as delineated by the ILROG Guidelines for HL [14]; and by delivering more conformal RT through modalities such as IMRT [15].

We used the National Cancer Database (NCDB) on stage I–IV HL patients to answer the primary endpoint of whether IMRT (compared to 2D/3D-CRT) impacted upon overall survival. As secondary endpoints, we examined the relationship between clinical and sociodemographic parameters, with use of advanced RT modality, and overall survival. We also examined the trends of IMRT utilization from 1998 to 2011. Our hypothesis was that the increased use of IMRT improves outcomes over historical methods.

Patients and methods

Data source

The National Cancer Database (NCDB), a national hospital-based oncology database, was used to conduct a retrospective, cohort study of HL patients diagnosed from 1998 through 2011. As a joint project of the American College of Surgeons' Commission on Cancer and the American Cancer Society, it is a prospectively collected registry from 1500 hospitals representing 75% of all cancers diagnosed in the U.S. with accumulated data on approximately 29-million cancer cases.

Variables captured include basic demographics, socioeconomic characteristics, cancer staging, treatment course, and vital status. This study period reflected a time during which inclusion of RT was accepted standard treatment for HL. At the time of analysis, 2011 data were the most recent data available.

Study patients

The flow CONSORT diagram in Fig. 1 shows the study exclusion criteria used to define the cohort. All patients (n = 76,672) diagnosed with classical HL from 1998 to 2011 were initially included. Only patients within the age range of 18–90 with Stage I–IV HL were included. Patients were excluded if they did not receive 2D/3D-CRT or IMRT or without a coded utilization of RT. For purposes of minimizing confounding effects from all known covariates, we also excluded patients with any missing data points in all clinicopathologic parameters of interest. As displayed in the flow CONSORT diagram (Fig. 1), with the above inclusion criteria, the study analysis was limited to 12,393 patients.

Study variables

Our variable of main interest was modality of radiation therapy (RT) utilized. This parameter was grouped into 2D and 3D-CRT versus IMRT. Demographic and clinical data included gender, race/ethnicity (white, black, or other), age ($\leqslant$40 vs. >40), indicators of income and education based on area of residence derived from Census data(the proportion of adults without a high school diploma according to patients' zip code of residence was categorized as <14%, 14–19.9%, 20–28.9%, and $\geqslant$29%, based on national quartiles and used as proxies for patient socioeconomic status), median household income, insurance status (categorized as private, Medicare, Medicaid, or uninsured), treatment facility type (categorized as Community Cancer Program, Comprehensive Community Cancer Program, and Academic/Research Program [including NCI-designated Comprehensive Cancer Centers]), geographic region (categorized into 9 predefined regions), Charlson–Deyo co-morbidity Score (CDCS) (categorized 0, 1, and 2+), clinical stage, involved site (categorized as head & neck, mediastinum/chest, or not otherwise specified [NOS]/other), presence of "B" symptoms, distance from facility (classified as <12.5 miles, 12.5–50 miles, $\geqslant$50 miles), and vital status.

The outcome variable-overall survival (OS) was calculated from the date of diagnosis to December 31, 2011, the date of death, or the date of last contact, whichever occurred first.

Statistical analysis

Categorical and continuous variable distributions were assessed by using standard descriptive statistics. Using chi-square tests, we assessed the association of RT modality with age, gender, race, socioeconomic status (education level, household income), insurance status, facility type, stage, involved site of disease, distance from facility, presence of B-symptoms, and CDCS. Overall survival after planned intervention was the primary outcome. Kaplan–Meier survival curves were stratified by RT modality, and log-rank tests were performed.

Propensity score analysis

As an observational cohort, use of particular RT modality was likely not random, and may be influenced by patient and disease-related characteristics, potentially leading to biased survival estimates due to confounding. Thus, rather than traditional covariate adjustment via multivariate hazards modeling, propensity score (PS) adjustments to our Cox model may have significant advantages when analyzing large observational cohorts like SEER or NCDB [16]. We calculated PS using multivariate logistic regression with the exposure variable (IMRT vs. 2D/3D-CRT) as the intervention of interest, and then subsequently compared the match samples with overall survival as the outcome of interest. The estimated PS was the used to match patients with similar propensity to receive the specific RT modality based on nearest neighbor matching without replacement using calipers of width equal 0.2 SD of the logit of the propensity score. The success in achieving covariate balance was evaluated using standardized differences of means <0.1 (<10% difference between the arms) indicative of acceptable balance. As two important prognostic factors, the Charlson–Deyo co-morbidity score (CDCS) and the presence of "B" symptoms, were coded only from 2004 onward, our propensity score analysis was restricted to patients diagnosed in 2004–2006, with available survival data (n = 3436).

Cox proportional hazards model

Unadjusted associations of individual covariates with survival were described using univariate Cox proportional hazards model. A multivariate Cox proportional hazards model was then fitted to estimate the hazard ratios associated with RT-use and other covariates with respect to OS and their 95% confidence intervals (CI's), after adjustment for the propensity score. The criterion $p < 0.05$ was used for retaining interactions in the model.

In accordance with NCDB participant user file data-use agreements, survival analysis excluded patients (n = 6380) diagnosed from 2007 to 2011, to allow for at least 5 years of follow-up for all patients. Thus, the survival analysis cohort was a total of 6013 patients. Survival was calculated in months from date of diagnosis to date of last contact or confirmed death.

All statistical analyses were performed using statistical software STATA version 12.1. For all statistical testing, we used a