Pediatric-protocol of multimodal therapy is associated with improved survival in AYAs and adults with rhabdomyosarcoma

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A B S T R A C T

Background. Multimodal therapy is the standard treatment for pediatric rhabdomyosarcoma, but for adolescents and young adults (AYAs: ages 15–39) and older adults with rhabdomyosarcoma, the use of adjuvant therapy is variable, and survival is greatly decreased compared with younger patients.

Methods. All patients with rhabdomyosarcoma who had a curative operative were identified from the 1998–2012 National Cancer Database. Regression analyses identified independent factors relating to receipt of multimodal therapy (resection + chemotherapy + radiation) and the influence of multimodal therapy on 5-year overall survival.

Results. Of 2,312 patients, 44% were pediatric (age <15 years), 22% AYA (ages 15–39), and 34% adult (age ≥40 years). Adults received multimodal therapy least often (pediatric: 62%, AYA: 46%, adults: 24%; P <.001), even after controlling for demographic characteristics, tumor features, and stage. In the entire cohort, multimodal therapy was associated with a decreased risk of death within 5 years (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.62–0.84), with similar findings after stratification by age (pediatric: HR 0.64, 95% CI 0.48–0.85; AYA: HR 0.72, 95% CI 0.55–0.95; adult: HR 0.74, 95% CI 0.58–0.93). In AYAs only, black and Hispanic patients had an increased risk of death within 5 years (black patients: HR 1.64, 95% CI 1.14–2.37; Hispanic patients: HR 1.62, 95% CI 1.11–2.36).

Conclusion. This first large national study suggests that multimodal therapy is independently associated with improved survival for both AYAs and adults with rhabdomyosarcoma, similar to pediatric patients, but multimodal therapy is appreciably underused. Implementation of multimodal therapy for all patients could potentially improve overall outcomes of patients with rhabdomyosarcoma.

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Rhabdomyosarcoma is one of the most common soft tissue sarcomas (STSs) in the pediatric population, representing more than 50% of all STSs in this age group, with an incidence of 0.4414 per 100,000 per year in the United States. Rhabdomyosarcoma in adults, however, occurs much less often, comprising only 3% of STSs and less than 1% of all malignancies. In an older review of data from the Surveillance, Epidemiology, and End Results (SEER) study, adults (older than age 19 years) accounted for 41% of all rhabdomyosarcomas diagnosed between 1973 and 2005. Rhabdomyosarcoma was thought initially to be derived from skeletal muscle; however, rhabdomyosarcoma now is known to arise from early rhabdomyoblasts that can be found in a wide variety of locations throughout the body with a varying degree of differentiation.

In the early 1970s, the Soft Tissue Sarcoma Committee of the Children’s Oncology Group (formerly the Intergroup Rhabdomyosarcoma Study Group) began a series of multidisciplinary and multi-institutional trials to improve the poor survival of rhabdomyosarcoma in children. At that time, the median overall survival was 19.2 months and the 5-year overall survival was 35%. With the implementation and advances in multimodal therapy (MMT: resection, chemotherapy, and radiation) in this age group, more than 70% of
pediatric patients with localized rhabdomyosarcoma are now cured.\textsuperscript{5} Likely because of the rarity of the disease, a similar adoption of MMT protocols and clinical trials in adults has never happened, and adult 5-year survival rates (27\%) continue to lag substantially behind those of children (70\%).\textsuperscript{2} Although many speculate that the differences in histologic subtype and primary site of disease between younger and older patients with rhabdomyosarcoma are the main determinants of this survival difference, it is just as likely that lack of use of MMT contributes equally.\textsuperscript{7} Two single-institution retrospective studies reported improved outcomes when adults were treated with pediatric rhabdomyosarcoma protocols, but this concept has yet to be studied on a larger scale with contemporary data or in a large randomized trial.\textsuperscript{1,11} Therefore, this study explores disparities for receiving MMT in both adolescents and young adults (AYAs: ages 15–39) and adults compared with younger children and the impact of lack of MMT on overall survival in each age group.

Methods

Data source

All cases of rhabdomyosarcoma diagnosed between 1998 and 2012 at a Commission on Cancer–accredited hospital were identified from a deidentified data set of the National Cancer Database (NCDB). The NCDB is a joint project from Commission on Cancer of the American College of Surgeons and the American Cancer Society, which includes more than 1,500 Commission on Cancer–accredited facilities. The NCDB is known to capture an estimated 70\% of cancer cases in the United States.\textsuperscript{6} The American College of Surgeons Commission on Cancer has not reviewed the data presented here and holds no responsibility for the results or conclusions determined from this data set.

Study population

Patients with primary, invasive rhabdomyosarcoma were identified by the International Classification of Diseases for Oncology, third edition (ICD-O-3), primary site codes: C380, C470–C479, C480, C490–C499, and histology codes: 8900/3: rhabdomyosarcoma, not otherwise specified (NOS); 8901/3: pleomorphic rhabdomyosarcoma, adult-type; 8902/3: mixed-type rhabdomyosarcoma; 8910/3: embryonal rhabdomyosarcoma; 8912/3: spindle cell rhabdomyosarcoma; and 8920/3: alveolar rhabdomyosarcoma; 8921/3. Only patients who underwent resection were included and those receiving any palliative care were excluded. Patients with tumors in the head and neck area, genitourinary system, and bile duct regions were classified as favorable sites, and all others were classified as unfavorable as described previously from the Soft Tissue Sarcoma Committee of the Children’s Oncology Group.\textsuperscript{5,8–11} Favorable histology was classified as embryonal, with all others classified as unfavorable, because this subtype is encountered most commonly in the favorable primary sites.

Other variables were coded according to the NCDB Participant Use Data File and in accordance with the Facility Oncology Registry Data Standards and the SEER*Rx Coding systems.\textsuperscript{12,13} Demographic variables included age, sex, race, ethnicity, insurance, socioeconomic status, and education level. Age categories were divided into pediatric (<15 years old), AYA (15–39 years old), and adult (40+ years old). Race was categorized as white non-Hispanic, white Hispanic, black, Asian/Pacific Islander, and other. Socioeconomic status and education level were divided into those who lived in a ZIP code with a median income (or percentage of residents who finished high school) that was in the lowest quartile (low), middle 2 quartiles (moderate), or the highest quartile (high). Insurance status was classified as “no insurance,” “government/military/Medicare/Medicaid insurance,” or “private/managed care.” Facility volume was defined as “low” if fewer than 10 rhabdomyosarcoma cases per year were treated at that facility and moderate if more than 10 were treated. MMT included patients who received chemotherapy, radiation, and resection as part of their first course of therapy. The number of months from diagnosis to death or last contact was used for survival analyses and to calculate median follow-up times; those with 0 or missing information in this field were excluded from the survival analyses.

Statistical analysis

Demographic, clinicopathologic, and treatment characteristics were compared among pediatric, AYA, and adult patients using $\chi^2$ tests or Student t tests as appropriate. Similarly, demographic, clinicopathologic, and treatment characteristics that predicted receipt of MMT were determined with Fisher exact or $\chi^2$ test, and all variables significant at the $P<.1$ level on univariate analysis were entered into a multivariable logistic regression model to determine predictors of MMT. Five-year overall survival was calculated using the Kaplan-Meier method and comparisons were made using the log-rank test. Multivariable survival analysis was performed with a Cox proportional hazard model, using a stepwise selection procedure that included factors with a $P<.05$. Hazard ratios and 95\% confidence intervals were calculated to evaluate the strength of association between each variable and survival. All analyses were conducted using SAS Version 9.3 (SAS Institute, Inc, Cary, NY). All tests were 2-sided.

Results

Of 2,312 primary RMS patients who underwent resection as part of their primary treatment for rhabdomyosarcoma, 44\% of the cohort was younger than 15 years old (pediatric), 22\% ages 15–39 (AYA), and 34\% 40+ years old (older adult). The median follow-up was 57.8 months for pediatric, 34.4 months for AYA, and 22.0 for the older adult group. Although the sex distribution was equal across the age groups, adults had a greater proportion of non-Hispanic white patients, whereas pediatric and AYA groups had the greatest percentage of white Hispanic patients ($P<.001$ (Table 1). Other sociodemographic variables were similar across age groups, except that a greater proportion of adults were treated at low-volume hospitals and had public insurance ($P<.001$).

Tumor characteristics and treatment varied significantly by age. Pediatric tumors had more favorable histology subtypes and sites of primary disease. The pediatric group had tumors in the head more commonly, and neck and embryonal histology comprised nearly half (45\%) of pediatric tumors, whereas only 30\% of AYA and a mere 12\% of older adults had this more favorable histologic subtype. Tumor size also increased with increasing age, and older adults presented with later stage disease (all $P<.001$ (Table 1). The most noticeable difference was in the use of chemotherapy, radiation, or MMT. Less than one quarter (24\%) of older adults were treated with MMT compared with 46\% of AYAs and 62\% of pediatric patients ($P<.001$). This difference mostly was due to the difference in patients receiving chemotherapy (pediatric 92\% vs older adult 44\%), which did not differ by histologic subtype, but radiation was also used less often with increasing age (though more often in older adults with pleomorphic histology, data not shown). The sequence of specific treatment, single versus multagent chemotherapy, and type of radiation are detailed in Supplementary Table S1.

Logistic regression modeling revealed that patients least likely to receive MMT were older adults (odds ratio [OR] 2.25, confidence interval [CI] 1.40–3.59), those with no insurance (OR 1.74, CI 1.06–2.87) or public insurance (OR 1.32, CI 1.08–1.62), and unfavorable primary tumor sites (OR 1.63, CI 1.29–2.06) (Table 2). Conversely, treatment at a greater volume center (OR 0.72,
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