Model to predict the survival benefit of radiation for patients with rhabdomyosarcoma after surgery: A population-based study

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Abstract. The aim of this study was to build a model to predict the survival benefit of radiotherapy for resected rhabdomyosarcoma at the individual level, to help clinicians and their patients make more informed decisions about adjuvant radiotherapy. Patients with resection of rhabdomyosarcoma between 1990 and 2010 were derived from the Surveillance, Epidemiology and End Results database. A multivariate Cox proportional hazard model was built to model cause-specific survival. We used inverse-probability weighting with propensity scores to minimize selection bias in the observation study. The Akaike information criterion technique was used to reduce variables in the model. Nomograms were created with the reduced model after model selection. The study cohort comprised 1578 patients. The 5-year cause-specific survival rate was 64.3% (95% confidence interval (CI) 61.7-66.9%) and the 10-year cause-specific survival rate was 61.4% (95% CI, 58.7-64.2%) for the entire cohort. Five-year cause-specific survival rates were 62.3% (95% CI, 58.6-66.2%) and 66.1% (95% CI, 62.6-69.8%) for patients with surgery alone and adjuvant radiotherapy, respectively (P<0.01). Age, size, histological type, tumor stage, positive regional nodes and adjuvant radiotherapy were retained in the reduced model. Model performance was good, with a c-index of 0.78 (95% CI, 0.76-0.80). This clinical predictive tool can quantify the benefit of adjuvant radiotherapy after resection of rhabdomyosarcoma, and provide patients and clinicians with assistance in treatment selection.

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Introduction

Rhabdomyosarcoma (RMS) is a rare form of cancer with an incidence of 0.50 per 100,000 in children 0-14 years old, and 0.23 per 100,000 for the overall population in 2010 according to Surveillance, Epidemiology, and End Results (SEER) statistics (1). RMS is commonly seen in children and adolescents and accounts for 3% of all pediatric tumors (2). The median age at diagnosis is only ~5 years. RMS originates from striated muscle cells or their mesenchymal precursors (3). Because of this origin in embryonic mesenchyme, RMS can arise anywhere in the body.

Survival has been improved greatly with multidisciplinary management including surgery and multiagent chemotherapy with or without radiation. Since 1972, the Intergroup Rhabdomyosarcoma Study Group (IRSG) has conducted a series of clinical trials aimed at improving survival, and has published a series of treatment guidelines for different primary sites. Such efforts have resulted in significant improvements in prognosis, with a cure rate of ~70% for localized RMS among children and adolescents (4). The 5-year overall survival (OS) rate for patients with RMS has increased from approximately 35% in the 1970s to ~50% in the 2000s, according to SEER statistics (1).

Surgery is an important component of the local management of RMS. The goal of surgery is not only to remove the tumor, but also to help determine risk stratification in the form of surgical-pathological group, stage, histology and age at initial diagnosis.

Multi-agent chemotherapy is required in the treatment of all patients with RMS to decrease the chance of relapse. Vincristine, dactinomycin and cyclophosphamide (VAC) represent the backbone of chemotherapy. Variations on VAS depends on the clinical group and site of disease based on the results of the Intergroup RMS studies (5).

Radiotherapy is another critical component of multimodal management for patients with RMS. Adjuvant radiotherapy is recommended for patients with microscopically positive margins or gross residual disease after surgery or distant metastases on initial diagnosis, and for all patients with alveolar histology according to the IRSG (6,7).

With improving survival, there is increasing recognition of the late sequelae of treatment among long-term survivors of childhood cancer (8). Many of these late sequelae relate to local therapy. Systematically using radiotherapy as a primary treatment for RMS might increase the rate of local control, but can result in important long-term problems, particularly in very young children (9).

In addition, analyses of data from the Cooperative Soft Tissue Sarcoma Study Group (CWS)-81, -86, -91 and -96 trials have indicated that although radiotherapy improved local control in patients with microscopically positive margins after surgery, radiotherapy did not improve OS except in patients with unfavorable histology (10). Studies comparing the Malignant Mesenchymal Tumors (MMT) 89 trial with other clinical studies have shown similar results (11,12). The MMT trials were designed to reduce local treatment using initial front-line chemotherapy followed by second-line therapy in patients with poor response. Subsequent surgical resection was preferred over radiotherapy. Radiation was used only after incomplete resection, documented regional lymph node involvement or poor clinical response to initial chemotherapy. Although event-free survival in the MMT-89 was significantly lower than in other studies, OS rate was consistent with the results of other collaborative groups, with a 5-year survival rate of 71% (13). These results imply that the local control benefits from radiotherapy may not translate into improved long-term survival in some subgroups. Toxic death, secondary leukemia and relapse beyond the local site may affect OS in patients with adjuvant radiotherapy. The decision on whether to administer radiotherapy after surgery thus represents a challenge for the radiologist and pediatrician.

The aim of this study was to provide a decision aid to the clinician that can give an individual estimation of the prognostic benefit of adjuvant radiotherapy, to facilitate the decision of whether adjuvant radiotherapy is appropriate. To achieve this objective, we constructed a prognostic model using a cohort derived from SEER, a population-based database. We also developed nomograms based on the model we built to predict the benefit of adjuvant radiotherapy for patients with RMS.

Materials and methods

Data source and study population. The study cohort was obtained from the registry of the SEER program of the National Cancer Institute (14). The SEER program collects information on incidence, prevalence and survival. Currently, registry in SEER covers approximately 28% of the US population, and the characteristics of the SEER population are comparable with the general US population (1).

The study population comprised all patients with a diagnosis of RMS between 1990 and 2010. Patients eligible for this analysis with ICO-O-3 morphology codes comprised: i) RMS not otherwise specified 8900/3; ii) pleomorphic RMS adult-type 8901/3; iii) mixed-type RMS 8902/3; iv) embryonal RMS 8910/3; v) spindle-cell RMS 8912/3; vi) alveolar RMS 8920/3; and vii) embryonal sarcoma 8991/3. Only patients diagnosed with the first primary malignant tumor were included in this study. Patients diagnosed at autopsy or by death certificate only and patients with no microscopic confirmation of the diagnosis were excluded. After applying the exclusion criteria, the study population comprised 1578 patients with RMS. The flow chart for data selection is shown in Fig. 1.

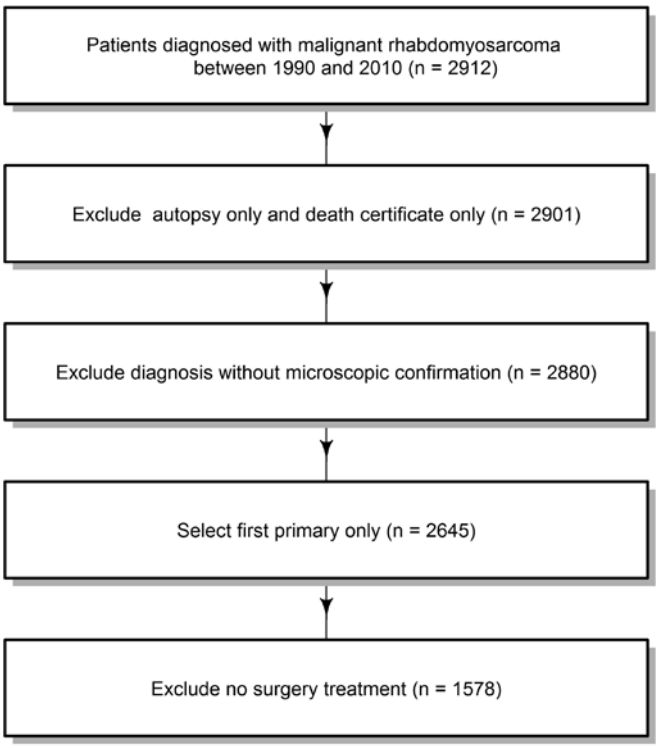

Figure 1. Flow chart for the creation of the Surveillance Epidemiology and End Results data set.

Demographic and clinical characteristics in analysis. Demographic variables in the analyses included age at diagnosis, gender and race. Age at diagnosis was assessed as a categorical variable in the description of variables and the calculation of cause-specific survival (CS). In other analyses, age at diagnosis was treated as a continuous variable. Clinical characteristics in the analysis included tumor site, histological subtype, tumor stage, tumor size, positive regional nodes and radiotherapy. Tumor site was collapsed to favorable and unfavorable sites according to the criteria for the staging of pediatric tumors (15).

The head and neck (non-parameningeal), genitourinary (non-bladder/prostate) and bile duct regions were defined as favorable sites. All other sites were regarded as unfavorable, and 'unknown' was regarded as missing. We used 'SEER Historic Stage A' to define tumor stage. 'Localized' was defined as a tumor confined entirely within the organ of origin. 'Regional' was defined as a neoplasm that had extended beyond the limits of the organ of origin directly into surrounding organs or tissues, or into regional lymph nodes by way of the lymphatic system, or by a combination of extension and regional lymph nodes. 'Distant' was defined as a tumor that had spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis (14). Tumor size was truncated at 30 cm. Tumor size was divided into categories for both character description and calculation of CS.

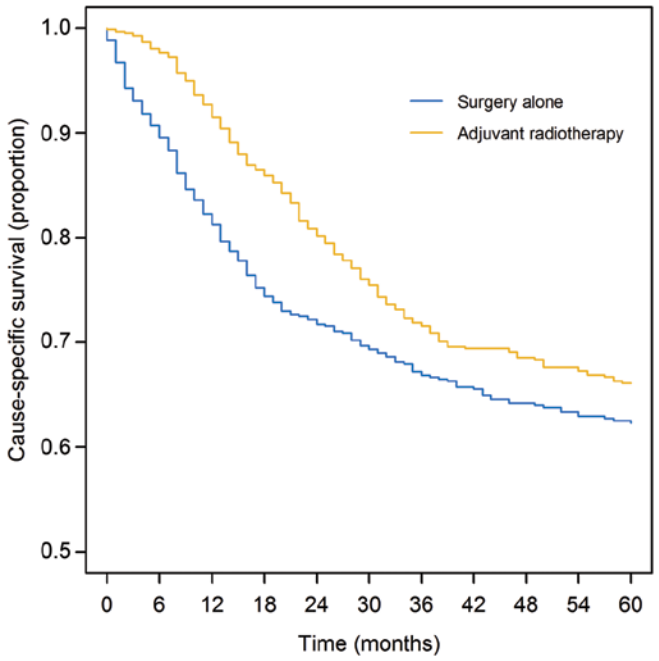

Figure 2. Kaplan-Meier cause-specific survival plot for patients with adjuvant radiotherapy and those with surgery alone.

In other modeling processes, size was treated as a continuous variable. Histology was classified as embryonal, alveolar, pleomorphic and other histological subtypes. Histology with RMS not otherwise specific (NOS) were treated as missing values. Positive regional nodes were grouped into 'pathologic node negative', '1-3 positive nodes', '≥4 positive nodes' and 'no nodes examined'. Radiation treatment was defined by SEER Item 'RX-Summ-Radiation' with codes of 0 and 7 as no radiation and 1-6 as radiotherapy. Other codes (8 and 9) were regarded as missing values.

Statistical methods. Missing values were imputed with the 'transcan' function provided from the rms package (16). Patients in the cohort were followed until: i) death; ii) last contact if before December 31, 2010; and iii) December 31, 2010, if the date of last contact was after December 31, 2010. Death from RMS was chosen as an end point. The Kaplan-Meier (KM) product-limited method was used to estimate CS, and the log-rank test was used to examine differences in survival between patient groups.

We used an inverse-probability weighting (IPW) with propensity scores method to balance observed covariates between treatment and observation groups (17). IPW can reduce treatment selection bias in nonrandomized observational studies. To obtain propensity scores, a logistic regression model was fitted in which treatment status was regressed on the baseline characteristics. Prior research for propensity score suggests that it is preferable to include either variables affecting the outcome, or variables affecting both treatment selection and outcome (18). We weighted the entire study cohort with inverse probability of treatment weights obtained from the propensity score. If Z denotes treatment status (0 or 1) and e denotes the estimated propensity score, IPW is defined by $Z/e + (1-Z)/(1-e)$.

A multivariate Cox proportional hazard model was built to model CS. Covariates included in the prediction model were chosen based on known clinically prognostic factors and availability in the SEER registry. To allow flexibility in representing nonlinear covariate effects on outcomes, we fitted the restricted cubic splines with three knots at the 10, 50 and 90% empirical quantiles for the variables of age at diagnosis and tumor size. Interaction terms between radiotherapy and positive regional nodes, histological subtype and stage were pre-specified in the model. The proportional hazard assumption was verified by examining residual plots. To avoid overfitting of the model, we used a model selection technique with the Akaike information criterion (AIC) to reduce variables in the model. A nomogram was then created with the beta coefficients of variables in the reduced model.

The prognostic prediction model was internally validated by evaluating both calibration and discrimination. Discriminating was measured using the concordance index (c-index) (19). A c-index of 0.5 indicates a random predictor, while 1.0 indicates a perfect predictor. Calibration represents the ability of a model to make unbiased estimates of outcome. A perfectly accurate nomogram would result in a plot where predictions should fall along a 45° diagonal line. Both discrimination and calibration were evaluated using bootstrapping with 200 resamples.

All statistical analyses were performed using R version 3.0.0 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org) (20). The R package rms was used for modeling and establishing the nomogram (16). All statistical tests were two-sided, and values of $P<0.05$ were considered statistically significant.

Results

Patient characteristics. A total 1578 patients met the inclusion criteria and were included in the study. Demographic and tumor characteristics are listed in Table I. In this cohort, embryonal subtype was present in 51.0% of all patients. SEER stage was localized in 42.9% of patients, regional in 36.9% and distant in 20.2%. More than half (52.0%) of patients had received radiotherapy.

The 5-year CS rate was 64.3% (95% CI, 61.7-66.9%) and 10-year CS rate was 61.4% (95% CI, 58.7-64.2%) for the entire cohort. Five- and 10-year CS rates by characteristic are shown in Table I. Five-year CS rates were 62.3% (95% CI, 58.6-66.2%) and 66.1% (95% CI, 62.6-69.8%) for patients with surgery alone and adjuvant radiotherapy, respectively ($P<0.01$) (Fig. 2).

Multivariate regression model and nomograms. Of the total 1578 patients, 821 patients (52%) received adjuvant radiotherapy. Table II shows a comparison of baseline characteristics between patients who received adjuvant radiotherapy and those who did not. Compared with the untreated group, the treated group included more patients with unfavorable site, positive regional nodes, alveolar histological type and non-localized stage. After propensity score weighting, all variables were balanced, and significant differences in distributions of variables between treated and untreated groups disappeared.

Table I. Patient demographics and cause-specific survival.

Characteristics	No. (events)	5-year CS% (95% CI)	10-year CS% (95% CI)	P-value
Entire cohort	1578 (513)	64.3 (61.7-66.9)	61.4 (58.7-64.2)	
Age (years)				
<2	157 (34)	77.4 (70.1-85.2)	73.7 (66.0-82.3)	<0.001
2-5	309 (51)	82.7 (78.2-87.5)	79.8 (74.8-85.1)	
6-11	232 (48)	77.4 (71.5-83.7)	73.2 (66.8-80.4)	
12-17	226 (68)	66.4 (59.9-73.5)	64.7 (58.0-72.1)	
18-44	303 (134)	52.7 (47.0-59.2)	48.8 (42.9-55.6)	
45-64	180 (87)	45.1 (37.7-54.0)	45.1 (37.7-54.0)	
≥65	171 (91)	36.7 (29.1-46.2)	33.4 (24.8-44.9)	
Size (cm)				<0.001
<5	594 (109)	80.2 (76.7-83.8)	77.5 (73.7-81.5)	
5-9	537 (174)	64.2 (59.8-68.9)	60.3 (55.6-65.3)	
≥10	447 (230)	42.2 (37.4-47.7)	40.2 (35.3-45.8)	
Gender				0.08
Male	914 (283)	66.2 (62.9-69.7)	63.1 (59.6-66.8)	
Female	664 (230)	61.5 (57.6-65.8)	59.0 (54.8-63.4)	
Race				0.98
White	1192 (387)	64.7 (61.8-67.7)	61.2 (58.1-64.5)	
Black	254 (83)	62.7 (56.5-69.6)	62.7 (56.5-69.6)	
Others	132 (43)	63.0 (54.2-73.3)	60.2 (51.2-70.9)	
Site				<0.001
Unfavorable	940 (358)	57.9 (54.5-61.5)	54.2 (50.6-58.1)	
Favorable	638 (155)	73.3 (69.6-77.1)	71.5 (67.7-75.5)	
Stage				<0.001
Localized	677 (130)	78.7 (75.4-82.3)	75.7 (72.0-79.6)	
Regional	583 (184)	65.7 (61.5-70.1)	62.3 (57.9-67.0)	
Distant	318 (199)	31.2 (26.0-37.3)	29.4 (24.3-35.6)	
Histology				<0.001
Embryonal	806 (196)	73.4 (70.1-76.8)	71.1 (67.6-74.7)	
Alveolar	356 (146)	55.4 (49.9-61.4)	51.1 (45.4-57.4)	
Pleomorphic	258 (125)	44.6 (38.3-51.9)	43.2 (36.6-50.9)	
Others	158 (46)	69.2 (61.5-77.8)	63.1 (54.4-73.2)	
Positive regional nodes				<0.001
Pathologic node negative	328 (80)	75.0 (70.1-80.4)	69.0 (63.1-75.4)	
1-3 positive nodes	103 (35)	62.0 (52.5-73.2)	60.4 (50.8-71.8)	
≥4 positive nodes	25 (13)	44.5 (27.4-72.4)	39.0 (22.4-67.7)	
No nodes examined	1122 (385)	61.7 (58.7-65.0)	59.6 (56.5-63.0)	
Treatment				0.01
Surgery alone	757 (260)	62.3 (58.6-66.2)	59.8 (55.9-63.9)	
Adjuvant RT	821 (253)	66.1 (62.6-69.8)	62.9 (59.2-66.8)	

RT, radiotherapy; CS, cause-specific survival.

We built a COX proportional hazard model with the variables listed in Table I. The assumption of proportional hazards was supported. After model selection, we obtained a reduced model including the variables age, size, stage, histological

Table II. Patient characteristics before and after propensity score weighting to balance covariates between surgery alone and adjuvant radiation groups.

	Original			PS-weighted		
Characteristics	Surgery alone	ART	P-value	Surgery alone	ART	P-value
Mean, age (years)	26.6	21.3	<0.001	23.8	24.0	0.79
Mean, size (mm)	88.2	70.8	<0.001	78.9	79.0	0.98
Gender (%)			0.80			0.88
Male	58.3	57.6		58.6	58.9	
Female	41.7	42.4		41.4	41.1	
Race (%)			0.11			1.00
White	76.5	74.7		75.6	75.6	
Black	16.6	15.6		16.3	16.3	
Other	6.9	9.7		8.1	8.1	
Site (%)			0.004			0.90
Unfavorable	55.9	63.0		60.7	60.5	
Favorable	44.1	37.0		39.3	39.5	
Stage (%)			<0.001			0.89
Localized	49.7	36.7		42.4	43.2	
Regional	30.4	43.0		38.0	37.2	
Distant	19.9	20.3		19.6	19.5	
Histology (%)			<0.001			0.95
Embryonal	52.8	49.5		50.8	51.3	
Alveolar	14.1	30.3		22.7	22.5	
Pleomorphic	17.8	15.0		16.7	16.9	
Others	15.2	5.2		9.8	9.2	
Positive regional nodes (%)			0.001			0.72
Pathologic node-negative	24.4	17.4		20.3	19.8	
1-3 positive nodes	4.8	8.2		7.7	6.8	
≥4 positive nodes	1.7	1.5		1.5	1.5	
No nodes examined	69.1	73.0		70.5	71.9	

ART, adjuvant radiotherapy; PS, propensity score.

type, positive regional nodes and adjuvant radiotherapy. Beta coefficients for this reduced model are listed in Table III.

Nomograms to predict 5- and 10-year CS rates were developed based on the beta coefficients from the reduced model (Fig. 3). To use the nomogram, we first draw a vertical line to the point row to obtain point values for each variable, then add up the point values for each variable to obtain total points, and drop a vertical line from the total points row to obtain the 5- and 10-year CS rates. Fig. 3A predicts CS with surgery alone, and Fig. 3B predicts CS with adjuvant radiotherapy. The survival benefit of adjuvant radiotherapy can be estimated using the difference between these two predictions.

Model performance was evaluated by internal validation. The model demonstrated reasonable accuracy, with a c-index of 0.78 (95% CI, 0.76-0.80). The calibration plots for 5- and 10-year CS are shown in Fig. 4. Points close to the 45˚ line show good agreement between CS estimates from the model and those derived from Kaplan-Meier estimates.

Discussion

Individual estimation of prognosis for a patient with cancer is useful to guide treatment selection. The present study reports a model for estimating the survival benefit of adjuvant radiotherapy in a patient after resection of RMS, and this model can easily be applied in the clinic. For example, given a 5-year-old patient with distant alveolar RMS, tumor size of 5 cm and 2 positive lymph nodes, our nomograms predict that 5-year CS rate would improve from 48% with surgery alone to 60% with adjuvant radiotherapy.

A number of nomograms have been published, including for cancers of the prostate, pancreas, breast and other sites (21-26). The first soft-tissue sarcoma nomogram for predicting

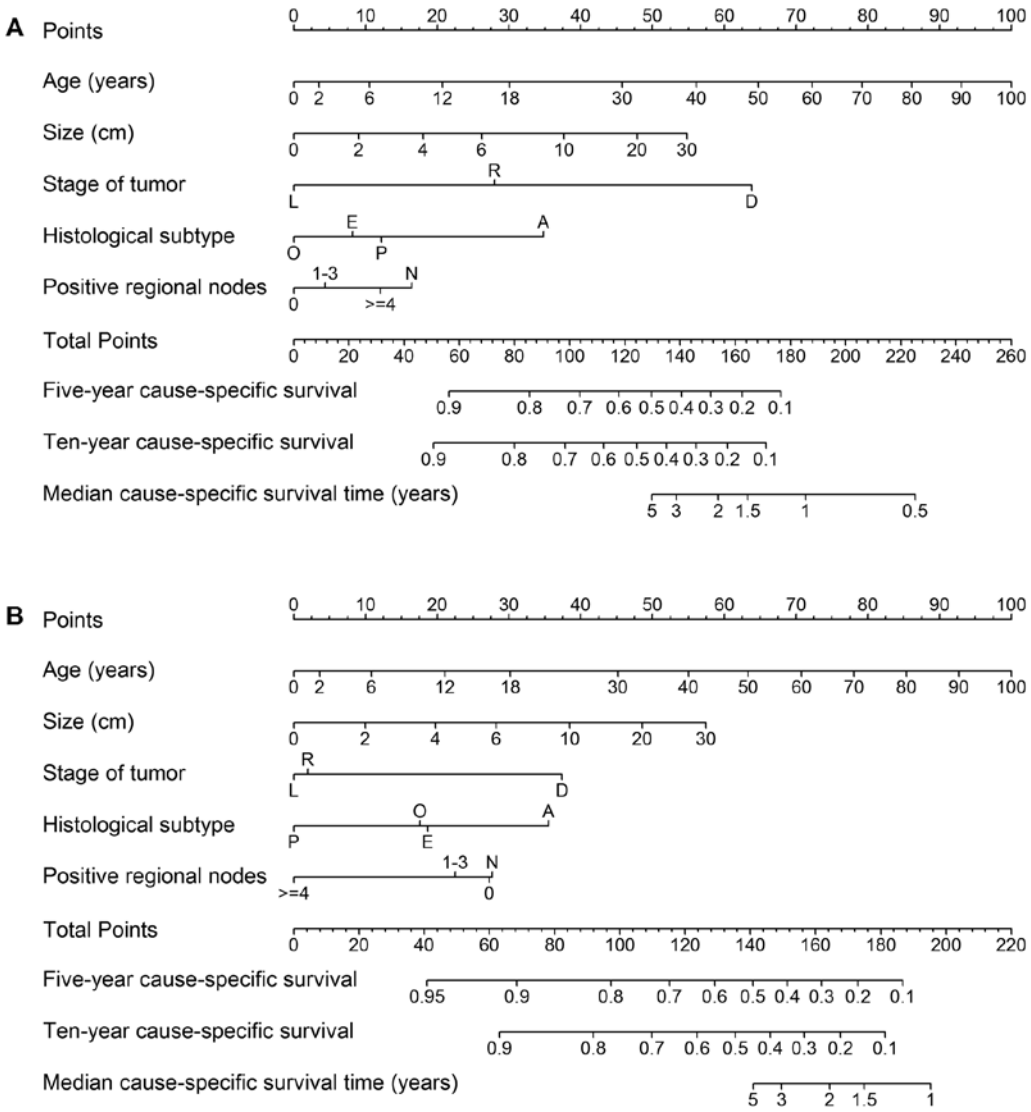

Figure 3. Nomogram for predicting 5- and 10-year cause-specific survival and median survival time. (A) Prediction for patients with surgery alone. (B) Prediction for patients with adjuvant radiotherapy (RT). Stage of tumor: L, localized; R, regional; D, distant. Gender: M, male; F, female. Histological subtype: E, embryonal; A, alveolar; P, pleomorphic; O, others. Positive regional nodes: N, no nodes examined. For an individual patient, first use (A) to calculate the expected survival without adjuvant RT, then use (B) to obtain the expected survival with adjuvant RT. The difference between these two estimates shows the survival benefit that a patient is predicted to obtain from adjuvant RT.

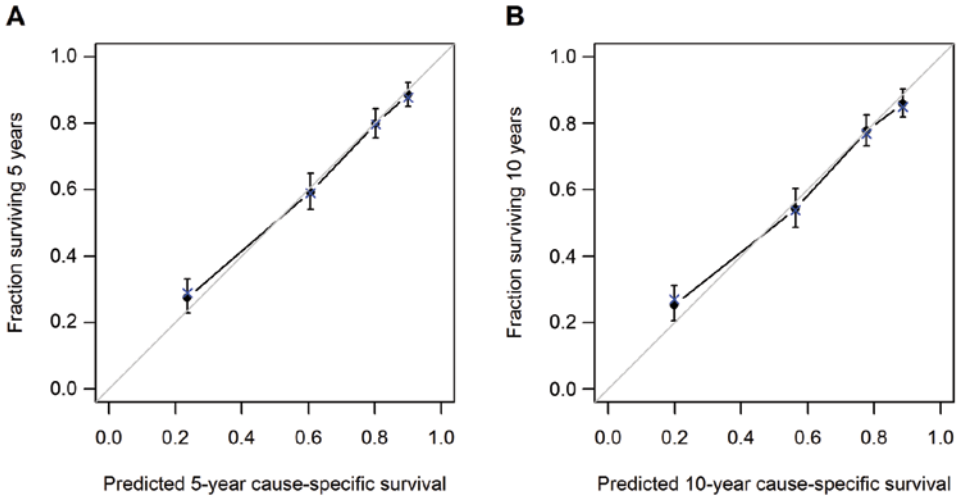

Figure 4. Calibration plot. The grey line represents the 'ideal' line of a perfect match between predicted and observed survival. Vertical arrows represent 95% confidence intervals for observed survival. (A) Five-year cause-specific survival. (B) Ten-year cause-specific survival. X marks the bootstrap corrected estimates.

Table III. Cox proportional hazards multivariate regression model parameters.

Covariate	Beta coefficient	Hazard ratio	95% CI	P-value
Age	0.05	-[a]	-	<0.001
Age'	-0.05	-[a]	-	0.02
Size	0.13	-[a]	-	<0.001
Size'	-0.12	-[a]	-	0.02
Histology				
Alveolar	0.68	1.98	1.36-2.88	<0.001
Pleomorphic	0.10	1.11	0.73-1.70	0.63
Others	-0.20	0.81	0.52-1.26	0.36
Stage				
Regional	0.71	2.04	1.44-2.92	<0.001
Distant	1.64	5.16	3.51-7.56	<0.001
Positive regional nodes				
1-3 positive nodes	0.11	1.12	0.56-2.22	0.74
≥4 positive nodes	0.29	1.34	0.62-2.87	0.45
No nodes examined	0.42	1.52	1.08-2.16	0.02
Received RT	0.70	2.00	1.11-3.62	0.02
Interaction term				
Alveolar x RT	-0.24	0.78	0.49-1.26	0.32
Pleomorphic x RT	-0.59	0.55	0.33-0.92	0.02
Others x RT	0.18	1.19	0.59-2.41	0.62
Regional x RT	-0.67	0.51	0.32-0.83	0.01
Distant x RT	-0.67	0.51	0.31-0.84	0.01
1-3 positive nodes x RT	-0.23	0.79	0.32-1.93	0.60
≥4 positive nodes x RT	-1.00	0.37	0.08-1.79	0.21
No nodes examined x RT	-0.41	0.66	0.39-1.12	0.12

RT, radiotherapy. [a]Age and size were modeled using a restricted cubic spline function with k=3.

sarcoma-specific mortality was published by Kattan *et al* in 2002 (27). More recently, Gronchi *et al* reported two nomograms to predict OS and disease-free survival in patients after resection of retroperitoneal soft tissue sarcoma (28). In addition, Chisholm *et al* published a nomogram for patients with relapsed RMS to define patients who can be salvaged with further therapy (29). In terms of treatment evaluation, Wang *et al* reported two models for predicting the benefit of adjuvant radiation and adjuvant chemoradiotherapy in patients with resected gallbladder cancer using SEER (30) and SEER-Medicare data (31). Recently, Albert *et al* used the SEER-Medicare dataset to develop a nomogram predicting the benefit of radiation for older patients with breast cancer treated using conservative surgery (32). To the best of our knowledge, the nomograms presented here represent the first to estimate the benefit of radiotherapy for individual RMS patients after surgery.

Given the low incidence of RMS, recruiting sufficient numbers of participants for randomized clinical trials to estimate the benefit of adjuvant radiotherapy may be difficult. Most studies have described results from single institutions, or from retrospective analysis of clinical trial data. Given the short follow-up period and the rarity of this disease, reports from a single institution often do not have sufficient power to identify true associations between prognosis and risk factors. SEER data provide a powerful tool for evaluating prognosis, particularly for rare diseases.

The use of radiotherapy has benefited many patients, but has also resulted in many adverse effects that must be considered carefully when selecting a treatment plan. For example, radiotherapy to the head may result in brain damage. In particular, the brains of small children are very sensitive to radiotherapy. Several studies have attempted to define subgroups for which adjuvant radiotherapy can be omitted to avoid late effects. In the European MMT84 protocol, radiotherapy was not provided for complete responders to chemotherapy. Although a high incidence of local relapse was seen in patients without radiotherapy, there was also a good chance of successful salvage therapy with additional treatment due to not receiving local control (33). Schuck *et al* analyzed group II RMS using data from CWS trials to evaluate local control and the survival benefit of radiotherapy. They found that it was possible to

cure some patients with microscopically incomplete resection without additional radiotherapy. Although a subset of group II patients who may be spared radiotherapy was not defined, they suggested that omission can be justified in patients with favorable histology where the side effects from radiotherapy would be severe, such as extremely young patients or patients with tumor at sensitive sites (10). Although the present study could not compare results with these studies directly due to a lack of detailed information on surgical margins, and did not identify a specific subgroup for which adjuvant therapy should be omitted, the nomograms we report here can quantify the survival benefit of adjuvant radiotherapy. Customized predictions are more relevant to individual patients than recommendations based on coarse groupings, because they can identify whether the individual patient is likely to benefit and calculate the likely magnitude of such benefit.

This study used observational data to estimate treatment effects. Unlike well-designed clinical trials, selection bias will be present between treated and untreated groups in observational studies, because the distribution of covariates is unlikely to be balanced between groups. Propensity score methods allow such biases to be minimized. Different propensity score methods can be used to adjust for selection bias, such as propensity score matching, stratification according to propensity score, propensity score weighting and covariate adjustment using the propensity score. A previous study compared the performance of these methods and indicated that both propensity score matching and inverse probability of treatment weighting using propensity score allow for the estimation of marginal hazard ratios with minimal bias when estimating effects of treatment on time-to-event outcomes (34). We therefore used the inverse probability of treatment weighting to adjust for selection bias in this analysis.

Although validation of the nomograms demonstrated good accuracy for predicting survival benefit from adjuvant radiation, caution is warranted when using these nomograms. It is not possible to include all risk factors in a nomogram, so the survival benefit predicted from a nomogram cannot represent the sole basis for treatment selection. The final decision of whether to use adjuvant radiotherapy should be made with careful consideration of multiple prognostic factors, quality of life and the wishes of the patient.

Some other limitations must also be mentioned. First, the study used SEER data, so the predictive factors included in the model are limited to those variables included in the SEER database. Factors such as comorbidities, use of chemotherapy and status of surgical margins are known to influence survival outcomes in RMS, but such information is not available from SEER and so could not be included in our model. Most children with RMS in America are treated according to national cooperative protocols, and every patient treated for RMS should receive chemotherapy based on those protocols, so predictions from our nomograms were considered biased toward those treated according to RMS protocols and receiving adjuvant chemotherapy, particularly for the pediatric population. The lack of a central review of pathology represents a second limitation to our investigation. Finally, internal validation was used to evaluate model building due to the small sample size. External validation is still needed. Despite these limitations, the SEER dataset provided sufficient patients to build a reasonably predictive model. Furthermore, the c-index of 0.78 (95% CI, 0.76-0.80) shows a model statistically better than chance ($P<0.001$), and suggests a sufficient level of accuracy, given the lack of published nomograms in this setting.

In summary, we have developed a survival model to evaluate the benefit of radiotherapy for resected RMS using a population-based database. Model performance was tested and found to be good. Our model and nomograms can quantify the benefit of adjuvant radiotherapy, and provides patients and clinicians with assistance in making treatment decisions.

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