Clinical characteristics and outcomes of pediatric patients with desmoplastic small round cell tumor

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Abstract

Desmoplastic small round cell tumor (DSRCT) is a rare malignancy that typically affects pediatric and young adult patients. There are limited data on the clinical features of pediatric DSRCT. We selected patients aged 0-21 years reported to the Surveillance, Epidemiology and End Results Program from 1991-2011. We estimated overall survival using Kaplan-Meier approaches and compared outcomes using the log rank test. The median age of the 95 pediatric patients was 15.3 years (range: 0-21). The majority of tumors originated in the abdomen and pelvis (84.4%) and the majority of patients had distant metastasis (72.6%). A minority of patients received radiation (34%). Overall survival at 5 years was poor (18.1%; 95% confidence interval 10.1-27.9%). Radiation therapy was associated with superior survival. Pediatric patients with DSRCT have significant disease burden. Outcomes for children are poor, though patients selected for radiation appear to have improved survival.

Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive malignancy that occurs in both pediatric and adult patients. Since the initial description in 1989 by Gerald and Rosai, the main data have been derived from case series of patients treated at major referral centers.[1-4] Based upon these reports, patients present at a median age of 19 years with a 90% male predominance.[5,6] They typically have an intra-abdominal mass with extensive peritoneal seeding and metastases at presentation. While uncommon, extra-abdominal primary DSRCT has been reported in the chest wall, thigh, hand, ovary, testes, pleura, bone, and salivary glands.[7] Metastases to the liver, lung, spleen or bones are often present at diagnosis. Molecularly, the tumor is characterized by a unique chromosomal translocation t(11;22)(p13q;q12) involving *EWSR1-WT1* fusion.[8] Despite multimodal treatment, survival remains poor, with one series reporting 5-year overall survival of 15%.[9,10]

Attempts to improve outcomes for DSRCT over the past 10 years have included cytoreductive surgery, hyperthermic peritoneal perfusion with cisplatin chemotherapy, autologous bone marrow transplant, targeted therapy with monoclonal antibodies, and whole abdominopelvic radiation.[8-13]

Typical chemotherapy regimens follow Ewing sarcoma protocols and include cyclophosphamide, doxorubicin, vincristine, ifosfamide, and etoposide, though a range of other agents have been used.[5,9,10] However, there is no standard chemotherapy regimen or standard approach to local control in this rare disease.

DSRCT affects both pediatric and adult patients. Little is known about the clinical presentation, treatment, or outcomes in pediatric patients with this disease. Given the extreme rarity of DSRCT, we used a large public registry to describe the clinical features, treatment, and overall survival of pediatric patients with this disease.

Materials and Methods

Patients

Patients diagnosed with DSRCT confirmed histologically and reported to the United States' National Cancer Institute's Surveillance, Epidemiology and End Results database (SEER) between 1991 (the first year in which DSRCT was included in SEER) and 2011 were eligible for inclusion. Only pediatric cases, defined as patients 0-21 years old at initial diagnosis, were included. This cut point was based upon the American Academy of Pediatrics (AAP) definition of pediatric patients.[14] There were no other exclusion criteria except missing at age diagnosis, which did not apply to any patients. The SEER database covers approximately 28% of the United States population from a wide variety of geographic areas including all or part of Alaska, California, Connecticut, Georgia, Hawaii, Iowa, Kentucky, Louisiana, Michigan, New Jersey, New Mexico, Utah, and Washington. The lack of any identifying information in the data collected from the SEER database made this study exempt from Institutional Review Board review.

Outcome variables

We described patient characteristics and overall survival described in this cohort. Variables of interest included year of diagnosis, sex, race, primary tumor site, tumor size (dichotomized at 10 cm), and receipt of any form of radiation therapy.

We also evaluated extent of regional and distant metastatic disease. Patients with disease involving only the primary site were considered to have localized disease. Patients whose only site of disease outside of the primary site was regional lymph node involvement were also considered to have localized disease, but coded as having regional node involvement. Regional lymph nodes were defined as the nodal basin anatomically closest to the reported primary tumor. Regional nodes were considered to be involved based upon positive evidence of involvement in any of the following SEER data fields: evidence of disease (EOD) 10 coding systems; regional node data field; and collaborative staging (CS) lymph node status. Regional extension was determined based on extension coding, either EOD or CS, and regional node positive status. Patients were categorized further based upon the extent of regional extension as follows: truly localized disease without extension into adjacent structures and without regional node involvement; positive regional nodes but no other regional extension; localized extension to adjacent structures (*e.g.* peritoneum), but no regional nodes; or localized extension and also positive regional nodes. This is important given that DSRCT is often disseminated regionally. Distant metastatic disease was defined according to the following SEER data fields: evidence of disease (EOD) 10 coding-extent and collaborative staging (CS) metastasis at diagnosis with coding stating metastasis; distant metastasis except distant lymph node; and distant metastasis with distant

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lymph node. SEER provides data on total months of follow-up as well as patient vital status at the time of last follow-up. These data were used to estimate overall survival from time of initial diagnosis.

Statistical methods

We estimated overall survival from the time of diagnosis using the Kaplan-Meier method with surviving patients censored at the time of last follow-up. Survival distributions between groups defined by receipt of radiation were compared using the log rank test. The SEER database was accessed using SEER*Stat version 8.1.5 and all statistical analyses were performed using STATA, version 12.0.

Results

Clinical features in pediatric patients with desmoplastic small round cell tumor

There were a total of 95 pediatric patients (0-21 years old), accounting for 36% of patients with DSRCT reported to SEER during the time period included in this study. Table 1 provides the characteristics for the entire cohort of pediatric patients. The mean age was 15.3 years (median 15 years). There was a male predominance (76.8% male patients).

Of 90 patients with known primary tumor sites, 84.4% arose in the abdomen or pelvis. Pediatric patients commonly had distant metastatic disease (72.6%). Regional disease extension (lymph node involvement, regional tumor extension, or both) was also common in pediatric patients. A minority of pediatric patients received radiation therapy (34.0%).

Poor overall survival for pediatric patients with desmoplastic small round cell tumor

Overall survival estimates are shown in Figure 1A. The 2-year and 5-year overall survival estimates in pediatric patients were 52.4% (95% CI: 41.1-62.5) and 18.1% (95% CI: 10.1-27.9). The overall median survival time was 2.1 years for pediatric patients. A small proportion of pediatric patients were alive beyond 10 years from initial diagnosis.

We assessed the impact of radiation therapy on overall survival in this cohort. We observed statistically significant prolongation of overall survival in pediatric patients selected to receive radiation (P= 0.001; Figure 1B).

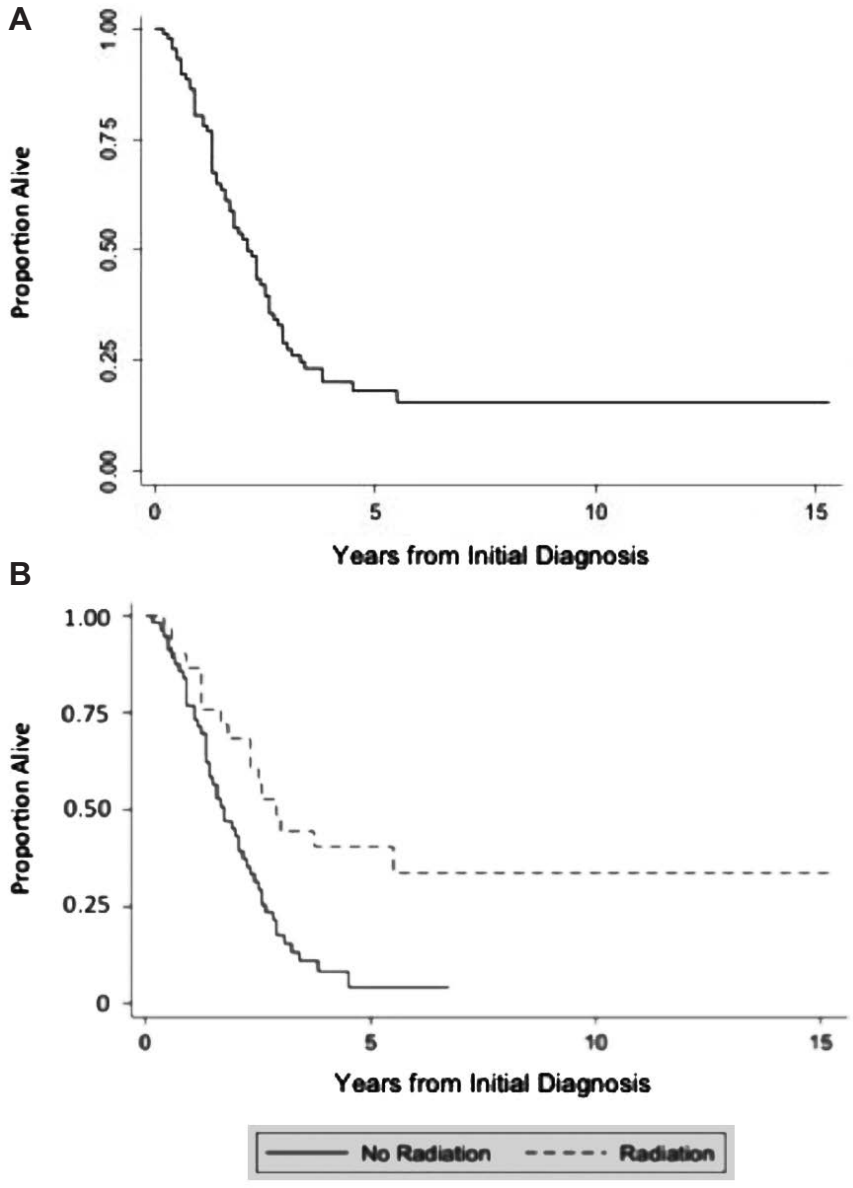

Figure 1. Estimated overall survival from initial diagnosis in pediatric patients with A) desmoplastic small round cell tumor; B) desmoplastic small round cell tumor treated with or without radiation (P=0.001).

Table 1. Characteristics of 95 pediatric patients with desmoplastic small round cell tumor.

Characteristic	No. (%)
Mean age (range)	15.3 (0-21)
Gender	
Male	73 (76.8)
Female	22 (23.2)
Race/ethnicity	
Caucasian, not Hispanic	42 (44.2)
Black, not Hispanic	26 (27.4)
Hispanic	20 (21.0)
American Indian/Alaskan Native	0 (0)
Asian/Pacific Islander	7 (7.4)
Primary tumor site*	
Abdomen	55 (61.1)
Pelvis	21 (23.3)
Reproductive organs	4 (4.4)
Head and neck	0 (0)
Other	10 (1.1)
Size°	
<10 cm	18 (36.7)
>10 cm	31 (63.3)
Extent of regional disease#	
Localized	10 (20)
Positive regional node only	3 (6)
Local extension only	19 (38)
Positive regional node and local extension	18 (36)
Distant metastasis§	
Yes	61 (72.6)
No	23 (27.4)
Radiation therapy^	
Yes	32 (34.0)
No	62 (66.0)

*Out of 90 patients with known primary site; °of 49 patient with known tumor size; #of 50 patients with known regional disease status; §of 84 patients with known metastatic status; ^of 94 patients with known radiation therapy data.

Discussion and Conclusions

Our results demonstrate that pediatric patients with DSRCT have a significant burden of disease. Only a minority of patients received radiation therapy, though pediatric patients selected for treatment with radiation showed a survival advantage. Overall survival was poor among pediatric patients with this disease.

The presenting features of DSRCT have been described in the literature. Our work adds to this literature by describing findings in pediatric patients. For example, the distribution of sites of disease observed in our study is consistent with previous reports. In a series of 11 pediatric and young adult patients, 3 had extra-abdominal primary tumors (submental, mediastinal, and paratesticular, respectively).[15] In another report, 6 of 33 patients who met our definition of *pediatric* had a pelvic primary tumor, an incidence that is similar to our current finding.[8] In our series, the large majority of pediatric patients presented with distant metastatic disease, a finding not previously reported in the literature. We report similar 2- and 5-year survival rates in our pediatric cohort compared to published literature. For example, a series that included both adult and pediatric patients reported pooled 3- and 5-year survival estimates of 44% and 15%, respectively.[9] Two pediatric case series likewise demonstrated poor overall survival. One pediatric study reported a 2-year event-free survival and overall survival of 14.4% and 50%, respectively.[8] In a cohort of 11 pediatric patients, 7 of 11 patients achieved a complete or partial remission, but nevertheless only 3 were alive at the time of their analysis.[15] Radiation therapy was associated with significantly prolonged overall survival. Other studies have reported on the use radiotherapy as an adjunct in combination with multimodal therapy, including whole abdominal radiotherapy.[12,16] Another study using the SEER database found a statistically significant survival advantage with the use of radiation after surgical intervention.[17] We acknowledge that our findings may be impacted by selection criteria clinicians may have used to identify candidates for radiation therapy. It is possible that these differences might reflect differential response to chemotherapy, differential ability to resect sites of disease, or some combination of these factors. These hypotheses are not testable with data available in SEER. The impact of radiation therapy on overall survival can be viewed in the context of other attempts to improve outcomes in this disease. For example, in a study with 26 pediatric and adult patients, median overall survival for patients undergoing complete cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) was 31.1 months compared to 12.8 months for those with incomplete cytoreduction.[13] In 19 pediatric and adult patients, overall survival following autologous stem cell transplant was 11%, with median overall survival for patients with complete remission after autologous transplant of 30.1 months compared to those who had measurable disease of 18.7 months.[18] These results, along with our current findings, highlight the importance of local control in the management of this disease. While the SEER database allowed access to a rare disease entity, there were limitations with using a registry. DSRCT is characterized by a recurrent reciprocal translocation,[19] and the results of this testing to confirm the diagnosis are not available in SEER. Therefore, it is possible that some cases coded as DSRCT were misclassified, potentially make our analytic cohort more heterogeneous. SEER does not include data on receipt of chemotherapy. Ability to obtain a complete surgical resection is thought to be an important determinant of survival in DSRCT and these data are not available in SEER.[9,13] SEER also does not contain data on new modalities being evaluated for this entity, including HIPEC and monoclonal antibody therapy. Our findings from a large registry study provide a comprehensive assessment of the clinical characteristics in pediatric patients. The poor overall survival rate seen in this study and in previous studies highlights the need to investigate potential novel therapies that might benefit children with this disease.

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