A retrospective analysis of potential prognostic factors in children with rhabdomyosarcoma

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Abstract: A retrospective study was done to identify significant prognostic factors in thirty-nine children with parameningeal or orbital rhabdomyosarcoma who were treated with a combination of chemotherapy and radiation. Statistical analysis was done using the Cox proportional hazard regression model and the study end-point was overall survival. The influence of the analyzed potential prognostic factors was found not to be statistically significant. The estimated 2-year and 5-year overall survivals were 88% and 55% respectively. Patients aged below 6 years, with embryonal rhabdomyosarcoma, who were treated using two-dimensional radiotherapy treatment plans, and girls with orbital rhabdomyosarcoma, had a better overall survival rate.
Keywords: Parameningeal, survival data, alveolar.

Introduction

Sarcomas are malignant tumors of mesenchymal cell origin [1]. Rhabdomyosarcoma (from Greek, rhabdo, meaning rod shape, and myo, meaning muscle) is the most common soft tissue cancer in children [2, 3]. Rhabdomyosarcoma is believed to arise from immature mesenchymal cells that are committed to skeletal muscle lineage. The tumor may occur in any site in the body. The disease was first described in 1854 by Weber but in 1946 Stout provided a clear histological definition when he recognized the distinct morphology of rhabdomyoblasts as being round, strap, racquet and spider forms [2].

Aim

Health systems use valuable resources and personnel thus if such a system is to be used to its greatest effect, the system must undergo regular evaluation, and critique, so that strategies are devised to optimize the service to the greater community. Patients who suffer from rhabdomyosarcoma are a very heterogeneous group. As their prognosis is dependent on a number of factors it is important to define an individual patient's prognosis for a number of reasons. For example

- Identifying those patients who are most likely to benefit from early radiation treatment.
- Providing the radiation oncologist with information to contribute to patient management and treatment.
- Gaining a better understanding of determinants of a disease which should stimulate future research.
- Planning of future clinical trials, for example, selection of patients, stratification, etc.

On the basis of these observations we conducted a retrospective study to identify prognostic factors of the observed clinical outcome in children with rhabdomyosarcoma.

Materials and methods

Thirty-nine patients ranging in age from 1-14 years (median age of 6 years) with histologically proven parameningeal or orbital rhabdomyosarcoma were treated with combined therapy between 01 January 1990 and 31 December 2000. Patient characteristics are summarized in Table 1.

Table 1: Patient characteristics

CHARACTERISTIC	
Age at diagnosis (years)	
Median	6
Range	1 - 14
Gender (number)	
Male	25
Female	14
Histological type (number)	
Embryonal	24
Alveolar	9
Unclassified	6
Primary Site of Tumor (number)	
Ear/ mastoid	6
Nasopharynx	7
Paranasal sinuses	3
Infratemporal/ pterygopalatine fossa	11
Orbit	12

All the patients received multiple-agent chemotherapy with some combination of vincristine (V), actinomycin-D (A), and cyclophosphamide (C) [VAC], ifosfamide, etoposide, VP16 and/ or carboplatinum.

Radiotherapy was delivered , with either a cobalt machine or a megavoltage linear accelerator, five days weekly. Twenty-six patients were treated using photons only, three patients were treated using electrons only and the remaining patients were treated using a combination of both modalities. Radiation doses ranged from 30 Gy to 60 Gy. The timing of radiotherapy relative to the start of chemotherapy varied greatly.

Statistical analysis was based on the patient data available as at June 2005. The statistical analysis was performed using the Cox proportional hazards regression model [4, 5]. Prognostic factors were analyzed and the level of statistical significance was set at 5% ($p < 0.05$).

Results

The overall observed survival, namely living with or without disease, at two years was 88% and at five years was 55%. All the evaluated potential

Table 2: A statistical significance test for prognostic factors in rhabdomyosarcoma.

Prognostic factor	5 year overall survival	5 year overall survival
	p-value	Hazard ratio
Age[1]	0.5657	1.3462
Type of plan[2]	0.5994	0.7500
Histology	0.4152	1.5625
Site of tumor	0.7021	1.2800
Sex	0.4389	1.5714

[1] *Patients stratified at median age*
[2] *2 dimensional - or 3 dimensional treatment plan*

prognostic factors were not found to be predictive of the 5-year overall survival as shown in Table 2.

The effect of the evaluated potential prognostic factors can be explained by the hazard ratio which compares two groups differing in treatments or prognostic variables. The hazard ratio for age was calculated to be 1.3462 at 5 years post treatment. This means that the hazard, namely poorer survival, associated with children above 6 years of age was 1.3462 times greater than those below the age of 6 years.

Children with alveolar rhabdomyosarcoma had a poorer survival rate than those with embryonal rhabdomyosarcoma. Also those patients who had parameningeal rhabdomyosarcoma had a poorer survival than those with orbital rhabdomyosarcoma.

In addition the hazard ratio relating to sex indicates that female patients had a better survival rate than male patients. Patients who were treated using two-dimensional radiotherapy plans had a better survival rate than those treated using three-dimensional plans [6].

Discussion

Results of this study confirm other reports in the literature which suggest a poorer prognosis for patients with alveolar rhabdomyosarcoma as shown by a hazard ratio of 1.5625 [2]. Patients with tumors of the orbit had a better survival than those who had a tumor at the parameningeal site. These findings confirm results from other clinical studies [2].

In general patients who were treated using two-dimensional plans showed a better survival rate than those treated using three-dimensional plans. This contrasts with the intuitive perception that three-dimensional plans should yield better survival rates. Nonetheless it should be appreciated that three-dimensional planning offers the ability to limit radiation dose to critical organs and this is of particular importance in a pediatric population whose maturing tissues have substantial risk of morbidity with high dose irradiation [7].

The inherent limitations of retrospective studies are recognized. Such studies can at best provide broad indications of effect and raise questions for future studies and be baselines for further data accrual. Patients who are lost to follow-up, and are not known to be dead, are one of main challenges in reporting retrospective studies. Three of the patients in this group were not followed-up after treatment because they were not resident in South Africa.

In addition to the above-mentioned limitations it is important to acknowledge that the sample size in this study was small. It should be appreciated that a prognostic factor is rarely a strong predictor in isolation from other prognostic factors. These limitations need to be taken into consideration when interpreting the results.

Conclusion

The present retrospective analysis of thirty-nine pediatric patients, with histologically confirmed rhabdomyosarcoma, shows that survival data on this patient population indicates that none of the investigated prognostic factors were statistically significant.

Analysis of the patient population based on the hazard-ratio method indicates that

a) Male patients had a poorer survival rate than female patients.
b) Patients with orbital rhabdomyosarcoma had a better survival rate than those with parameningeal rhabdomyosarcoma.
c) Patients treated using two-dimensional radiotherapy treatment plans had a better survival rate than those treated using three-dimensional plans.
d) Patients aged 6 years and below had a better survival rate than those older than 6 years.
e) Patients with embryonal rhabdomyosarcoma had a better survival rate than those with alveolar rhabdomyosarcoma.

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