



Characteristics and oncologic outcomes of patients with Ewing Sarcoma of the scapula

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ABSTRACT

Background and objectives: Ewing sarcoma is the second most common bone sarcoma of childhood. Ewing sarcomas of the scapula are rare, with little known about their characteristics and outcomes. In this study, we describe the demographic characteristics, tumor characteristics, and oncologic outcomes of patients with Ewing sarcoma of the scapula.

Methods: This is a retrospective case series of 34 patients treated at 3 urban hospitals between 1993 and 2014 for Ewing sarcomas affecting the scapula. Their demographic data, tumor characteristics, and oncologic outcomes are reported and contrasted with data on Ewing sarcoma described in the literature.

Results: Patients in our case series were 59% male. The average age at diagnosis was 16 years. 44% of patients had metastatic disease at presentation. 26% of patients had a tumor size >8 cm in largest dimension at diagnosis. 9 patients in our series had the t(11; 22) translocation present. Patients had a survival rate of 68% at five years. No patients had local recurrence of disease. **Compared with findings reported in the literature concerning Ewing sarcoma affecting other locations, patients with Ewing sarcoma of the scapula were slightly older at time of diagnosis, had a lower percentage of tumors with size > 8 cm in largest dimension at presentation, and more commonly had metastatic disease at presentation. Patients in our cohort had a 5-year survival rate of 68%, which is higher than the rate of approximately 55% as reported in the general literature.**

Conclusions: In this study, we describe a retrospective case series of thirty-four patients with Ewing sarcomas of the scapula. This is the largest case series to date of Ewing sarcoma affecting this location to our knowledge. These results will contribute to the understanding of the clinical profile and oncologic behavior of Ewing sarcomas affecting the scapula.

1. Introduction

Ewing sarcoma is a malignant tumor of mesenchymal origin that is the second most common malignant bone tumor of childhood, accounting for 16% of all primary bone tumors [1]. Ewing sarcoma arises in the lower extremities, pelvis, or chest wall as the three most common locations, respectively. By contrast, Ewing sarcomas arising from other locations in the body are rare, and those arising from the scapula comprise fewer than 4% of all Ewing sarcomas [2]. As such, there is a

paucity of literature on Ewing sarcomas affecting this location, with only several small case reports published [3–6]. In addition, very little is known about the demographics, tumor characteristics, or oncologic outcomes of patients with Ewing sarcomas of the scapula. Given the lack of information available on Ewing sarcomas affecting the scapula, we sought to identify 1) the demographic characteristics, 2) the tumor characteristics, and 3) the oncologic outcomes of 34 patients with Ewing sarcomas of the scapula, and compare these parameters with those of patients with Ewing sarcoma described in the general literature.

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2. Methods

This is a retrospective case series of 34 patients who were treated at three large, urban, adult hospitals between 1993 and 2014 for Ewing sarcomas affecting the scapula. In this IRB-approved protocol, informed consent was waived. Patients were identified from databases at each hospital and patient data was collected from paper and electronic medical records. All patients were de-identified and assigned a study number for purposes of statistical analyses.

All patients in our database with a diagnosis of Ewing sarcoma affecting the scapula were included in this study. Diagnoses of Ewing sarcoma were confirmed by tissue biopsy in each patient. Those who met the inclusion criteria of a tissue diagnosis of Ewing sarcoma involving the scapula were included in this study. Exclusion criteria were patients with extra-skeletal Ewing sarcoma affecting the scapula.

The diagnosis and location of Ewing sarcoma affecting the scapula was confirmed in all patients by tissue diagnosis. The ethnicity of each patient was noted where recorded. Any prior history of malignancy was confirmed via electronic and paper medical record review. The presence of the t (11; 22) translocation, tumor viability, tumor size in largest dimension, and any tumor markers present in the tumor tissue were obtained from the pathology reports for each patient. The 5-year survival status of each patient was obtained from chart review. The status of local recurrence was obtained at each patient's last follow-up appointment.

3. Results

3.1. Demographic characteristics

Patients in our case series were 59% male (20/34) and 41% female (14/34) (Table 1), similar to 60% male and 40% female as reported from the Surveillance, Epidemiology, and End Results (SEER) database [7]. 53% (18/34) of patients in our series were white compared to 92% from SEER [7]. They had an average age at diagnosis of 16 compared to an average age at diagnosis of 15 for Ewing's sarcoma in general [1].

3.2. Tumor characteristics

In our case series, 26% (6/34) of patients had a tumor size >8 cm in largest dimension at diagnosis compared with 56% of patients at time of

Table 1

Demographic and tumor characteristics and outcomes of ewing sarcoma of the scapula compared to data reported in the literature.

	Case Series Data	As reported in literature
Male vs. Female	59% male (n = 20), 41% female (n = 14)	60% male, 40% female
% White Ethnicity	53% (n = 18)	92%
Average age at diagnosis	16	15
% of Patients with Tumor Size > 8 cm in Largest Dimension	26% (n = 6)	56%
% of Patients with t(11;22) Translocation	75% where reported (9 of 12 patients)	92%
% of Tumors Positive for Vimentin	35% where reported (6 of 17)	74%
% of Tumors Positive for CD99	82% where reported (14 of 17)	90%
% of Tumors Positive for NSE	18% where reported (3 of 17)	58%
% of Tumors Positive for Leu-7	6% where reported (1 of 17)	58%
% of Tumors Positive for S100	24% where reported (4 of 17)	25.4%
5-Year-Survival	68% (n = 23)	55%
% of Patients with Metastatic Disease at Presentation	44% (n = 15)	27%

diagnosis in the SEER database [7]. Average tumor viability for surgical cases was 21%.

75% (9/12 patients) of patients with known data in our series (9 of 12 patients) had the t (11; 22) translocation present compared with 92% in published literature [8]. Tumors in this case series had 35% (6/17 of tumors) and 82% (14/17 of tumors) expression of vimentin and CD99 among reported data, respectively, compared with 74% and 90% as reported in prior studies [9–12]. In addition, 18% (3/17 of tumors) of tumors in the case series expressed neuron-specific enolase (NSE) compared with 58% reported in prior literature [13]. Tumors in this case series also expressed Leu-7 and S100 at a rate of 6% (1/17 of tumors) and 24% (4/17 of tumors) respectively, compared with 58% and 25.4% in published literature, respectively [13,14].

3.3. Oncologic outcomes

Twelve of thirty-four patients received multimodal therapy consisting of surgical resection and pre- and post-operative chemotherapy. Three patients received surgery and adjuvant chemotherapy. Eleven patients received surgery, chemotherapy, and radiation. One patient was treated with surgical resection alone. Three patients were treated with chemotherapy and radiation. One patient was treated with chemotherapy alone. Four patients did not have treatment regimens recorded from the available records.

The most common reported chemotherapy regimen was vincristine, cyclophosphamide, and doxorubicin alternating with ifosfamide and etoposide (CAV-IE) which was used in 9 patients. Other chemotherapy regimens used (in the case of reduced cardiac ejection fraction) included adjuvant vincristine, irinotecan, and temozolomide following neo-adjuvant CAV-IE (n = 2 patients), CAV-IE plus vincristine, topotecan, and cyclophosphamide (n = 3 patients), actinomycin substituted for doxorubicin in CAV-IE (n = 1 patient), and CAV-IE plus irinotecan and temozolomide (n = 1 patient).

Patients in our series had a 5-year survival rate of 68% (23/34) compared to an overall 5-year survival rate of 55% for Ewing sarcoma from SEER [7]. 44% (15/34) of patients in our series had metastatic disease at presentation compared with 18–25% in the general literature [2,15]. Fourteen patients (41%; 14/34) had pulmonary metastases at the time of presentation. Other locations of metastases at the time of presentation were chest wall (n = 1 patient), cerebrospinal fluid (n = 2 patients), retroperitoneum (n = 1 patient), spinal cord (n = 1 patient), bone (n = 3 patients), and lymph nodes (n = 1 patient). The data that support the findings of this study are available from the corresponding author upon reasonable request.

4. Discussion

To date, there are few studies of Ewing sarcomas affecting the scapula, and correspondingly little comparison of the results of these studies with the current literature concerning Ewing sarcomas in other locations in the body [3–6]. Here, we have described a retrospective case series of thirty-four patients with Ewing sarcomas of the scapula and contrasted the findings from our case series with those reported in the current literature. This is the largest case series of Ewing sarcoma affecting this location to our knowledge. In addition, we present a focused review of the literature comparing the descriptive statistical findings in our series of scapular Ewing sarcoma with those reported in other studies of Ewing sarcoma.

This study was notably limited by a lack of sufficient power to conduct inferential statistics, which is often an unavoidable limitation of studies investigating an overall uncommon tumor in an even more uncommon location. In addition, we do not investigate a particular intervention or surgical technique for the treatment of Ewing sarcomas arising specifically in the scapula in this case series. Nevertheless, we do describe the demographic and tumor characteristics as well as oncologic outcomes of these rare tumors when they are treated with the standard

of care for Ewing sarcomas in other locations in the body, and contrast these parameters with those of Ewing sarcomas occurring in other locations in the body as described in the existing literature. Given that our case series is the largest of any existing case report or series describing Ewing sarcoma involving the scapula in the literature, it is our hope that our results will help to inform larger future studies investigating the clinical profile and oncologic outcome of Ewing sarcomas affecting the scapula. Indeed, we hope that despite our small cohort size, our case series will promote discussion on potential underlying mechanisms of disease pathogenesis that might serve to explain the subtle differences noted between the Ewing sarcomas described in our case series versus Ewing sarcomas in general.

Patients with Ewing sarcomas of the scapula are slightly older at time of diagnosis in our series. Ewing sarcomas of the scapula were also associated with Caucasian ethnicity with lower frequency than Ewing sarcomas reported in the general literature. It is interesting to note that the patients in our case series had an above average 5-year survival when compared patients with Ewing sarcomas in other locations as described in the literature, despite the fact that the patients in our series were older than the average Ewing sarcoma patient at time of diagnosis [1,2]. In fact, patients that are older at time of diagnosis have actually been reported to have poorer outcomes when compared with younger patients [2,16–19]. For example, studies in North America have demonstrated that patients aged 10–17 years have a higher relative risk of 1.4 when compared with patients younger than 10 years of age; in addition, patients older than the age of 18 were found to have an even poorer relative risk of 2.5 compared with patients younger than 10 [20–22].

The above average survival stands in contrast to prior studies that have shown that patients with Ewing sarcoma in the distal extremities have the best prognoses, followed by patients with tumors in the proximal extremities, followed by tumors in central or pelvic sites [2,16,17]. Given the centrality of the scapula to the body, it might be expected that these tumors should actually have a relatively poorer prognosis and thus be associated with lower 5-year survival rates than Ewing sarcomas in general.

There was a smaller proportion of patients with a tumor size greater than 8 cm in largest dimension at time of diagnosis when compared to patients with Ewing sarcoma in general. This observation, taken together with the observation of improved 5-year survival in our series, is supported by the literature, in which tumor size has been demonstrated to be an important prognostic factor. Indeed, the cutoff value of a single dimension greater than 8 cm has been used to define larger tumors, which are associated with unfavorable sites [17,23].

In our case series, Ewing sarcomas of the scapula also had a lower occurrence of the t (11; 22) translocation than reported for Ewing sarcomas in other locations. There were also lower rates of vimentin, CD99, NSE, and Leu-7 positivity in Ewing sarcomas of the scapula than reported for Ewing sarcomas in previous investigations. Current literature is less clear in demonstrating a convincing association between the presence of these markers and tumor prognosis. For example, one report analyzing the histological and immunohistochemical features of a large series of patients with Ewing sarcomas failed to demonstrate a difference in survival based on vimentin or NSE positivity. Another study, however, demonstrated a higher median survival in patients with NSE positivity. This report also suggested that Leu-7 positivity was associated with increased median survival in localized disease [11,14].

The tumor markers of CD99 and S100 as reported in our series have also not been conclusively shown to hold prognostic value in current literature. However, one report did demonstrate that genetic knock-down of CD99 in human Ewing sarcoma cells reduced their tumor-forming potential when xenografted into mice [24].

Patients in our series had an average tumor viability of 21%, or an average tumor necrosis of 79%. Prior literature has suggested that tumor necrosis directly correlates with disease prognosis, with one large study demonstrating increasingly poor outcomes corresponding with degree

of tumor necrosis, reporting a median survival of 28 months for grade I necrosis (less than 10%), 16 months for grade II (10–50%), and 11 months for grade III (greater than 50%) [11].

Patients with Ewing sarcomas affecting the scapula more commonly had metastatic disease at presentation compared with patients with Ewing sarcomas in other locations. Most patients with metastases in our series had lung involvement. Metastatic sites can offer prognostic information as the literature demonstrates that patients with metastatic disease confined to the lung confer a better prognosis than Ewing sarcoma which has spread to extrapulmonary sites [2,17,25]. Additionally involvement of only one lung has been shown to have better outcomes than those with bilateral lung involvement [26]. However, the number of pulmonary lesions in metastatic Ewing sarcoma does not appear to correlate with outcome [26].

5. Conclusion

In summary, Ewing sarcomas affecting the scapula have several subtle differences with regard to demographics, tumor characteristics, and oncologic outcomes when compared with Ewing sarcomas affecting other locations in the body. Although this case series is small, it is our hope that the descriptive findings of this study, coupled with a focused comparison of our case series study parameters to those reported in the current literature, will promote discussion and serve to prompt larger future studies further investigating the understanding and treatment of Ewing sarcomas arising in the scapula.

Study locations

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Author statement

Caleb M. Yeung: Conceptualization, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing; Courtney Kaiser: Conceptualization, Investigation, Formal analysis; Manuel Peleteiro-Pensado: Investigation; Irene Barrientos-Ruiz: Investigation; Eduardo J. Ortiz-Cruz: Investigation, Supervision; Megan E. Anderson: Supervision, Conceptualization; Kevin A. Raskin: Supervision, Conceptualization; Santiago A. Lozano-Calderon: Supervision, Conceptualization, Project administration, Writing – review & editing

Declaration of competing interest

None.

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