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Original research article

The impact of local control timing in Ewing sarcoma

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ABSTRACT

Aim: To assess the impact of delay in local control on survival outcomes of Ewing sarcoma (ES) patients.
Background: The cornerstone of therapy of localized ES includes chemotherapy and local control with surgery or radiotherapy. We sought to assess the impact of delay (>15 weeks) in timing of local control on survival outcomes of ES patients.
Methods: Data of consecutive patients with primary non-metastatic ES of the extremities, treated at a single institution were collected. The impact of delay of timing for local control, demographics, and disease characteristics on overall survival (OS) was analyzed.
Results: A total of 43 patients with ES of the extremity were included. All patients received neoadjuvant chemotherapy. Local control was by surgery in 36 patients and definitive radiation in 7. A total of 16 patients had delay in local control. At a median follow of up of 48 months, patients with delay in local control had significantly inferior OS compared to those with optimal local control timing (5-year OS 56% vs. 80%, respectively, $p = 0.044$). Other factors that predicted inferior OS included definitive radiation as opposed to definitive surgery (5-year OS 25% vs. 79%, respectively, $p = 0.041$) and tumor necrosis <90% as opposed to ≥90% (5-year OS 55% vs. 90%, respectively, $p = 0.01$).
Conclusion: Delay in definitive therapy, local control with radiation as opposed to surgery and poor post-chemotherapy tumor necrosis predict inferior OS in ES. Adopting strategies to minimize delay in local control could improve survival outcomes.

1. Introduction

Ewing sarcoma (ES) is a rare malignant bone tumor that has a predilection to the pediatric and adolescent age groups. It is an aggressive malignancy; treatment usually includes chemotherapy and intensive local control of the disease by surgical resection, radiation therapy, or both. This approach has resulted in a 5-year event free survival (EFS) of 65–75% in patients with localized disease.[1–6]

The American Intergroup Ewing's sarcoma trial (INT-0091 - POG-8850/CCG-7881) has shown that adding ifosfamide and etoposide (IE) to vincristine, actinomycin-D, cyclophosphamide, and doxorubicin (VDC) improves the EFS of patients with localized ES and has introduced IE alternating with VDC (VDC-IE) as a standard chemotherapy regimen.[5] Further improvement in outcome was achieved by interval compression of the cycles through a Children's Oncology Group AEWS-0031 randomized trial.[7]

Complete tumor resection is a critical prognostic factor for ES. Patients who present at locations that are not amenable for complete resection such as the spine or pelvis have inferior oncologic outcomes compared to ES of the extremities.[4–6] For this reason, we focused this review on the extremity location in order to decrease the confounding factors and to test the merit of local control delay on outcomes of ES patients.

Complete surgical resection is considered a standard local control modality. Radiotherapy is another standard option that is usually selected for patients with unresectable tumors, and for patients who refuse or do not accept the surgical morbidities. Adjuvant radiotherapy is indicated for patients with positive surgical margins and those with poor tumor necrosis.[6–8]

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In the current paper, we intended to assess the impact of such delays on disease recurrence and survival.

2. Methods

2.1. Patients population

We searched the electronic records of patients with ES treated between Jan 2006 and Dec 2017 at the King Hussein Cancer Center, Amman-Jordan, to identify eligible cases. Data collection commenced following acquisition of institutional review board approval. Patients were required to have a pathologically confirmed diagnosis of ES and presented with a primary localized disease. Patients with localized non-extremity ES and those who progress on primary VDC-IE chemotherapy were excluded. We collected data on age, gender, location of primary tumor, details of chemotherapy, and type of definitive therapy (surgery or definitive radiotherapy). Data on margin status, extent of tumor necrosis and any adjuvant radiotherapy were documented for patients who underwent local control by surgical resection. Timing of local control was defined as interval between the start of neoadjuvant chemotherapy and date of surgery or first radiotherapy fraction. Local control is typically performed on week 12 of the VDC-IE protocol. Delay in local control was defined as implementing local control modality later than 15 weeks from initiating VDC-IE chemotherapy. Additionally, we gathered data on dates of any local or systemic recurrences, and time of last follow up or death. Overall survival (OS) was defined as the time from diagnosis until last follow up or death. Survival of patients who lost follow up was censored at the time when they were last seen. Disease free survival (DFS) was defined as the time of diagnosis until first documentation of disease recurrence, last follow up or death.

2.2. Treatment protocol

All patients were treated with a standard chemotherapy protocol; the VDC-IE chemotherapy regimen. At week 10–11, all patients had computed tomography (CT) for the chest and magnetic resonance imaging (MRI) of the extremity for assessment of response. Selection of the optimal local control was determined following discussion of each case at the multidisciplinary sarcoma meeting with the intention to provide local control at week 12. Whenever feasible, local control was preferably done by surgery. Radiotherapy was selected for tumors that were deemed unresectable or when surgery was thought to be significantly morbid. Adjuvant radiotherapy was considered for positive surgical margins or poor tumor necrosis (extent of necrosis <90%). The definitive radiation dose was 55.8 Gy in 1.8 Gy per fraction, radiation target was the initial tumor volume for phase one (45 Gy) then boost (10.8 Gy) to the same bony volume and post-chemotherapy soft tissue volume with 2 cm margin. Chemotherapy was typically continued in an adjuvant setting following surgery or definitive radiotherapy per VDC-IE protocol.

2.3. Statistical analysis

We utilized descriptive statistics to describe the characteristics of the patient population through proportions, means, and medians. OS was estimated by the Kaplan-Meier method. The primary objective was to compare the OS between the group who had local control within 15 weeks and those whose local control was delayed. In addition, we performed univariate analysis and assessed the effect of age (at cutoff = median age), gender, location of the tumor, type of definitive therapy, and extent of tumor necrosis on OS. The log-rank test was utilized to compare survival between groups. All p-values of <0.05 were considered statistically significant. The chi-square test was used to compare proportions. All statistical analyses were performed using SPSS version 17 (SPSS Inc, Chicago, IL).

Table 1
Baseline demographic and treatment characteristics for the 43 patients with ES of the extremity.

Characteristic	N (%) or mean/median
SSAge	Median: 13 Range: 1–20
Follow up time	Median: 48 months Range: 8–158 months
Male	24 (56%)
Female	19 (44%)
Location:	
Femur	12 (28%)
Tibia	11 (26%)
Humerous	10 (23%)
Foot	5 (12%)
Fibula	2 (4.5%)
Radius	2 (4.5%)
Hand bones	1 (2%)
Type of definitive therapy (local control):	
Surgery	36 (84%) (30 had LSS and 6 had amputations)
Definitive radiotherapy	7 (16%)

LSS, limb salvage surgery.

3. Results

3.1. Patients' characteristics

Between January 2006 and Dec 2017, 182 pathologically confirmed ES cases presented to our center. Seventeen patients (9%) presented for opinion or were referred to receive local control with surgery or radiation and then they lost follow up; those patients were excluded from analysis. Of the remaining cases, 42 (25%) were not eligible because they presented with metastatic disease. All the remaining 123 patients presented with primary localized ES and were treated and followed up at our center. Sixty-nine patients had non-extremity locations and were deemed non-eligible. Two patients were excluded for refusal of local therapy, three because they lost follow up within a month after local control, 3 because of missing/ unclear data about the date and type of local control, and 3 because of significant progression on primary neoadjuvant chemotherapy.

A total of 43 patients remained eligible for analysis; 5 (12%) had extra-osseous disease, whereas the rest (38; 88%) had osseous disease. The median age of included patients was 13 years. All patients initiated the VDC-IE protocol with the intention to provide local control at week 12. Discussion of local control for all patients was carried out at the sarcoma multidisciplinary meeting between weeks 9 and 12 of the protocol. Majority of tumors were located in the lower extremity (n = 30; 70%). Median interval from diagnosis to local control was 18 weeks, range 3.0–13.5 months. Other relevant patient and treatment characteristics are summarized (Table 1).

3.2. Operative outcomes

A total of 36 patients had surgical resection of the primary tumor (Table 1). Limb salvage surgery (LSS) was performed for 30 patients (83%), whereas 6 (17%) had amputations (below knee amputation for 4 patients; one patient had first ray foot amputation, and one had shoulder disarticulation). The surgical margins were negative (R0) in 34 patients (94%) and positive (R1) in 2 6%). Necrosis was significant (≥90%) in 19 patients (53%), poor (<90%) in 13 (36%), and not reported for 4 (11%). Post-operative adjuvant radiotherapy was delivered for 8 patients (22%), while 26 (72%) did not receive

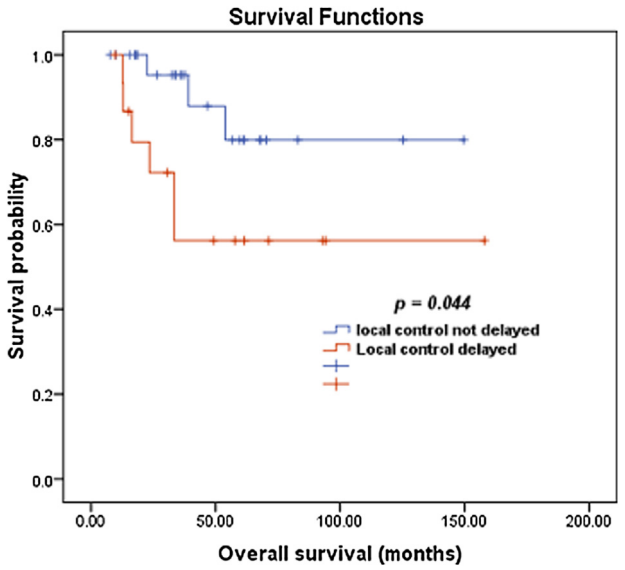

Fig. 1. Kaplan–Meier overall survival estimation according to timing of local control.

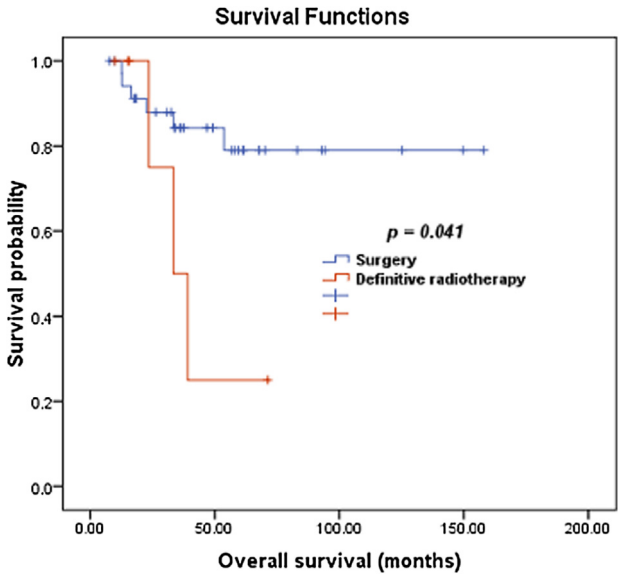

Fig. 2. Kaplan–Meier overall survival estimation according to type of definitive therapy.

adjuvant radiotherapy, and data was missing for additional two (6%).

3.3. Survival outcomes

At a median follow up of 48 months, the 5-year OS for the entire series was 71%.

A total of 13 patients developed a recurrence (systemic with or without local) at a median time of 21.5 months from definitive local therapy (range: 1–29 months). Local recurrence was observed in 5 patients at 2, 20, 22, 22, and 26 months of local therapy. The 5-year DFS was 63%, while median DFS was unreached.

In univariate analysis, OS was significantly superior in patients with optimal timing of local control compared to patients whose local control was delayed, with 5-year OS rate of 80% and 56%, respectively, $p = 0.044$ (Fig. 1).

There was a non-significant trend towards better DFS in patients who had optimal timing of local control compared to those with a delay, with 5-year DFS of 71% vs. 51%, respectively, $p = 0.16$.

Overall survival was superior for patients treated with definitive surgery compared to definitive radiation, median OS unreached vs. 33.4 months; 5-year OS 79% vs. 25%, respectively, $p = 0.041$ (Fig. 2). Among patients who underwent surgery, tumor necrosis ≥90% was associated with superior OS compared to necrosis <90%.; 5-year OS 90% vs. 55% respectively, $p = 0.01$ (Fig. 3). Other factors including age, gender, and location of tumor did not influence OS. The effect of margin status on OS was not tested because of the small number of patients with positive margins (only two patients).

We did not observe a significant difference in local recurrence rate between the 16 patients who had delay in local control and the 31 patients who had optimal timing of local control; local recurrence occurred in 2 (13%) and 3 patients (11%), respectively, $p = 0.62$.

Finally, we underwent an exploratory analysis to assess factors that could be associated with delay in local control. Patients with tumors in the humerous had a non-significant trend towards a higher frequency of delay in local therapy (Table 2).

4. Discussion

Local disease control is the corner stone in management of patients with ES, selection of treatment modality is optimal under the umbrella of multidisciplinary clinic. A large analysis from the

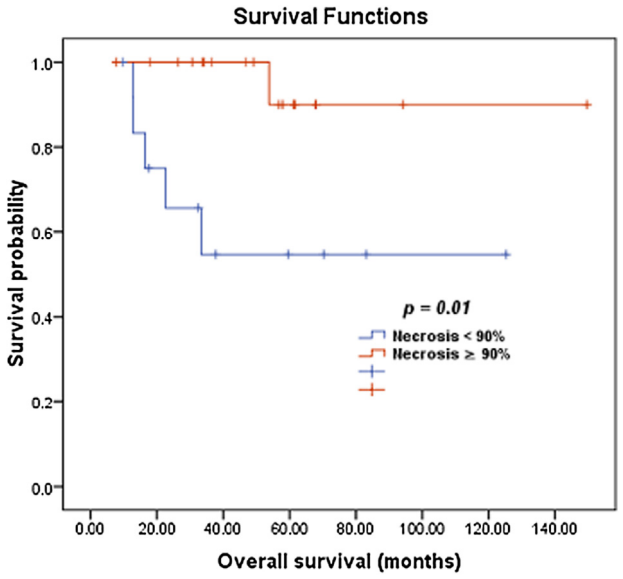

Fig. 3. Kaplan–Meier overall survival estimation according to extent of tumor necrosis in the resected tumor.

Children's Oncology Group revealed a greater risk of local failure in patients treated with radiation alone when compared with surgery; our results were compatible with this finding. Currently, surgery is the preferred modality of therapy, especially in resectable tumors where risk of morbidity is low.[7,9] Nevertheless, radiotherapy remains the backbone of successful local treatment in large, locally advanced tumors and those involving axial skeleton. For this reason, we performed this analysis solely on extremity tumors in order to make this group more homogenous and to decrease the potential confounding factors.[10]

Multiple factors influence the outcomes of ES patients. For instance, percent of necrosis (>90) has been correlated with improved treatment results.[11–14] In this cohort, we observed a statistical significant improvement in OS for patients with good necrosis. Surgical margin is another reported prognostic factor; however, in this study it was not tested because only two patients had positive surgical margins.[11,15–16] Age is another factor, which

Table 2
Frequency of delay in local therapy by patient and treatment characteristics.

Variable	Local control delayed	Local control not delayed	*p*-Value
Age:			
<12 (n = 13)	5 (39%)	8 (61%)	0.59
≥12 (n = 30)	8 (27%)	22 (73%)	
Gender:			
Male (n = 24)	8 (33%)	16 (67%)	0.39
Female (n = 19)	8 (42%)	11 (58%)	
Location:			
Femur (n = 12)	5 (42%)	7 (58%)	0.49
Others (n = 31)	11 (36%)	20 (64%)	
Location:			
Humerous (n = 10)	6 (60%)	4 (40%)	0.093
Others (n = 33)	10 (30%)	23 (70%)	
Location:			
Upper extremity (n = 13)	7 (54%)	6 (46%)	0.13
Lower extremity (n = 30)	9 (30%)	21 (70%)	
Type of local control:			
Surgery (n = 36)	12 (33%)	24 (77%)	0.22
Radiotherapy (n = 7)	4 (57%)	3 (42%)	
Requirement of amputation:			
Yes (n = 6)	2 (33%)	4 (67%)	0.61
LSS or radiotherapy (n = 37)	14 (38%)	23 (62%)	

was evaluated in multiple series, adults seem to carry worse prognosis than pediatric patients, in this study almost all of our patients were pediatric or adolescent, so it was not feasible to look at this postulation.[17]

Although many prognostic factors have been tested in the literature, the effect of delay in timing of local control remains unclear. Only few retrospective series investigated the correlation between treatment delay and disease outcomes.[12,17] Current pediatric protocols call for local control at week 12 from starting neoadjuvant chemotherapy, and at our institution, we follow a similar approach. The Cooperative Ewing's Sarcoma Study (CESS-86) showed that the 5-year survival after local control by radiotherapy alone was nearly identical to those who had surgery alone: 67% and 63%, respectively. However the EICESS-92 showed significantly worse survival in the definitive radiotherapy treatment group compared to other modalities. One explanation could be the timing of delivering radiotherapy as dictated by the protocol; radiotherapy was started at week 9 after starting chemotherapy in the CESS-86 protocol while it was after 12–18 weeks in the EICESS-92 protocol.[18,19] In another observation, Burgers et al. found that the mean length of neoadjuvant chemotherapy prior to starting radiation therapy in pelvic ES tended to be shorter in patients without local relapse.[20,21]

A review of 53 adult and pediatric ES patients treated at Hospital for Sick Children, Toronto, showed that the outcome of adult patients with localized ES was inferior compared with pediatric patients, this difference was partially attributed to the timing of local therapy, where the median time for local control was 3.7 months in pediatric patients compared to 7.4 months in adults ($p = 0.0003$), the 3-year OS was 81% for pediatric patients and 59% for adults ($p = 0.02$).[17] Another study by Lin et al. investigated disease outcomes in patients treated with local control at 6–15 weeks after chemotherapy compared with ≥16 weeks. In that large cohort, they found a statistical significant difference in OS at 5-year 78.7% vs. 70.4% and 10-year OS 70.3% vs. 57.1%, respectively. This effect was more pronounced in patients who received radiation alone.[22] In our study, the OS in patients with delayed local control (>15 weeks) was significantly inferior when compared with early treatment (5-year OS: 56% vs. 80%, $p = 0.044$), which came in concordance with previous studies. Furthermore, we demonstrated better DFS in patients who had optimal timing of local control compared to those with delay (5-year DFS: 71% vs. 51%, $p = 0.16$), but it was not powered to detect a statistical significant difference.

Delay in local control can occur for variety of reasons. Such factors include patients' hesitancy about surgery or radiotherapy and initial refusal of local control due to patients' concern about the morbidity of surgery or the toxicity of radiotherapy. Additionally, delay may be related to long waiting lists for surgery and radiation, or waiting for endoprosthesis.

In this review, the local relapse occurred exclusively in the first two years of follow-up, this fact is consistent with previous reports in the literature, which demonstrated local recurrence in the first 24 months of follow-up.[11,13]

We acknowledge limitations of this analysis, the retrospective nature and associate selection bias, in addition to relatively small number of patients. However, the patients in this study were managed under the care of a multidisciplinary team who treated them according to the contemporary guidelines. To the best of our knowledge, only one study in the literature investigated mainly the effect of treatment delay in patients with ES.[22] Our results come in concordance with their findings and it will add to the current body of evidence.

5. Conclusion

This study investigated the effect of local control delay (>15 weeks) after neoadjuvant chemotherapy in patients with ES. Our results suggest that this delay is associated with inferior oncologic outcomes. A multidisciplinary team should provide timely local control, through adopting strategies to minimize the delay; such as discussing the management options earlier with the patients and their families and counseling them on the effects of local control delay. Additionally, these patients should be given priority on waiting lists.

Patients managed with radiation alone showed inferior results as opposed to surgery, although this conclusion may be influenced by multiple confounding factors. Another factor is poor tumor necrosis, which is a sign of poor tumor response and is associated with worse OS.

Further prospective trials are warranted to investigate the optimal treatment timing, and to examine other prognostic factors.

Conflict of interest

All authors declare no conflict of interest, and this work was accomplished without funding or grant.

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