HAND (2015) 10:602–606
DOI 10.1007/s11552-015-9760-0

REVIEW

Extraskeletal osteosarcoma of the hand: the role of marginal excision and adjuvant radiation therapy

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Published online: 17 April 2015

Abstract
Background Extraskeletal osteosarcoma of the hand is rare, and its optimal modality of local control is not currently known.
Methods A literature search was performed to identify studies that describe the treatment and outcomes of extraskeletal osteosarcoma. A second literature search was performed to identify studies that describe the treatment and outcomes of extraskeletal osteosarcoma of the hand specifically.
Results The role of adjuvant radiation for extraskeletal osteosarcoma is not well defined. All cases in the literature describing treatment of extraskeletal osteosarcoma of the hand utilized amputation, and none of the patients described received radiation therapy. However, there are multiple reports showing excellent local control, minimal toxicity, and superior functional outcome with limb conservation and radiation rather than amputation of the hand in pediatric and adult soft tissue sarcoma.
Conclusion For extraskeletal osteosarcoma of the hand, we recommend a treatment approach with the goal of preservation of form and function using limb-sparing surgery and planned postoperative radiation.

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Keywords Limb salvage · Radiation therapy · Soft tissue sarcoma · Osteosarcoma · Hand

Background

Extraskeletal osteosarcoma (ESOS) is a soft tissue sarcoma (STS) characterized by the production of malignant osteoid or bone. By definition, ESOS does not involve or attach to the skeleton. ESOS is rare, accounting for 2–5 % of osteosarcomas and <1 % of STS [12, 18]. ESOS of the hand is even more unusual, with three reported cases in the literature [2, 4, 20].

Adjuvant treatment with radiation therapy (RT) for ESOS is not well defined. The hand specifically is a uniquely challenging site to irradiate given its functional importance. Surgery with chemotherapy is the accepted standard for treatment of osteosarcoma of osseous origin, including osteosarcoma of the bones of the hand [6, 13]. RT is used rarely as primary treatment for osteosarcoma of bone and more commonly reserved for palliation or distant metastases. While extremity STS is commonly approached with limb-sparing surgery and adjuvant RT [10, 16], limb conservation with adjuvant RT for ESOS of the hand has not previously been published. We review the current literature describing the characteristics, treatment, and outcomes of ESOS. We then review the literature describing ESOS of the hand specifically and discuss preservation of form and function using marginal excision and RT.

Methods

To review the characteristics, treatment, and outcomes of ESOS, we performed a MEDLINE literature search

identifying studies that met the following inclusion criteria: (1) reported on 15 or more cases of ESOS (all sites of disease included); (2) described the treatment modalities employed; (3) reported on local control and/or survival. We found a total of 10 retrospective reports meeting criteria. Only studies published in English and involving human subjects were considered. No reports were excluded based on study quality given the paucity of reports.

To review the treatment and outcomes of ESOS of the hand specifically, a second MEDLINE literature search was performed with the following inclusion criteria: (1) reported on ESOS arising specifically from the hand; (2) identified the treatment modality used; (3) reported on outcome. Three case reports describing ESOS of the hand were identified.

Results

ESOS Characteristics

There are less than 400 cases of ESOS reported in the literature [1, 3]. The median age at diagnosis is during the sixth to seventh decade, rather than the second decade as with primary osteosarcoma of the bone. The most common location at presentation is the lower extremity, specifically the thigh, and the most common site of distant spread is the lungs [3, 5, 17]. Histologic sections demonstrate a spindle cell proliferation with a chondromyxoid background and osteoid formation (Fig. 1). ESOS is almost always a high-grade sarcoma, with less than 10 cases of low-grade ESOS described [1, 17, 21].

ESOS Treatment and Outcomes

Table 1 summarizes the 10 retrospective literature series describing ESOS. Surgery is the primary modality of treatment, with RT and chemotherapy given inconsistently and without standardized indications. The 3–5-year overall survival reported among the different reports varies widely, ranging from 25 to 77 %, while local tumor control has

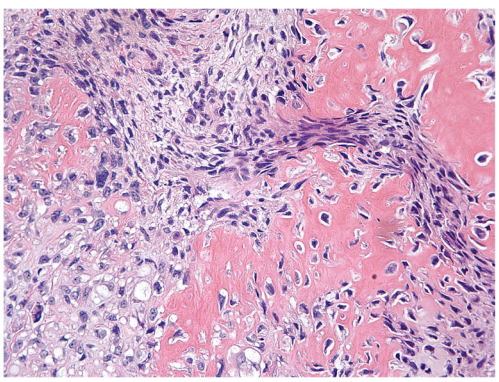

Fig. 1 Histologic sections show a malignant neoplasm with high-grade nuclear pleomorphism and osteoid formation (300×)

Table 1 Retrospective series describing extraskeletal osteosarcoma

Study	Number of patients	Median age (years)	Surgery (%)	Radiation (%)	Chemotherapy (%)	Local control (%)	Overall survival (%)
Sordillo (1983) [18]	48	51	82	13	0	31[a]	34[a]
Chung (1987) [5]	88	59	89	11	15	57[a]	38.5[a]
Lee (1995) [9]	40	51 (mean)	100	28	5	55[a]	37[c]
Lidang Jensen (1998) [11]	25	67	100	28	14	64[a]	<25[c]
McCarter (2000) [12]	15	61	100	33	40	93[a]	50[c]
Ahmad (2002) [1]	60	55	92	16	63	82[c]	n/a
Goldstein-Jackson (2005) [7]	17	44	94	6	94	71[a]	77[b]
Torigoe (2007) [21]	20	50 (mean)	95	40	75	75[c]	66[c]
Sio (2014) [17]	37	55	85	48	42	80[c]	52[c]
Choi (2014) [3]	53	64	100	43	31	81[a]	61[b]

[a] Crude rate
[b] 3-year rate
[c] 5-year rate

been similarly variable, with median values of 73 % [1, 3, 5, 7, 9, 11, 12, 17, 18, 21].

A retrospective series from MD Anderson Cancer Center demonstrated doxorubicin-based chemotherapy was not effective in ESOS, with only 19 % of patients experiencing radiograph partial or complete response and 6 % achieving pathologic complete response [1]. An earlier report suggested that ESOS was relatively resistant to platinum-based therapies [14]. Conversely, other studies suggest that multi-agent chemotherapy as used in osteosarcoma of osseous origin may be effective in ESOS [7]. Thus, the role of chemotherapy in the treatment of ESOS is not well defined and requires further study.

A study from Memorial Sloan Kettering Cancer Center evaluated the influence of RT among 42 patients with localized ESOS. The authors found no difference in event-free survival between those who received RT and/or chemotherapy and those who did not [3]. However, the patient numbers in each treatment subgroup were small, and the results thought to be influenced by selection bias; the patients who received postoperative RT and/or chemotherapy had more unfavorable characteristics such as tumor size >5 cm or positive margins. This report did not evaluate the influence of RT on local control, the primary endpoint when evaluating efficacy of RT. Thus, the role of adjuvant RT, like the role of adjuvant chemotherapy, is not well defined.

ESOS of the Hand

Three previous case reports of ESOS of the hand have been described (Table 2) [2, 4, 20]. All three patients were treated with either a partial amputation or below-elbow amputation (2 as the initial procedure, and 1 after local recurrence), and none received RT. One patient received chemotherapy. At our institution, we successfully treated a 29-year-old man with ESOS arising from a lumbrical muscle (Fig. 2) with function-preserving marginal excision and adjuvant RT. The patient has no functional deficits and retains full range of motion and sensation of his hand following his excision and adjuvant RT.

Discussion

Due to the variability in clinical and anatomic presentation of ESOS and its extreme rarity, it is difficult to obtain a sufficient sample size to evaluate its clinicopathologic characteristics and response to neoadjuvant or adjuvant therapy. It is necessary to extrapolate from either osteosarcoma of osseous origin or general adult STS data when assessing the role of marginal excision and RT for ESOS given the scarcity of reports in the published literature. The American Joint Committee on Cancer classifies ESOS as a STS. Many of the studies in Table 1 also report that ESOS is more similar in its behavior and response to chemotherapy to other STS than its histologic

Table 2 Case reports of extraskeletal osteosarcoma of the hand

	Age (years)	Size (cm)	Grade	Initial surgery	Chemotherapy	RT	Recurrence	Time to recurrence	Treatment of recurrence	Status
#1 [20]	56	3.9×2.9×2.5	3	Marginal excision	No	No	Yes, local	4 months	Below-elbow amputation + chemotherapy	Dead from metastatic disease to lung
#2 [4]	63	5.5×5×5	3	Below-elbow amputation	No	No	Yes, distant in lungs	18 months	None	Unknown
#3 [2]	18	3×2.5×2	3	Partial amputation of fourth + fifth distal rays	Yes[a]	No	None	–	–	23 months, NED

RT radiation therapy, *NED* no evidence of disease

[a] Neoadjuvant doxorubicin and ifosfamide and adjuvant methotrexate, doxorubicin, and cisplatin

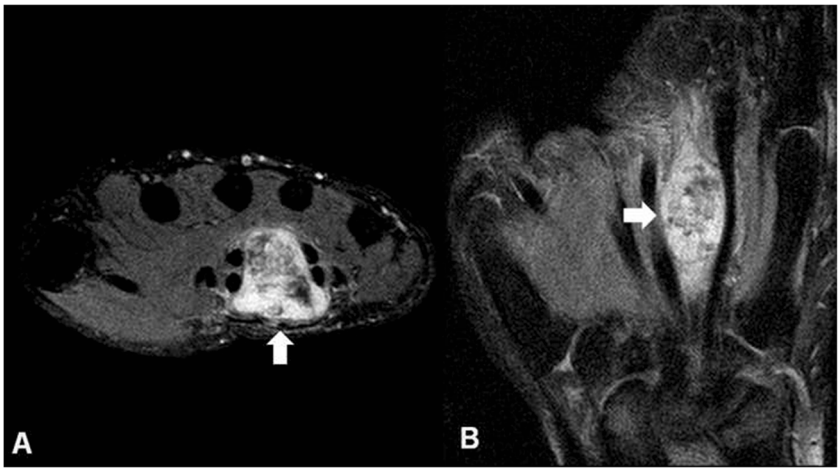

Fig. 2 **a** Axial and **b** coronal proton density MRI with fat saturation demonstrate a hyperintense 2.2×1.6×2.9-cm solid mass in the palm between the flexor tendons of the third and ring finger, replacing or arising from the lumbrical muscle

counterpart in the bone [1, 3, 12]. Thus, extrapolation from STS literature appears most appropriate.

Optimal treatment of extremity STS usually involves the combination of limb-sparing surgery and RT. Over 30 years ago, a National Cancer Institute (NCI) prospective trial showed that amputation provided no survival advantage over limb-sparing surgery and RT for extremity STS [15]. A second prospective trial from the NCI then explored if radiation could be omitted after limb-sparing surgery. Patients with high-grade extremity STS who underwent limb-sparing surgery were randomized to receive adjuvant chemotherapy versus adjuvant chemoradiation and patients with low-grade tumors to adjuvant RT versus observation [22]. RT improved local control in patients with both high- and low-grade disease. Local control was 100 % in patients with high-grade STS treated with gross total resection and adjuvant RT [22].

For sarcomas of the hand or foot specifically, complete surgical resection with wide margins is challenging without amputation due to anatomic constraints and lack of expendable tissue. All three case reports in the literature describing ESOS of the hand utilized amputation, and none of the patients described received radiation therapy [2, 4, 20]. However, there are multiple reports showing excellent local control, minimal toxicity, and superior functional outcome with limb conservation and RT rather than amputation of the hand in pediatric and adult STS [8, 10, 16, 19]. In particular, RT improves local control in patients with hand STS who do not undergo re-excision to achieve wide margins [10].

The morbidity of irradiating the distal extremity using modern conformal techniques today is low, with very few patients developing limb dysfunction [16, 19]. Posttreatment physical therapy and careful treatment techniques such as avoidance of circumferential radiation while limiting the dose to the skin and joint can minimize treatment-related effects. The decision to add RT in the setting of a margin-negative resection is based on risks and benefits. Even with negative margins, high-grade tumors can recur locally. Additionally, in this anatomic area, local recurrence would almost certainly result in partial or complete amputation of the hand. Therefore, we consider the small risk of secondary cancers, fractures, and other potential radiation morbidities to be acceptable given the severity of the consequences of local recurrence.

In summary, ESOS of the hand is a rare diagnosis, and its optimal modality of local control is unknown. Based on the current literature, we recommend a treatment approach with the goal of preservation of form and function using limb-sparing surgery and planned postoperative radiation.

Conflict of Interest Dana L. Casey declares that she has no conflict of interest, commercial association, or intent of financial gains regarding this article. Matt van de Rijn declares that he has no conflict of interest, commercial association, or intent of financial gains regarding this article. Geoffrey Riley declares that he has no conflict of interest, commercial association, or intent of financial gains regarding this article. Ka-Wah Tung declares that he has no conflict of interest, commercial association, or intent of financial gains regarding this article. David G. Mohler declares that he has no conflict of interest, commercial association, or intent of financial gains regarding this article. Sarah S. Donaldson declares that she has no conflict of interest, commercial association, or intent of financial gains regarding this article.

Statement of Human and Animal Rights This article does not contain any studies with human or animal subjects.

Statement of Informed Consent No patient-identifying information was included in this article.

Funding None

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