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Teaching Case

Saving the hand: Role of multimodality therapy for Ewing's sarcoma family tumor of the palm

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Introduction

The Ewing's sarcoma family of tumors (EFTs) are a rare subtype of tumor that include primitive neuroectodermal tumors (PNETs), typical Ewing's sarcoma, and atypical Ewing sarcoma. EFTs of the hand are extremely rare, and none have been reported to our knowledge beyond the fifth decade of life.[1-3] EFTs present most frequently in the second decade of life and have a male predominance.[3] Multimodality therapy is typically used to treat patients.

We present a case that is unique for several reasons. First, this patient presented in the sixth decade of life, which is later than most cases. Second, treatment included an amputation-sparing resection followed by adjuvant radiation therapy with electron beams. The patient was left with complete functionality of the hand and remained free of recurrent disease 4 years later.

Case report

A 56-year-old Caucasian male was initially referred to an orthopedic surgeon for an enlarging mass in the palm of his right hand, which was associated with pain, numbness, and tingling down his fingers. His symptoms had started to cause functional impairment and begun interfering with his ability to work on a farm and operate heavy machinery. During the initial physical examination, a superficial, fluctuant, and mobile mass was present between the third and fourth digits and appeared to decompress with palpation. The mass measured approximately 4×3 cm, and the patient subsequently underwent wide local excision, which entailed resection down to the deep palm. A third digit release was also performed through the same incision. The ulnar aspect of the third digit and the radial aspect of the fourth digit were encompassed by the mass. The mass was found to be adherent to the flexor tendon sheath as well as the deep lumbricals. During the operation, the flexor tendon demonstrated significant scarring with flexor tenosynovitis secondary to the mass. Immediately after the operation, the patient had decreased strength and range of motion in the right hand; however, he had no associated numbness, tingling, or loss of sensation.

The pathology was reviewed externally and the report revealed a mass measuring $3 \times 2.5 \times 1.0$ cm. The mass was positive for a grade 3 small blue cell malignant tumor and stained negative for immunostains such as leukocyte common antigen, thyroid transcription factor-A, cytokeratin, synaptophysin, chromogranin, and Human Melanoma Black-45, overall favoring a soft tissue Ewing's sarcoma. Molecular analysis using a break-apart probe revealed a Ewing sarcoma breakpoint region 1 (EWSR1) gene translocation in 100% of 300 interphase nuclei that, upon examination, confirmed Ewing's sarcoma or PNET that was staged as

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T1b/N0/M0. Final pathology also demonstrated positive surgical margins.

A magnetic resonance imaging (MRI) scan of the right hand showed high T2 and low T1 signal and contrast enhancement in the soft tissues volar to the third and fourth metacarpals and proximal phalanges. There was no nodular enhancement to suggest residual or recurrent tumor. A positron emission/computed tomography (CT) scan showed postoperative changes without evidence of metastatic disease. Subsequently, the patient received 3 cycles of induction vincristine, adriamycin, and cyclophosphamide and was started on concurrent chemoradiation therapy with vincristine and cyclophosphamide.

Upon presentation to the radiation oncology department, the patient underwent CT-simulation with a custom immobilization mold (Image 1 and 2). The most recent postoperative MRI of the right hand was then fused with the CT simulation images to help better delineate the postoperative bed. To adequately cover the tumor bed, multiple electron beam energies were simultaneously used to ensure adequate depth coverage. Specifically, the target volume was prescribed at 46 cGy per fraction using 6 MeV enface electrons and 119 cGy per fraction using 9 MeV electrons to a total dose of 5445 cGy at a cumulative 165 cGy per fraction. The dose distribution is shown in Image 3, and the patient's on-treatment setup was verified clinically prior to every treatment with initial digitally reconstructed radiographs appreciated in Image 4. Weekly port films were used to confirm the setup.

During the course of treatment, the patient developed a tender, brisk, erythematous reaction in the palmar and dorsal aspects of the hand, necessitating several short breaks from treatment. In relation to this, the first 5 treatments were administered with a 0.5 cm bolus placed on the skin; however, due to the development of brisk erythema on the palmar surface of the hand, the remainder of the fractions were delivered without the bolus. The patient's course was

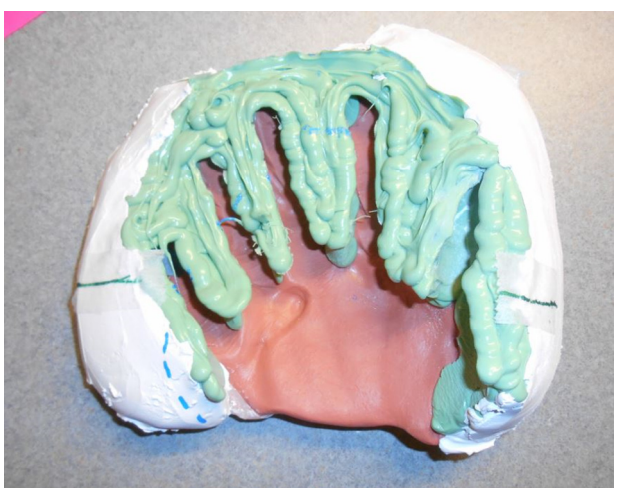

Image 1 Right Hand Mold.

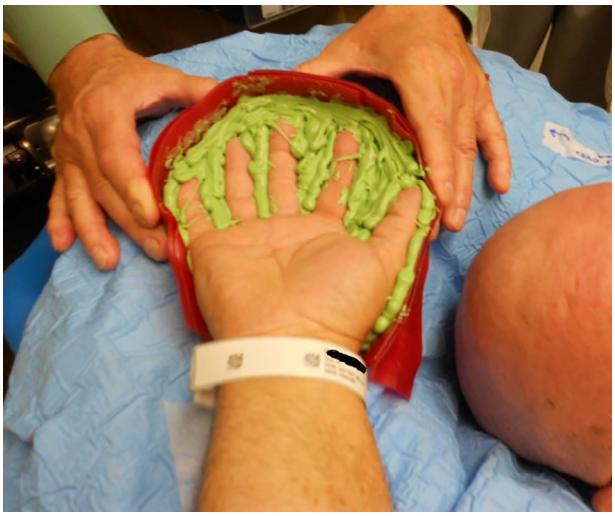

Image 2 Right Hand Setup.

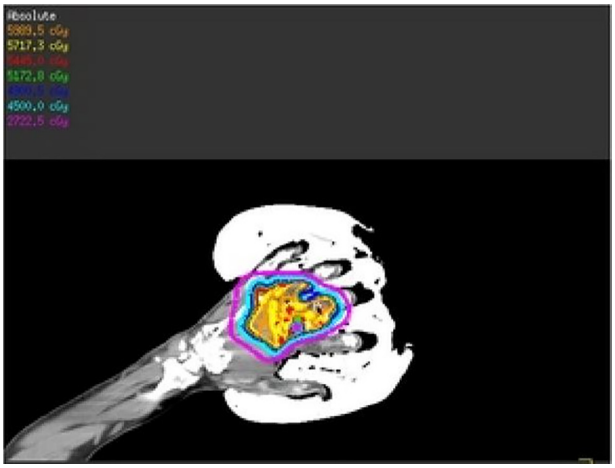

Image 3 Beams Eye View (BEV) of Isodose Lines.

complicated by dry desquamation involving palmar aspect of the right hand, along with erythema, and dry desquamation and blisters involving the dorsal aspect of hand despite daily use of Aquaphor (Beiersdorf AG Inc.) cream after each treatment. The patient subsequently completed his course of chemotherapy for a total of 8 cycles.

Since the first posttreatment MRI of the right hand, every subsequent MRI of the right hand revealed no evidence of recurrence. As seen in Image 5 and eVideo 1; available as supplementary material online only at www.practical.radonc.org, acquired during the latest follow-up at 42 months since completing radiation therapy, the patient's skin has returned to a normal appearance with little to no evidence of radiation treatment, and he has full range of motion of his hand.

Discussion

PNETs, like other EFTs, are composed of small round cells originating from neuroectodermal tissue in young chil-

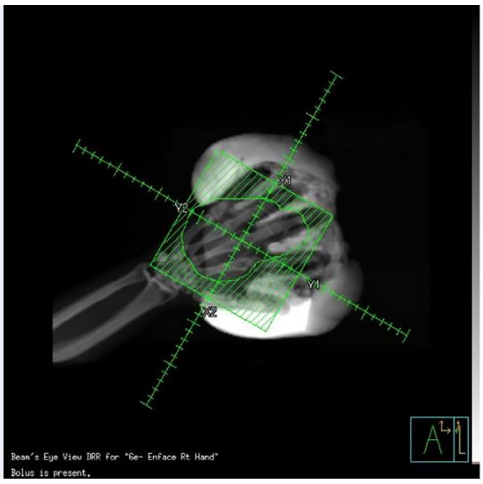

Image 4 Beams Eye View (BEV) DRR for Enface electrons to Right Hand.

dren and adults. They were originally described by Stout in 1918,[4] have a predilection for truncal and axial soft tissues and morphologically and clinically resemble other tumors such as neuroblastoma, extraosseous Ewing's sarcoma, and rhabdomyosarcoma. Arbitrarily, the presence of neuroectodermal differentiation has been used to define PNETs and its absence to assign a diagnosis of Ewing sarcoma.[5] Histologically, the cutoff point of neuroectodermal differentiation that separates PNETs from other EFTs is not well defined.[6] Both demonstrate immunoreactivity for surface antigen CD99/MIC2, which is expressed in up to 97% of cases. However, PNETs demonstrate more immunohistochemical evidence of neuroectodermal differentiation by positivity for antigens such as neuron-specific enolase, synaptophysin, protein gene product 9.5, neurofilament, and Leu-7.[6] However, no correlation exists between neural differentiation and prognosis.[7]

Molecular analysis is commonly performed with fluorescence in-situ hybridization or reverse transcriptase polymerase chain reaction techniques that are now part of the standard workup to confirm the diagnosis for these tumors. EFTs are characterized by translocations of the EWSR1 gene on chromosome 22q12. In 85% to 90% of EFT cases, a recurrent chromosomal translocation, t(11;22)(q24;q12), fuses the 5' portion of the EWSR1 gene on chromosome 22 to the 3' portion of the FLI1 gene on chromosome 11.[8] The EWSR1-ERG translocation,described by Sorensen et al and characterized by [t(21;22)(q22;q12)], is present in 5% to 10% of EFT, but the other translocations are less common.[9] In our patient, the exact chromosomal translocation partner was not identifiable because a break-apart probe was used in the molecular analysis.

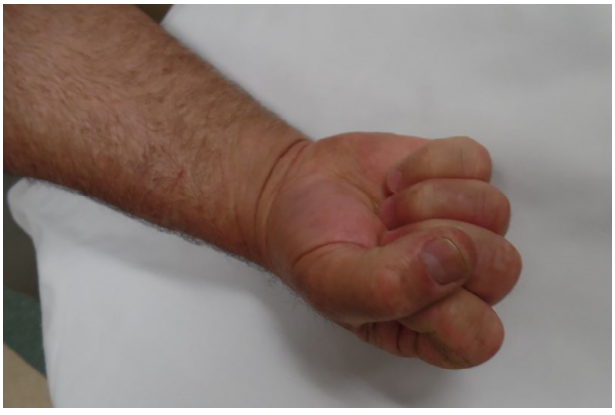

Image 5 Presence of complete range of motion of Right Hand at 42 months Follow-up.

A review of the St Jude experience by Marina et al of 26 patients with PNET over a 25-year period advocated combined modality therapy.[10] Of these 26 patients, only 8 received aggressive surgery as first-line treatment. Nine of the 26 were alive and disease-free for a median of 109 months. On the basis of the St Jude experience, aggressive surgery was recommended as the frontline therapy and radiation therapy was recommended in cases in which residual disease was thought to be present and repeat limb-sparing surgery was not an option.

Prior to the European Intergroup Cooperative Ewing's Sarcoma Study Group (EICESS) report on 33 patients, the authors note that between 1971 and 2001, only 43 patients with Ewing sarcoma of the hand had been published.[1] The EICESS patients included those enrolled in studies by the German Association for Pediatric Oncology/Hematology and the EICESS from 1997 to April 2001. A total of 9 of the 33 patients had PNET, but none involved the hand. The remaining patients had Ewing sarcoma, with only 4 involving the hand.

Patients received multimodality treatment that may have included chemotherapy, surgery, radiation, or a combination. Chemotherapy used included drugs on clinical trial protocol; vincristine, actinomycin-D, and adriamycin were the backbone, with the possible addition of either cyclophosphamide or ifosfamide. This may have been given either pre- or postoperatively. Chemotherapy was also used in instances of treatment failure with recurrence or distant metastases. Surgical intervention may have included local resection with an attempt to reconstruct with bone grafting techniques or amputation. The authors note that all distal upper extremity amputations in their report were done before 1994.

Furthermore, 11 of the 14 published cases with Ewing sarcoma of the hand before 1995 received amputations. The dose of radiation therapy was either 45 Gy postoperatively or 60 Gy for patients who received definitive irradiation. The authors concluded with their findings that negative predictors included age greater 14 years at diagnosis, metastases at diagnosis, and poor response to initial therapy. The 5- and 10-year overall survival rates were 84.1% (95% confidence interval [CI], 71.2%-96.9%) and 74.1% (95% CI, 56.8%-91.5%), respectively. Both the 5- and 10-

year event-free survival rates were 71.3% (95% CI, 55.4%-87.1%). Significantly, limb-salvage surgery appears to not have resulted in worse survival outcomes.[1]

Given the rarity of tumors of the hand, there is an overall dearth of literature on radiation treatment techniques for such tumors. Previously, a case has been described using CT-based electron dose calculations, with a customized compensating wax bolus to deliver dose coverage to tumor volume while sparing the draining lymphatics of the hand and digits.[11] A similar technique was employed in the treatment of this patient. The current patient received a higher dose than our historic patient, which is consistent with modern practice trends in which doses up to 60 Gy are used for postoperative radiation therapy for sarcoma of the hand and foot.[12]

Supplementary data

Supplementary material for this article (https://doi.org/10.1016/j.adro.2018.01.005) can be found at www.practicalradonc.org.

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