



# Collaborative Pediatric Bone Tumor Program to Improve Access to Specialized Care: An Initiative by the Lebanese Children's Oncology Group

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abstract

**Background** Children with malignant bone tumors have average 5-year survival rates of 60% to 70% with current multimodality therapy. Local control modalities aimed at preserving function greatly influence the quality of life of long-term survivors. In developing countries, the limited availability of multidisciplinary care and limited expertise in specialized surgery and pediatric radiation therapy, as well as financial cost, all form barriers to achieving optimal outcomes in this population.

**Methods** We describe the establishment of a collaborative pediatric bone tumor program among a group of pediatric oncologists in Lebanon and Syria. This program provides access to specialized local control at a tertiary children's cancer center to pediatric patients with newly diagnosed bone tumors at participating sites. Central review of pathology, staging, and treatment planning is performed in a multidisciplinary tumor board setting. Patients receive chemotherapy at their respective centers on a unified treatment plan. Surgery and/or radiation therapy are performed centrally by specialized staff at the children's cancer center. Cost barriers were resolved through a program development initiative led by St Jude Children's Research Hospital. Once program feasibility was achieved, the Children's Cancer Center of Lebanon Foundation, via fundraising efforts, provided continuation of program-directed funding.

**Results** Findings over a 3-year period showed the feasibility of this project, with timely local control and protocol adherence at eight collaborating centers. We report success in providing standard-of-care multidisciplinary therapy to this patient population with complex needs and financially challenging surgical procedures.

**Conclusion** This initiative can serve as a model, noting that facilitating access to specialized multidisciplinary care, resolution of financial barriers, and close administrative coordination all greatly contributed to the success of the program.

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## INTRODUCTION

Improvements in clinical outcomes in pediatric oncology have largely been attributable to a multidisciplinary team-based approach to management and well-designed, consecutive cooperative group clinical trials.<sup>1,2</sup> Optimal treatment of children with cancer relies on multidisciplinary management, preferably within a cancer center, with availability of specialized pediatric oncologists, surgeons, radiation therapists, and other pediatric subspecialists with expertise in oncologic diseases.<sup>3</sup> In the developing world, the care of children with cancer is, in many cases, suboptimal because of several barriers. These include limited financial coverage for treatment, suboptimal

medical supportive care, physician time constraints affecting the feasibility of multidisciplinary planning, and abandonment of therapy as a result of a multitude of reasons, including concern for loss of function/organ and lack of financial means.<sup>4</sup>

Lebanon is a small country in the Middle East, with a population of approximately 4.5 million and, accordingly, fewer than 20 pediatric oncologists. In 2012, with the help of a program development initiative sponsored by St Jude Children's Research Hospital (SJCRH), the majority of pediatric oncologists agreed to establish a cooperative group aimed at providing collaborative standardized treatment of various childhood tumors. The hypothesis is that centralized diagnosis and staging and

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coordinated treatment would result in better patient outcomes. Access to technically specialized and expensive procedures by eliminating financial barriers and ensuring expert care would optimize short- and long-term results. As such, children across the country would have access to specialized procedures and therapies, accurate diagnostic modalities, central review of pathology, and multidisciplinary treatment planning, with unified treatment plans for each specific tumor type.

To establish feasibility, the newly formed group (Lebanese Children's Oncology Group [LCOG]) focused first on pediatric bone tumors. The most common malignant pediatric bone tumors are osteosarcoma and Ewing sarcoma. Successful outcomes of both types of bone tumors depend on a multidisciplinary approach that uses both chemotherapy as well as appropriate local control: surgical resection is necessary for successful treatment of osteosarcoma, whereas surgery and/or radiation therapy are needed for Ewing sarcoma.<sup>5</sup> Pediatric oncologic orthopedic surgical expertise and pediatric radiation oncology expertise are essential for proper planning and treatment of such patients to ensure not only good oncologic control but also long-term functional outcomes in developing children and adolescents.<sup>2</sup> In addition, limb-salvage surgeries require significant and ongoing surgical experience, and prostheses can be prohibitively expensive, in particular, expandable devices needed for children who have not yet undergone the growth spurt.<sup>6,7</sup> Decisions regarding the appropriate type of local control (radiation v surgery) and type of surgical intervention require significant experience and a multidisciplinary approach to ensure optimal oncologic and functional outcomes. Such expertise had already been previously developed at an institutional level at the Children's Cancer Center of Lebanon (CCCL) at the American University of Beirut, with the support of SJCRH in the United States.<sup>8,9</sup> Thus, the LCOG collaborative bone tumor program was established to ensure collaboration and uniform access to multidisciplinary decision making for all patients across the country. We report the formation and progress of this bone tumor program over a period of 3 years, present patient characteristics and outcomes, and discuss this program as an example of a successful national collaboration for optimal clinical care of pediatric patients with cancer.

## METHODS

The LCOG collaborative bone tumor program was initiated in July 2012. Through this program, all newly diagnosed children (defined as < 18 years

of age) with bone tumors treated by any of the collaborative oncologists undergo central pathology review and staging at the Children's Cancer Institute at the American University of Beirut Medical Center. Chemotherapy is administered at the referring/treating institution on a unified treatment plan on the basis of current standards of care. The unified treatment plan for Ewing sarcoma consists of 14 alternating cycles of vincristine, doxorubicin, cyclophosphamide, and ifosfamide and etoposide (IE), per the Children's Oncology Group trial protocol AEWS0031 Regimen B.<sup>10</sup> Treatment of osteosarcoma consists of a three-drug regimen for localized disease (methotrexate, cisplatin, and doxorubicin), administered as two induction cycles before surgical control, then four maintenance cycles.<sup>11-15</sup> Patients with metastatic osteosarcoma received a five-drug regimen, adding IE to the three-drug combination,<sup>16</sup> as had been the practice locally since 2002 in view of the lack of standard therapy for this subgroup of high-risk patients. Of note, patients with osteosarcoma enrolled in the program after July 2015 now receive the three-drug regimen regardless of stage, because the recent results of the European and American Osteosarcoma Study<sup>17</sup> showed a lack of improved outcomes with the addition of IE in patients with osteosarcoma.

Local control decisions are made in a centralized multidisciplinary tumor board setting, and local control (surgery and/or radiation therapy) is centralized as well, ensuring expertise and continued development of such expertise in a small country where such patients are relatively rare. In this study, surgical approaches were individualized to each patient and included limb salvage surgeries, such as prosthesis placement, allografting, and autografting of long bones. For patients with Ewing sarcoma, radiation therapy doses and delivery conformed to guidelines of the AEWS0031 protocol, administered in 1.8-Gy fractions. Specifically, for nonresectable tumors, a dose of 45 Gy to the initial volume and 55.8 Gy to the final volume was administered, 50.4 Gy to tumor areas that showed a complete response after chemotherapy, and 45 Gy for vertebral bone tumors and for positive lymph node areas. Finally, patients with lung metastases also received 15 Gy of radiation to the lung fields.

All centralized procedures (pathology review, staging, and local control procedures such as surgery and radiation therapy) were financially covered by the CCCL Foundation, initially through a program development initiative by SJCRH in Memphis, TN, and later by program-directed fundraising efforts.

This ensured that patients could receive this integral component of specialized treatment, because financial barriers are the primary reason they are not delivered. A coordinator for the program at the Children's Cancer Institute ensured appropriate communication among physicians and coordination of patient visits, treatment plans, evaluations/interventions, and other logistics. Information regarding chemotherapy administration dates, associated delays and toxicities, and patient clinical status was collected on a monthly basis by the coordinator.

The review and reporting of patient characteristics and outcomes were approved by the institutional review board at the American University of Beirut Medical Center. One patient was excluded from this analysis because of the legal guardian's signed preference not to use medical record information for research purposes. All other patients/guardians consented to use of the medical record information for research studies.

## RESULTS

The LCOG was formed in June 2012. When the bone tumor program was initiated in July 2012, 13 oncologists who treated children with cancer at nine hospitals committed to enrolling patients with bone tumors. A few months later, a collaborating pediatric oncology unit in Damascus, Syria, was also added. By July 2015, the number of oncologists enrolling patients had increased to 17 oncologists at 12 hospitals. The major components of the program included (1) centralized pathology review and assessment of imaging and staging; (2) centralized multidisciplinary tumor board discussion of the most appropriate local control modality and centralized local control at one tertiary cancer center where surgical and radiation oncology expertise was available; and (3) treatment with common unified chemotherapy protocols that can allow proper assessment of outcome and prognostic factors. The LCOG group met on a monthly basis for the first year to discuss progress of the program and any issues with coordination. After that and once the program became well established, the LCOG meetings were changed to once every 3 months. Over the 3 years reported here (July 2012 to June 2015), 45 patients were evaluated for enrollment and 35 were enrolled. [Table 1](#) lists the patient demographic characteristics, including nationalities and distribution among treating institutions. Ten patients were evaluated but not treated within the program as a result of previous therapy (n = 5), relocation to another country

**Table 1** – Patient Demographic Characteristics

Characteristic	No. (%) (N = 35)
<b>Nationality</b>	
Lebanese	17 (48)
Syrian	9 (26)
Iraqi	9 (26)
<b>Age, years</b>	
< 10	11 (32)
10-15	18 (51)
> 15	6 (17)
<b>Sex</b>	
Male	20 (57)
Female	15 (43)
<b>Treating institution</b>	
Children's Cancer Center	19 (54)
Collaborative centers	16 (46)
<b>Location of collaborating centers</b>	
Beirut, Lebanon	32 (91)
Other area, Lebanon	1 (3)
Damascus, Syria	2 (6)

(n = 1), parental preference for surgery elsewhere (n = 1), and revised noncancer diagnosis (n = 3).

In the remainder of this section, we report the characteristics and outcomes for 34 patients, excluding the one patient with a lack of consent for use of medical records for research purposes. Of the 34 patients, 14 were diagnosed with osteosarcoma and 20 with Ewing sarcoma. The characteristics, treatment details, local control modalities used, and outcomes for each group are listed in [Table 2](#). The median follow-up time since diagnosis at the time of writing this report was 26 months (range, 8 to 42 months), and two patients were receiving active treatment.

The first component of the program, centralized pathology review, resulted in a change of diagnosis for three patients. Centralized review of imaging resulted in a request for repeat and/or additional studies as a result of either incomplete evaluations or poor imaging quality in eight patients and change in assigned stage in two patients. In the first year of the program, there were recurrent delays in submitting pathology samples and imaging studies for central review, and three patients assessed after initiation of therapy were found to have a change in diagnosis (n = 2) or inadequate imaging precluding proper planning for local control (n = 1). After addressing coordination issues in the ensuing LCOG meetings, a clear administrative

**Table 2** – Patient Characteristics and Outcomes

Characteristic	Osteosarcoma		Ewing Sarcoma	
	Localized	Metastatic	Localized	Metastatic
Total No.	8	6	12	8
Median age, years (range)	10.5 (4-13)	13.5 (12-17)	7 (3-19)	13 (6-17)
Tumor site				
Extremities	7	6	4	5
Trunk/other	1	0	8	3
Treatment				
VDC/IE	—	—	12	8
MAP	8	—	—	—
MAP/IE	—	6	—	—
Local control				
Surgery	8	4	3	1
Radiation	0	0	3	4
Surgery + radiation	0	0	5	1
Type of surgery				
Expandable prosthesis	3	0	0	1
Modular prosthesis	3	3	0	0
Allograft	1	0	1	0
Autograft	0	0	1	1
Amputation	0	1	1	0
Resection/other	1	0	5	0
Outcome				
Complete remission	5	3	9	2
Relapse/progression	2	3	2	4
Toxic death	1	—	—	—
Receiving therapy	—	—	—	2
LTFU	—	—	1	—

Abbreviations: LTFU, lost to follow-up; MAP, methotrexate, doxorubicin, and cisplatin; MAP/IE, methotrexate, doxorubicin, and cisplatin/ifosfamide, etoposide; VDC/IE, vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide.

process for patient enrollment was agreed on and circulated, and delays rarely occurred thereafter. Indeed, during the third year of the program, all evaluated patients had prompt and smooth submission and review of imaging and pathology evaluation, resulting in clear staging before the start of therapy and prompt enrollment in the program.

The second component of the program, centralized multidisciplinary tumor board discussion of local control modality and centralized local control, was achieved through establishment of a musculoskeletal tumor board meeting every 2 weeks, with attendance of pediatric oncology, orthopedic surgery, pediatric surgery, radiation oncology, and radiology specialists. Surgical procedures performed included 14 limb salvage

operations: 10 prosthesis placements (four expandable), three allografts, and one autograft. Other limb surgeries included one below-knee amputation, one forequarter amputation, and one partial internal hemipelvectomy. In addition, there were three chest wall tumor resections, one scapulectomy, and one total spondylectomy. Of note, two patients with multiple bone metastases at diagnosis had early tumor progression and did not undergo local control. Delays in surgery occurred in three patients because of a delay in prosthesis availability, with a median delay of 5 weeks (range, 1-8). These delays are primarily due to local supplier limitations, specifically when ordering custom-made expandable prostheses, and remain a challenge. Acute postoperative complications included posterior tibial nerve injury in one patient, postsurgical subcutaneous emphysema in two patients, and postsurgical skin dehiscence in four patients, all of which resolved with minor long-term sequelae. Late postoperative complications to date have included episodes of loosening at the site of the prosthesis in two patients, which resulted in bony bridging between the remnant and the graft in one of the patients and one episode of septic arthritis at the site of the prosthesis.

The third component of the program was treatment with common unified chemotherapy protocols to allow proper assessment of outcome and prognostic factors. Before establishment of this program, patients were being treated on a number of treatment plans, mostly based on the results of either the North American cooperative group studies or the European International Society of Pediatric Oncology studies. The treatment plan agreed on by the group for Ewing sarcoma was based on a recent study by the North American cooperative group (Children's Oncology Group) showing improved overall survival for patients with localized disease,<sup>10</sup> whereas that for osteosarcoma was based on standard treatment of pediatric osteosarcoma. Overall, the implementation of the treatment plans was feasible. Acute therapy-related toxicities included reversible hepatic enzyme elevation, hematologic toxicity, mucositis, febrile neutropenia, bacterial sepsis, and methotrexate-related skin toxicity. Invasive infections encountered included febrile neutropenia (n = 13), mucositis (n = 5), gram-negative bacteremia (n = 3), chickenpox (n = 2), cellulitis (n = 2), urinary tract infection (n = 1), pneumonia (n = 1), oral herpetic lesions (n = 1), and typhlitis (n = 1). Delays in chemotherapy administration were due to toxicities (n = 6), delayed hematologic

recovery (n = 4), fever (n = 2), febrile neutropenia (n = 4), elevated hepatic enzymes (n = 2), and invasive infections (n = 2). One patient died from sepsis while in clinical remission.

Of the 20 patients with initially localized disease, one (5%) died of toxicity, one (5%) was lost to follow-up as a result of relocation to another country, four (20%) had tumor recurrence at a median follow-up of 9 months (range, 7-26), and 14 (70%) were in continued first remission at a median follow-up of 25.5 months (range, 8-42). As for the 14 patients with initially metastatic disease, two (14%) were receiving active therapy, seven (50%) had primary tumor progression (n = 2) or relapse (n = 5) at a median follow-up of 9 months (range, 3-23), and five (36%) continued to be in first remission at a median follow-up of 17 months (range, 12-34). All tumor recurrences occurred at distant sites, with no local failures.

## DISCUSSION

The establishment of LCOG as a collaborative clinically focused group to facilitate the development of uniform guidelines for the treatment of children with cancer in Lebanon and allow identification of outcome measures and areas for improvement had been discussed for several years among the practicing pediatric oncologists in Lebanon. Designation of a central administrative site, clear pathways for efficient and timely patient enrollment, centralized diagnosis review, and timely coordination with member oncologists was a critical component for the success of this initiative.

The provision of funding to assist in the coverage of medical costs of high-expense centralized procedures helped to ensure the ability to enroll patients on common treatment plans. This is especially important in a country such as Lebanon, where relatively high health care costs, coupled with suboptimal financial coverage by national health care plans and a low proportion of patients with private insurance coverage, result in a large proportion of medical expenses falling on the individual, with secondary inequalities in care as a result of differences in financial means. To put this in perspective, it is worth mentioning that although Lebanon is listed by the World Bank as a country of upper-middle-income economy,<sup>18</sup> 28.6% of the population lives below the poverty level,<sup>19</sup> and total expenditure on health per capita is \$1,092, constituting approximately 7.2% of gross domestic product.<sup>20</sup> Since 2011, there has also emerged a continually growing population of Syrian refugees, for whom there is limited governmental, third-party, or personal financial means to

support cancer therapy. In addition, since 2007, the regional conflict has led to many Iraqi nationals seeking medical treatment in neighboring countries, including Lebanon, and the majority can only afford partial therapy and are prone to abandonment of treatment. The characteristics of patients recruited into the collaborative bone tumor program reflected the nationalities of pediatric oncology patients being treated in Lebanon during this period. This first LCOG collaborative program, first through a start-up grant and continuing via directed local fund-raising efforts, has now enabled access for all enrolled patients to standard-of-care diagnostic modalities, multidisciplinary management, and specialized local control procedures, with attention to best achievable functional outcomes.

Importantly, before initiation of the program, surgery for pediatric bone tumors as well as radiation therapy were being delivered at multiple hospitals across the country and performed by several surgeons and radiation oncologists with variable pediatric expertise. Assessment of outcomes and opportunities for improvement was not possible because of the small number of patients seen at each single institution. Through the collaborative program, centralized local control now allowed such procedures to be performed by experienced personnel in a tertiary-care setting and thus enhanced continuing development and improvement of local expertise by increasing the caseload for specialized procedures (surgery, radiation therapy), rather than having it diluted across multiple hospitals with episodic patients per surgeon or radiation therapist.

In addition, the uniform treatment of pediatric patients diagnosed with bone tumors, using common treatment plans across the country, now enables the collection of outcome data and encountered toxicities. Because of a lack of availability of national data on cancer outcomes, it is difficult to compare the outcomes of enrolled patients with those of patients treated in the previous era. However, we are confident that the continued collection of clinical and outcome data will now enable comprehensive prospective assessment of clinical features, prognostic factors, and areas for improvement in the care of pediatric patients with bone tumors across all participating institutions.

Yet, even with this program, we estimate that we are capturing only a subset of eligible patients. Although the total number of eligible non-Lebanese patients is difficult to determine, we can attempt to estimate the number of eligible Lebanese patients. The national cancer registry established by the

Lebanese Ministry of Public Health has made the data for the years 2005 to 2007, in which there were 77 new patients with pediatric bone tumors younger than 20 years of age, publically available.<sup>21</sup> The current 3-year period (2012-2015) may be estimated to have somewhat similar numbers. In the United States, the age-adjusted incidence rate for osteosarcoma in children 1 to 19 years of age is approximately 10 per million and 5.7 per million for Ewing sarcoma.<sup>22</sup> In Lebanon, children 0 to 18 years of age comprise approximately 33% of the population, with the total population estimated at 4.5 million in 2014.<sup>19</sup> Thus, the expected number of pediatric patients with osteosarcoma and Ewing sarcoma of bone would be approximately 14 and 8 per year, respectively, corresponding to 66 cases in 3 years. On the basis of these two data sources, we therefore estimate that the total number of Lebanese children with bone tumors likely ranged between

65 and 80 patients within the 3-year period studied. Because we evaluated 20 Lebanese patients, we can account for approximately 25% to 30% of estimated eligible patients. There is one pediatric oncology unit in Lebanon that is not part of the collaborative program, accounting for one to three patients per year (5%-10% of patients). The remaining 60% to 70% are thus unaccounted for, likely being treated by adult oncologists. Additional efforts should therefore be directed at reaching out to adult oncologists and orthopedic surgeons across the country to encourage centralization of treatment, delivery of multidisciplinary therapy, and minimizing barriers to effective local tumor control. We hope that demonstration of the success of this collaborative program will assist in this process.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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