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Research Article

Ilizarov Distraction Osteogenesis for Reconstruction of Long Bone Defects Following Primary Malignant Bone Tumour Resection

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ABSTRACT

Aims: Primary malignant tumours of long bones (PMTLB) are rare and pose considerable reconstructive challenges. Distraction osteogenesis is one of the reconstruction options available. We present a systematic review of bone transport reconstruction following resection of PMTLB. We also present the results of our own retrospective case series. The review aims to identify the magnitude of global experience using distraction osteogenesis for reconstruction of bone defects resulting from PMTLB along with associated outcomes. Specific questions asked include: What is the number of cases reported? What is the tumour recurrence rate? Are high grade tumours or chemotherapy a contraindication?

Methods: A systematic review of PubMed, Ovid Medline and Embase databases was performed in accordance with PRISMA guidelines. A retrospective review of our institution's experience was also undertaken.

Results: We identified 67 clearly documented cases among 21 papers in the literature of distraction osteogenesis being used primarily in the reconstruction of bone defects from PMLTB. There was a large proportion of high grade tumours with 64% requiring chemotherapy, and the reported local recurrence rate was 1.5%. Our own case series of 8 patients resulted in successful limb salvage in 7 cases, with excellent outcomes, and one case of local recurrence following initial misdiagnosis.

Conclusions: Distraction osteogenesis offers an effective but rarely used biological reconstruction option for bone defects in the management of PMTLB. In selected cases, excellent long term functional outcomes can be achieved, and chemotherapy for high grade tumours need not be a contraindication.

Keywords: Ilizarov, Sarcoma, Bone tumour, Distraction osteogenesis, Bone transport

Introduction

Primary malignant tumours of long bones (PMTLB) are rare and pose considerable reconstructive challenges [1]. Successful treatment usually requires en-bloc resection, plus chemotherapy for high grade tumours. Contemporary chemotherapy and surgical strategies have resulted in improved survival rates compared with earlier outcomes and limb salvage is now the gold standard with no survival differences between amputation and limb salvage provided adequate resection is undertaken [2].

Following tumour resection, reconstruction options include non-biological and biological techniques as well as amputation. The choice of reconstruction can determine cosmetic and functional outcome. According to Tsuchiya (1997), the ideal reconstruction "should have biological affinity, resistance to infection, sufficient biomechanical strength, and durability" [3]. Due to the predilection of these tumours for periarticular sites, reconstruction is most commonly achieved with endoprostheses. Despite advances with this technology, long term outcomes remain complicated by prosthetic loosening, wear and infection [4-6]. For intercalary reconstruction, prostheses play a smaller role [7], and alternative strategies have focused on the use of allografts, devitalized tumour-bearing autograft bone, vascularised bone flaps or combinations of allograft or autograft with vascularised flaps [8-12]. The free vascularised fibular graft (FVFG) has become a workhorse for biological intercalary reconstruction, but in the lower limb particularly is associated with high rates of fracture, non-union and return to theatre [11-13].

An alternative biologic reconstruction option is distraction osteogenesis [14]. When undertaken with a stable fixation construct, distraction osteogenesis permits immediate mobilisation, weight bearing and functional rehabilitation, and fulfils the above requirements for an ideal reconstruction in that it is truly biological, strong, durable, resilient, resists infection and responds normally to subsequent physiological trauma. Distraction osteogenesis has been increasingly applied in the management of bone defects due to trauma and infection, however application for the primary reconstruction of PMTLB is rare and little is reported regarding indications, contraindications and outcomes. We present a systematic literature review of the use of distraction osteogenesis for primary reconstruction of long bone defects resulting from resection of PMTLB. This review aims to identify the number of cases reported along with outcomes including tumour recurrence. In addition, we report the experience from our institution of bone transport reconstruction in a series of 8 patients with primary malignant tumours of long bones.

Patients and Methods

Literature review

A systematic literature review was undertaken in compliance with PRISMA-P guidelines [15] to evaluate global experience of bone transport reconstruction following resection of PMTLB.Specific questions asked include: What is the number of cases reported? What is the tumour recurrence rate? Are high grade tumours or chemotherapy a contraindication?In April 2017, a search of the PubMed (1950 to present), Ovid Medline (1946 – present) and Embase (1974 – present) databases was made for all English language papers, articles, books and book chapters containing the following search terms within the title or abstract and Boolean operators; ((Ilizarov OR bone transport OR distraction osteogenesis OR distraction histiogenesis OR callotasis) AND (tumor OR sarcoma)).The abstracts and papers were all read by the first author(NJ) and assessed against the following inclusion criteria. Only articles regarding human cases of primary malignant tumours of long bones were included. Maxillofacial cases, benign tumours and conditions including Giant cell tumours and osteofibrous dysplasia were excluded as were cases of secondary deformity correction or limb lengthening procedures plus salvage procedures following failed alternate tumour reconstructions. Cases were also excluded if insufficient detail was provided to determine exact diagnosis or treatment. In addition to pure bone transport techniques, cases utilizing Ilizarov compression-distraction techniques were also included, provided distraction was undertaken within the bone affected by the malignant tumour. Thus, cases of medial fibular transport were excluded, as were cases of arthrodesis with distraction osteogenesis undertaken on the other side of the original joint from the tumour. Initial search identified 127 articles, which was reduced to 21 after screening for inclusion criteria. Individual cases satisfying the inclusion criteria were mined from the various studies identified, and care was taken to avoid duplicate inclusion of cases where reported in more than one paper.

Case series from our institution

We retrospectively reviewed a consecutive series of eight patients managed with bone transport reconstruction of an intercalary defect arising from resection of a PMTLB during a 13-year-period between January 2002 and May 2015. All except one of the patients (case 1) presented to our institution via the multidisciplinary sarcoma board, and reconstructive surgery was performed by one of the 2 senior authors in all cases. Initial tumour workup confirmed that the patients had an isolated diaphyseal bone tumour without metastatic spread, and the reconstructive surgery was undertaken simultaneously with the tumour resection in all but one case (case 1). All primary malignant tumours regardless of grade were included, and adjuvant therapies were not Ilizarov circular frame constructs (Smith & Nephew, Memphis, USA) were used for bone transport in all but one case, in whom an LRS rail (Orthofix, Verona, Italy) mono lateral external-fixator was used. A latent period of 1 week was prescribed before commencing distraction at a rate of 1mm per day in 4 increments of 0.25mm. Bone transport was performed over an intramedullary nail in 3 cases. At the time of frame removal, patients were put into a protective brace or cast and partial weight bearing prescribed for 2 weeks.

Histological diagnosis was confirmed by a specialist osteoarticular pathologist. All patients were contacted to determine final status according to ASAMI [16] plus MSTS outcomes [17].

Complications of the Ilizarov treatment were classified using the system defined by Paley (1990), as 'problems' if they were resolved by the end of treatment with non-operative intervention, 'obstacles' if they were resolved by the end of treatment using operative intervention and true 'complications' if they resulted from intra-operative injury or were not resolved by the end of treatment [18].

Results

Literature review

Twenty-one papers met our inclusion criteria as illustrated in (Figure 1). Seven were single case reports, while 14 were case series. Within these series, not all reported patients had undergone distraction osteogenesis for a primary malignant bone tumour. In total, 67different cases of clearly documented distraction osteogenesis for the primary reconstruction of a defect resulting from resection of a PMTLB were identified [3,19-39]. Full details of these cases are provided as a table in the supplementary (Table S1).

Of the 67 cases, 34 were male (51%), mean age 21 years (range 4 - 72 years). Histological diagnosis was osteosarcoma in 43 cases (64%), Ewing's sarcoma in 11 (16%), adamantinoma in 5 (7%), chondrosarcoma in 5 (7%) and MFH in 3 (4%). Use of chemotherapy was documented in 43 cases (64%).

The mean defect size reconstructed was 12.4cm (range 4.5 - 24cm), with a mean external-fixator index of 36.3 days/ cm (range 12.4 - 191 days/ cm). At least 57 cases were reconstructed using bone transport and at least 8 utilised bifocal compression distraction techniques. In 2 cases, it was not completely clear whether the distraction osteogenesis technique was bone transport or bifocal compression-distraction. Adjuvant use of IM nail was documented in 7 cases and locking plate

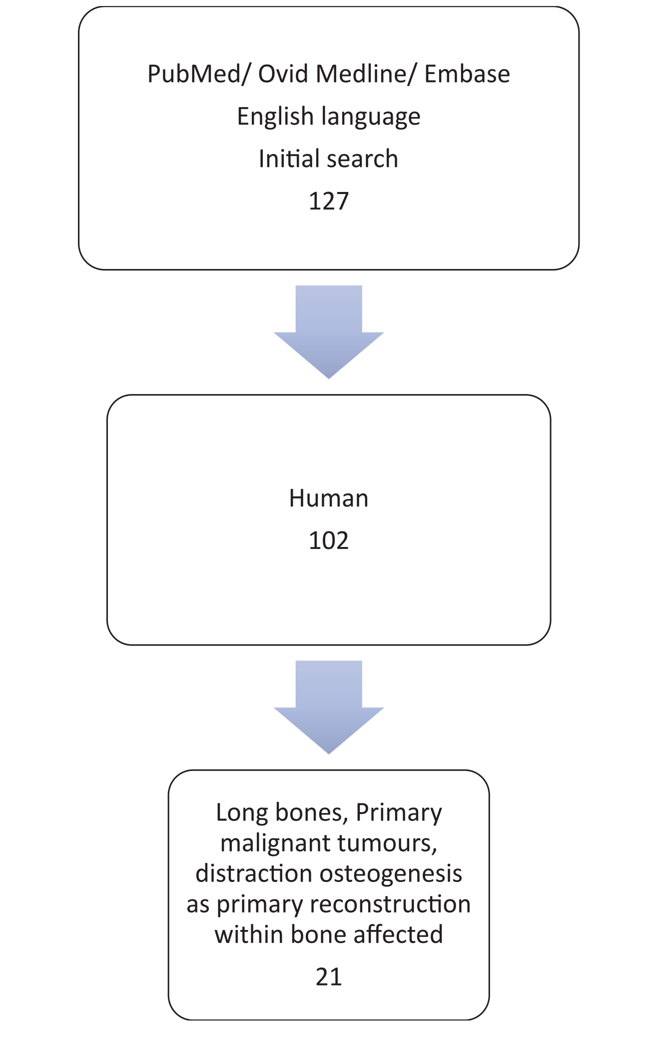

Figure 1: Flowchart of literature search.

in 3. There were 14 documented cases of mono-lateral and 42 cases of circular external-fixation, while the method of stabilisation was not made clear in 11 cases. Median follow-up was 48 months (range 10 - 237 months). MSTS functional outcome scores were provided in 35 cases, with a mean score of 91% (range 60% - 100%).

Eighteen cases (27%) had a documented pin site infection, 15 (22%) had significant contracture/ stiffness of the knee or ankle joint, 15 (22%) experienced delayed-union or non-union of the docking site requiring a docking site procedure, 13 (19%) had delayed consolidation, 6 cases (10%) suffered deep infection, and 2 (3%) experienced hardware failure (one broken IM nail, one broken external-fixator pin). Nine cases (13%) had a resultant leg length discrepancy (reported range 2cm – 6cm), 4 (7%) had a reported mal-union, and 1 patient suffered a peroneal nerve palsy. There were 5 cases (7%) of reported fractures, one involving an adjacent bone segment and one the result of a road traffic accident 4 years post-surgery. Among the 67 cases identified, there was only one documented case of local recurrence (1.5%) at 5 years following resection of intra-cortical osteosarcoma. Nine further cases (13%) developed systemic disease leading to death in 7 at mean time following surgery of 38 months (range 13 - 84 months).

Case series

Eight cases were identified (7 female and 1 male), with average age 40 years (range 23 - 60 years).Details are provided in (Table 1). One case (case 1) had undergone a previous allograft reconstruction elsewhere at the time of tumour resection, but was referred to our institution with infected non-union. None of the patients required chemotherapy during their treatment. Mean follow up was 82.6 months (range 18 – 174 months). There were 2 true complications: one case of knee stiffness which resolved after quadriceps plasty, and one case of local tumour recurrence. There were no cases of deep infection or fracture.

The case with local recurrence (case 5) initially presented as pathological fracture and, after assessment by the sarcoma board and biopsy, was incorrectly diagnosed as an aneurysmal bone cyst (ABC). Attempted fracture fixation failed and she was referred to our unit. Segmental resection was undertaken with bone transport over an IM nail. All histology up until this point supported the diagnosis of ABC and so the resection was as for a benign tumour. Subsequent histological analysis confirmed grade 1 MFH. The sarcoma board decided to continue close observation and after completion of bone transport and locking of the IM nail, the transport segment was noted to undergo osteolysis in keeping with local recurrence. Despite plans for a staged total femoral replacement, she later underwent through-hip disarticulation. She completed chemotherapy and remains alive and disease free.

The remaining 7 cases all healed without recurrence or metastases. They achieved excellent ASAMI outcomes for bone reconstruction, excellent or good ASAMI outcomes for function, and MSTS functional outcomes of 90%and greater (Table 1). At final follow-up, these patients were satisfied with their reconstructions and would recommend the treatment to other patients with similar problems. No patient has required further reconstructive surgery. Radiographs and photographs illustrating the reconstructions and outcomes for cases 3 and 7 are provided in figure 2A-G and figure 3A-C respectively.

Discussion

Our literature review revealed only 67 clearly reported cases of distraction osteogenesis for the primary reconstruction following resection of PMTLB. Although these are rare cases, this most likely represents a significant under-reporting as some centres may have undertaken this type of surgery but not published due to low numbers.

We perceive there is anxiety regarding use of distraction osteogenesis immediately after malignant tumour resection, not only due to unfamiliarity with Ilizarov reconstruction methods and principles, but also due to fear of mitogenicity with this technique. This is a reasonable fear, although there is only one published report of malignancy arising in a bone regenerate, in a single case of Ilizarov lengthening through an area of fibrous dysplasia [40]. Our review of the literature demonstrates a local recurrence rate of only 1.5% among the 67 cases reported, which include a large proportion of high grade tumours. However, given the considerable heterogeneity of the different cases including follow-up periods, direct comparisons and analysis are difficult and extrapolation should be undertaken with caution.

Our own series includes one case of recurrence with catastrophic

Table 1: Summary of case series patient details.

Case	Sex	Age	Tumour	Bone	Defect (cm)	Surgery	Frame time (days)	Frame Index (days/ cm)	Complications	Further surgery	Follow up (months)	Outcomes ASAMI Bone	ASAMI Function	MSTS (%)
1	F	40	CS	Femur	11	CF, internal BT	284	25.8	Lack of knee flexion	Quadsplasty, removal of IM nail	174	Excellent	Good	90
2	F	30	CS	Femur	11.5	CF, internal BT over IM Nail	180	15.7	Breakage of transport mechanism, PF	Revision corticotomy & transport mechanism, BGDS	144	Excellent	Excellent	90
3	F	23	Ad	Tibia	13.5	CF, antegrade BT	561	41.6	PSI with ulcer, DS	SSG to ulcer, DSP	115	Excellent	Excellent	100
4	F	60	MPNST	Tibia	17	CF, retrograde BT	468	27.5	PSI, skin tethering, DS	soft tissue release, BGDS	75	Excellent	Excellent	97
5	F	47	MFH	Femur	10	ML, BT over IM nail	193	19.3	PSI, local recurrence	Amputation	61	n/a	n/a	n/a
6	F	46	CS	Tibia	17	CF, retrograde BT	642	37.8	skin tethering, wire breakage, DS	soft tissue release, BGDS	30	Excellent	Excellent	93
7	M	45	MFH	Tibia	12	CF, retrograde BT	443	36.9	PSI, DS	DSP	44	Excellent	Excellent	93
8	F	27	Ad	Tibia	16	CF, retrograde trifocal BT over retrograde IM hindfoot fusion nail	151	9.4	Pin cut-out from transport segment	Replacement of pin with transport cable, BGDS	18	Excellent	Good	93
Av		40			13.5		365	26.8			82.6			93.7

Ad - Adamantinoma, CS - Chondrosarcoma, MFH - Malignant Fibrous Histiocytoma, MPNST – Intra-Osseous Malignant Peripheral Nerve Sheath Tumour BT - Bone Transport, CF - Circular Frame, IM - Intramedullary, ML - Monolateral External Fixator. DS - Docking Site Non-Union, PF - Premature Fusion, PSI - Pin Site Infection, BGDS - Bone Graft Of Docking Site, DSP - Docking Site Procedure. MSTS – Revised Musculoskeletal Tumor Society functional outcome score (Enneking et al. 1993)

outcome necessitating amputation. Initial incorrect diagnosis on biopsy, followed by intra-lesional surgery and subsequent inadequate resection contributed to this outcome. This is in keeping with recent conclusions by Gaston, et al. [41].

Potential adverse effects of adjuvant chemotherapy on the quality of bone regenerate is a particular issue of concern for distraction osteogenesis. Chemotherapy was not indicated in any of our successful salvage cases but was in 64% of the literature cases identified, with mixed results. Ozaki, et al. [31] reported poor regenerate in their series with prolonged frame index (average 95 days/ cm), although this was a challenging series with 4 of the 5 cases requiring chemotherapy and several needing wide resection of knee joint and 2 cases also requiring vascular reconstruction of popliteal vessels. Similarly, both Dormans, et al. [22] and Yang, et al. [38] also reported poor quality regenerate with chemotherapy necessitating a reduced distraction rate. In contrast, the Kanazawa group report little concern with bone regenerate quality despite chemotherapy for high grade sarcomas [3,35-37,42], as do Demiralp, et al. [21]. Animal studies specifically investigating the effects of chemotherapy on distraction osteogenesis have also been mixed in their findings and conclusions. Monsell, et al. [43] used a rabbit model to test effects of adriamycin and cisplatinum regimens on bone regenerate. They found that isolated pre-operative chemotherapy resulted in reduced bone mineral content and density, without altering the mechanical properties, while peri-operative chemotherapy produced no observed effect on mineralisation but did alter the mechanical properties of the bone regenerate [43]. In contrast, Jarka, et al. [44] were unable to demonstrate any histologically or radiologically apparent effect of methotrexate on distraction osteogenesis in their rabbit model [44]. This is clearly a multifactorial issue which is likely dependent on the specific chemotherapy regimen utilized, which may account for some of the clinical differences observed between different centres.

There were 7 documented uses of IM nail to reduce external-fixation time in the literature case series, including cases of high grade osteosarcoma and MFH. In 3 of our cases bone transport was undertaken over an intramedullary nail. This is a well described technique [45,46] to reduce frame time, however may be considered controversial in the setting of malignant bone tumour. If the tumour

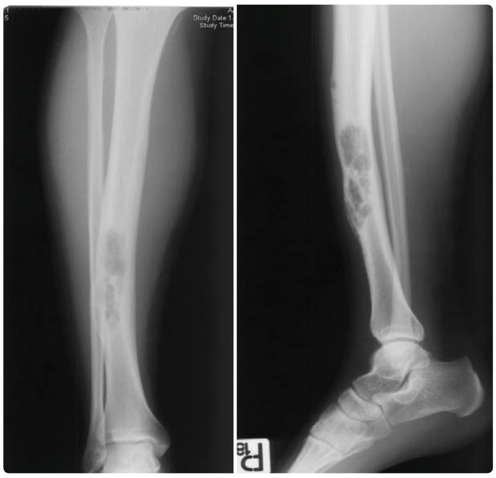

Figure 2a: Adamantinoma requiring 13.5cm resection.

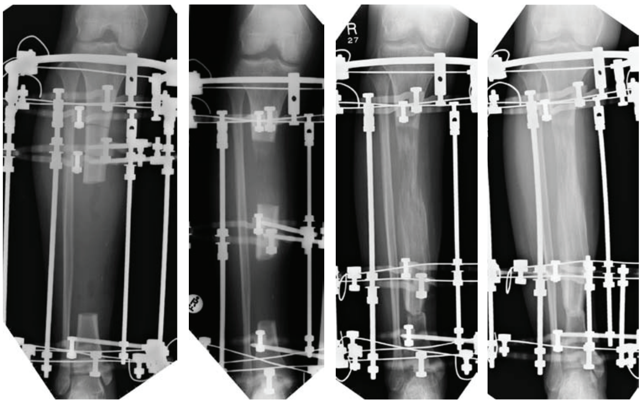

Figure 2b: Serial radiographs demonstrating bone transport with regenerate formation and consolidation up to 15 months. Frame was removed at 18 months.

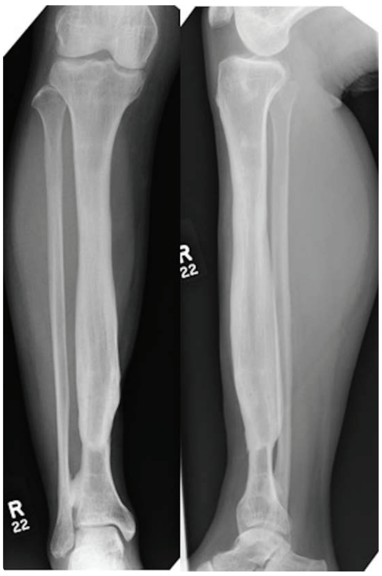

Figure 2c: Radiographs and clinical photographs of outcome at 22 months (4 months post frame removal).

Figure 2d-g: Clinical photographs showing appearance and function of limb from Case 3 at 22 months (4 months post frame removal).

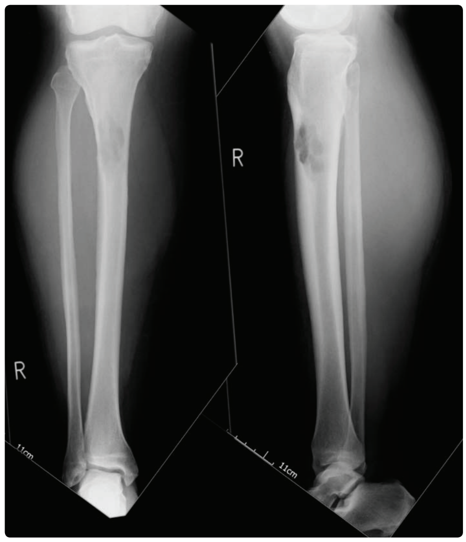

Figure 3a: MFH of proximal tibia requiring 12 cm resection.

surgeon and pathologist are confident that successful resection has been achieved then we believe there is no contraindication to the use of an IM nail, however this decision must be made on an individual case basis and in discussion with the sarcoma board. As our experience with case 5 demonstrates, if diagnosis is incorrect or resection inadequate, then use of IM nail may contribute to poor outcome. Among the 7 cases of IM nail use in the literature, there was no local recurrence, but 2 cases of systemic disease.

Our own case series demonstrates outcomes comparable with the literature, although our external fixation indices appear shorter than average. The small size of our case series limits the study, however this is a rare solution for an uncommon problem and our eight cases equate to 11% of the published experience. Only 4 groups worldwide

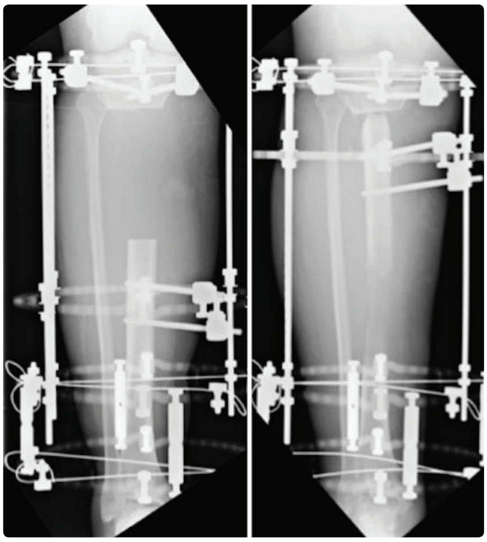

Figure 3b: Progress of retrograde bone transport.

Figure 3c: Final successful reconstruction.

have reported similar sized series [3,21,23,25,35-37]. The Kanazawa group in Japan appear to have the greatest experience of this technique and have producedseveral of the case series included in our literature review. These were among the largest series and, despite considerable overlap of the cases and repeated reporting, account for 23 of the included cases (34%) [3,35-37]. This centre also reports the longest follow-up, up to 237 months, in one of its series focusing purely on osteosarcoma cases with a minimum follow-up of ten years [37].

In conclusion, we have presented a systematic review of distraction osteogenesis for reconstruction of bone defects following PMTLB, along with a case series from our own institution. Distraction osteogenesis by Ilizarov principles offers an effective but rarely usedbiological reconstruction option in the management of PMTLB. In selected cases, excellent long term functional outcomes can be achieved, and chemotherapy for high grade tumours need not be a contraindication.

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Supplimentary Table:

Systematic review: Summary of reported clinical cases of use of distraction osteogenesis for the primary reconstruction of defects following PMTLB.

Case	Author(s)	Age	Sex	Diagnosis/ stage	Bone	Defect size [length gained] (cm)	Surgery	Chemo	DI (days/ cm)	EFI (days /cm)	Outcome	Reported Complications	Recurr-ence?	Further treatment	F/U time (mon-ths)
1	Apornchayanon, 2011	21	F	Intracortical OS	DT	14	CF, BT	-		32.1			LR, 5yrs	Repeat resection, chemotherapy, strut graft and ankle arthrodesis	>84
2	Demir, 2016	36	M	MFH	PT	12	Staged CF, BT along LP	+ (prior to reconstruction)	11.8	12.7	ASAMI Bone - Excellent ASAMI Function - Good	EC		ORIF & bone graft DS at frame removal, TAL	71
3	Demir, 2016	42	M	OS	DT	14	Staged CF, BT along LP	+ (prior to reconstruction)	11.4	12.4	ASAMI Bone - Excellent ASAMI Function - Excellent	Exposed metalwork		ORIF & bone graft DS at frame removal, r/o metal and reapplication of CF	49
4	Demir, 2016	34	M	ES	MT	15	Staged CF, BT along LP	+ (prior to reconstruction	11.5	12.5	ASAMI Bone - Excellent ASAMI function - Exellent	PSI		ORIF & bone graft DS at frame removal,	22
5	Demiralp, 2014	14	F	Parosteal OS (G1T1M0)	MT	9	CF, BT	-	11.11	31.6	MSTS 93%	PSI			
6	Demiralp, 2014	15	F	OS (G1T1M0)	MT	21	CF, BT	+	11.19	22.8	MSTS 90%		DOD		84
7	Demiralp, 2014	24	M	OS (G1T1M0)	DF	24	CF, BT	+	11	22.5	MSTS 90%	PSI, SI, EC, MU			
8	Demiralp, 2014	7	M	ES (G1T1M0)	DF	11	CF, BT	+	11.7	40	MSTS 86%	PSI, DC			
9	Demiralp, 2014	10	M	ES (G2T1M0)	DF	16	CF, BT	+	11.25	18.8	MSTS 90%	PSI, DS, DC, LLD			
10	Demiralp, 2014	19	M	OS (G1T1M0)	DF	14	CF, BT	+	10.42	24	MSTS 86%	EC			
11	Demiralp, 2014	10	F	ES (G1T1M0)	DF	12	CF, BT	+	11.4	29.8	MSTS 93%	LLD			
12	Demiralp, 2014	33	M	OS (G1T1M0)	DT	17	CF, BT	+	10.5	31.7	MSTS 90%	TE, DC			
13	Demiralp, 2014	17	M	OS (G1T1M0)	DT	14	CF, BT	+	11.4	26.7	MSTS 96%	PSI, TE			
14	Demiralp, 2014	21	M	OS (G1T1M0)	DT	15	CF, BT	+	10.6	26	MSTS 83%	TE			
15	Dormans, 2005	13	F	ES	Tibia	13	ML, BT	+	16.2*	53.8	MSTS 80%	PR, DS, LLD 3.6cm	DOD	Bone graft docking site	41
16	Erler, 2005	14	F	OS/ IA	MT	9	CF, BT	+	11.1	31.6	Enneking (1987) - Excellent	PSI			128
17	Erler, 2005	15	F	OS/ IA	MT	21	CF, BT	+	11.1	22.8	Enneking (1987) - Excellent	PSI, # distal femur		ORIF fracture	53
18	Erler, 2005	24	M	OS /IB	DF	24	CF, BT	+	11	22.5	Enneking (1987) - Poor	PSI, SI, MU, EC		Soft tissue release	44
19	Erler, 2005	21	M	OS/ IA	Ulna	8	ML, BT	-	11.2	26.2	Enneking (1987) - Excellent	PSI, DS, Inf		ORIF DS, R/o metal, bone graft & DBM to DS non-union	34
20	Erler, 2005	7	M	ES/ IIA	DF	11	CF, BT	+	11.7	40	Enneking (1987) - Good	PSI, DC			31
21	Erler, 2005	10	M	ES/ IIA	DF	16	CF, BT	+	11.2	18.7	Enneking (1987) - Good	PSI, DS, DC			27

22	Futani, 2012	11	M	small cell OS	PT	13	CF, BT	+		32	MSTS 73%	DS, LLD 3cm		ORIF and bone graft DS at frame removal	48
23	Kapukaya, 2000	17	M	CS	PF	20	ML, BT	-	13	32					30
24	Kapukaya, 2000	8	F	OS	DF	12	CF, BT	+	14.8	33.3					24
25	Kapukaya, 2000	7	F	ES	DF	13	CF, BT	+	12.7	32.8					20
26	Kapukaya, 2000	37	M	CS	PF	11	ML, BT	-	14.5	33.4		Inf			21
27	Kapukaya, 2000	8	F	OS	DF	12	CF, BT	+	15.7	32.5			DOD		20
28	Kapukaya, 2000	13	M	OS	DF	10	ML, BT	+	14.5	34.5		SI			20
29	Kitsoulis, 2009	31	F	Ad	DT	5.8	ML, BT	-		31.0*					36
30	Lammens, 1992	20	M	Parosteal OS	Ulna	10	CF, BT			24.0*		DS			18
31	Lee, 2006	8	F	Ad	MT		CF, BT	-				PSI, EC, DS			39
32	Lee, 2006	11	F	Ad	MT		CF, BT	-				PSI, Inf			37
33	McCoy, 2013	16	M	CS	MT	18	CF, BT	-		22.5	ASAMI Bone - Excellent MSTS 100%	DS, LLD 2.3cm		IM nail and plating docking site	≥36
34	McCoy, 2013	18	F	Parosteal OS	Femur	11.7	ML, BT over IM nail	-		24.2	ASAMI Bone - Excellent ASAMI Function - Good MSTS 90%	PSI, HF, DS, LLD2cm, EC		I&D abscess, Exchange IM nail, Quadriceps-plasty	
35	Ouyang, 2015	23	M	CS	DT	[8]	ML, BT, tibiotalar arthrodesis	-	11.1	36	MSTS 94%	LLD			36
36	Ozaki, 1998 Ozaki, 1998a	11	F	OS	DF	23 [18]	Wide excision knee. CF, trifocal BT	+		32.2	Enneking (1987) - Poor	PSI, PR, TE, LLD6cm	DOD	Removal of pin, MUA	66
37	Ozaki, 1998a	6	M	ES	Tibia	10	CF, trifocal BT	+		n/a	Enneking (1987) - Poor	PR, SN, pseudarthrosis of subsequent FVFG		FVFG, pedicled skin flap, centralisation of ipsilateral fibular	48
38	Ozaki, 1998a	44	M	CS	Femur	19 [7]	CF, trifocal BT	-		191	Enneking (1987) - Poor	PR, TE, SN, #, Inf		TAL, AKA for osteomyelitis	45
39	Ozaki, 1998a	26	F	OS	Femur	14 [12]	CF, trifocal BT, VR	+		104	Enneking (1987) - Fair	PR, PSI, HF		Insertion of pin	43
40	Ozaki, 1998a	27	F	OS	Femur	18 [15.5]	CF, trifocal BT, VR	+		53	Enneking (1987) - Fair	Thrombosis, MU, TE, DS		By-pass of popliteal vessels, valgus osteotomy, TAL, IM nail	40
41	Said, 1995	41	F	MFH	DF	11 [9]	CF, CD arthrodesis	-		18*					10
42	Stoffelen, 1993	18	M	Parosteal OS	Distal Ulna	10	CF, BT		11	25		DS, stiffness of forearm rotation		-	36
43	Tsuchiya, 1997	17	M	OS/ IIIB	PT	11.8	BT	+	8.5	27.9	Enneking (1987) - Fair		DOD		13
44	Tsuchiya, 1997	15	F	Low grade OS	MT	13.5	ML, BT	-	10.3	28.6	Enneking (1987) - Excellent				62

45	Tsuchiya, 1997 Tsuchiya, 2002 Tsuchiya, 2006	43	F	OS	PT	5.5	Subarticular reconstrn., CF, BT	+	17.6	63.5	MSTS 100%	TE			94
46	Tsuchiya, 1997 Tsuchiya, 2002 Tsuchiya, 2006 Watanabe, 2013	20	M	Low grade OS	PT	5.5	CF, BFCD	-	10.1	32.7	MSTS 93%	DU, SN, Peroneal NP		bone graft, tendon transfer	231
47	Tsuchiya, 1997 Tsuchiya, 2002 Tsuchiya, 2006	13	F	OS	DF	15	BFCD	+	7.3	34.8	MSTS 77%	#, EC, knee instability			103
48	Tsuchiya, 1997	10	F	ES	PF	8	BFCD	+	10.8	34.8	Enneking (1987) - Good		DOD		32
49	Tsuchiya, 1997	72	M	MFH/ IIIB	MF	8	ML, IM nail	-	21.1	24.8	Enneking (1987) - Excellent		AWD		32
50	Tsuchiya, 1997 Tsuchiya, 2002 Tsuchiya, 2006	38	M	OS/ IIIB	DF	15	MR, CF, BT, IM nail	+	14.9	15.9	Enneking (1987) - Fair	Inf	DOD		13
51	Tsuchiya, 1997 Tsuchiya, 2006 Watanabe, 2013	22	M	OS	DF	9.2	ER, CF, BFCD	+	14.2	39.4	MSTS 83%	DC, EC		IM nail at time of frame removal	237
52	Tsuchiya, 1997 Tsuchiya, 2002 Tsuchiya, 2006 Watanabe, 2013	34	F	Parosteal OS	DF	6.6	ML, BFCD over IM nail	-	15.2	18.2	MSTS 100%				225
53	Tsuchiya 2002 Tsuchiya, 2006 Watanabe, 2013	15	M	OS/ IIB	PT	12.5	CF, BT	+	20.6	39.7	MSTS 100%	Inf, LLD 2cm, MU,Tibial plateau # 4yrs		Resection of infected docking site with compression distraction. Ilizarov # fixation and residual deformity correction	218
54	Tsuchiya 2002 Tsuchiya, 2006 Watanabe, 2013	9	F	OS/ IIB	DF	7 [9]	ML, BFCD over IM nail	+	12.9	13.8	MSTS 100%				213
55	Tsuchiya 2002 Tsuchiya, 2006 Watanabe, 2013	26	F	low grade OS	DF	9	CF, BT	-	9.7	30.8	MSTS 90%				211

56	Tsuchiya 2002 Tsuchiya, 2006	13	F	OS	PT	5.7	ER, CF, BT	+	20	56.5	MSTS 100%				43
57	Tsuchiya 2002 Tsuchiya, 2006 Watanabe, 2013	9	M	OS	DF	12.6	CF, BT	+	8.8	25.7	MSTS 93%	DS	DUC	Bone graft docking site	125
58	Watanabe, 2013	52	F	Low grade OS	MF	9	BFCD	-	15.3	17.7	MSTS 100%	DC		Bone graft	145
59	Watanabe, 2013	8	M	ES	MT	9.5	BT	+	13.4	31.7	MSTS 100%	DS	AWD	bone grafting	180
60	Watanabe, 2013	14	F	Low grade OS	MT	13.5	BT	-	10.2	28.6	MSTS 100%				278
61	Watanabe, 2013	4	M	Ad	MT	7.8	BT	-	9.9	24.5	MSTS 100%				168
62	Watanabe, 2013	71	F	Ad	MT	4.5	BT	-	18.4	72.9	MSTS 100%	PSI			175
63	Watanabe, 2013	18	F	OS	DF	14	BT	+	8.8	37.4	MSTS 83%	regenerate #		re-fixation	187
64	Watanabe, 2013	46	F	OS	PT	5.5	BT	+	17.3	100.4	MSTS 100%	DC, EC		bone graft	192
65	Watanabe, 2013	17	F	OS	PT	5.7	BT	+	20	56.5	MSTS 100%				131
66	Yang, 2016	29	M	Parosteal OS	PT	11	ML, BT	+	43.6*	51.2*	MSTS 73.3%	PR		Bone graft	51
67	Yang, 2016	16	F	OS	DT	15	ML, BT	+	56*	62*	MSTS 60%	PR, NU		Bone graft and internal fixation with plates	56
Av		21				12.4				36.3	MSTS 91%				Med-ian 48

Ad – Adamantinoma, CS - Chondrosarcoma, ES - Ewings Sarcoma, MFH - Malignant Fibrous Histiocytoma, OS - Osteosarcoma, DF - Distal Femur, DT - Distal Tibia, MT-Mid-Tibia, PF - Proximal Femur, PT - Proximal Tibia, BT- Bone Transport, BFCD - Bifocal Compression-Distraction, CD - Compression-Distraction, CF - Circular Frame, ML - Monolateral External, Fixator, ER - Epiphyseal Reconstruction, LP – locking plate, MR - Metaphyseal Reconstruction, VR - Vascular Reconstruction, Chemo - Neoadjuvant / Adjuvant Chemotherapy, + Received Chemotherapy, - did not Receive Chemotherapy, DI - Distraction Index, EFI - External Fixator Index, * Estimated From Available Data, MSTS – Revised Musculoskeletal Tumor Society Functional Outcome Score (Enneking et al. 1993), DC - Delayed Consolidation, DS - Docking Site Non-Union/ Delayed Union, DU - Delayed Union, EC - Extension Contracture, HF - Hardware Failure, Inf - Deep Infection, LLD - Leg Length Discrepancy, MU - Malunion, NP - Nerve Palsy, PR - Poor Regenerate Formation, PSI - Pin Site Infection, SI - Skin Invagination, SN – Skin Necrosis, TE - Talipes Equinus, # - fracture, TAL - Tendoachilles lengthening, AKA - Above Knee Amputation, LR - local Recurrence, AWD - Alive With Systemic Disease (Metastases), DOD - Died Of Disease, DUC - Died From Unrelated Cause.