Paediatric Cervical Spine Chordoma: A Review

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Abstract: *Objective:* Although new insights on paediatric chordomas have been described in recent publications, few are devoted to those arising from the cervical spine. This study reviews cervical spinal chordoma in the paediatric population with reference to clinical features, imaging and management strategies and prognostication.

Materials and Method: Retrospective observation and analysis of publications (in the English language): a search of the MEDLINE and PubMed database from 1987 to November 2015 has been performed. The key words used are "paediatric chordoma", "cervical spine", "radiology", "symptoms", "therapy" and "prognosis".

Thirty papers meet the criteria, including 11 case-reports on paediatric chordomas that affect the cranio-axial junction and other cervical levels. Ten other research papers emphasising different aspects of the tumours' histopathology, treatment strategies and prognosis form the core material. Also recruited to the study are small cohorts of paediatric patients appearing in 9 mainly surgical papers on cervical chordomas among adults.

Results: Presence of cellular atypia, within a special sub-group, is an indicator of poor prognosis. Apart from children aged five and below, prognostication of conventional cervical chordomas does not differ from those at other sites of the mobile spine. Current trend advocates use of molecular/genetic biomarkers in predicting tumour recurrence in young children. Loss of SMARCB1/INI-1 (a tumour suppressor gene) expression and a raised level of MIB-1 (a protein expressed by proliferating cells) are reliable in such predictions.

A multi-disciplinary approach is ideal in managing cervical chordoma. MRI shows the extent of tumour displacement and encasement of the vertebral artery. Tender anterior neck masses with symptoms of cord compression are common complaints. Complete surgical excision is the goal of treatment but limited physical reserves in children to withstand extensive surgery leads invariably to residual disease. Adjuvant radiotherapy can contain tumour progression but is used with caution to limit toxicity to the cervical cord. Some reports state that cervical tumours have a less favourable rate of successful treatment compared to those in the clivus, but this is a debatable point.

Conclusion: There is close similarity in the clinico-radiological features and management of cervical spinal chordoma among children and adults. Although our understanding of the nature of this tumour in children is incomplete, a child affected by this rare but serious condition has a profound impact on the family.

Keywords: Spinal tumours, children, MRI, therapeutic strategy, prognosis.

1. INTRODUCTION

Chordoma is an uncommon low-grade malignant bone tumour that originates from notochordal remnants of the axial skeleton with an incidence of 0.8 in each million of the population each year. It generally presents in adults from the 5th to 7th decade of life [1]. Chordoma among patients of paediatric age is even more infrequent. Sources from the literature show fewer than 5% of chordomas occur in patients aged 20 years or younger [1, 2]. It is in this age group that enormous interest has been centred on the tumour's nature and uncertain biological behaviour [2]. That the prognosis in young patients afflicted with chordoma is poorer compared to that in adults is a point of much debate [3, 4]. Recent developments in surgery, imaging, immunohistochemistry, genetic/molecular testing and radiotherapy have contributed positively to our study of paediatric cranio-spinal chordomas. There are many interesting facets of this lesion that may justify its classification into a separate entity. The objective of this paper is to review the current literature with reference to this tumour's clinico-radiological findings, management strategies and prognostication.

2. MATERIAL AND METHODS

A search of the MEDLINE and PubMed database on studies pertaining to paediatric cervical spinal chordomas in the English language from 1987 to November 2015 was conducted. Searches on this particular theme were undertaken using the following keywords: "paediatric chordoma", "cervical spine", "radiology", "symptoms", "therapy" and "prognosis".

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E-ISSN: 2311-8687/16

Forty-seven articles have been found following the primary search. Of these results 30 papers meet the criteria. All recent review articles on this topic have been excluded but are retained as sources of reference.

3. RESULTS

There are 11 case-reports devoted to paediatric cervical spine chordoma. These and ten other research papers on paediatric chordomas form the core material of this review. Nine publications on cranio-spinal chordomas in adult patients containing small cohorts in the paediatric age group (up to 19 years old) are also included.

The clinico-radiological features, treatment strategies and prognostication of all those affected are listed in Tables **1** to **4**.

3.1. Clinico-Radiological Findings

3.1.1. Clinical Presentations

The clinical presentations are diverse, being dependent on the tumour's location, histopathological grades and biological behaviour. Thus, pain and stiffness in the neck constitute the main complaints in six of 11 patients in the case-report series. There are multiple levels of involvement, usually from C3 to C5 (Table **1**). Progressive upper extremities weakness from cervical root compression is noted in a similar number of children in this group (Table **1**). Limitations of neck movement, torticollis and quadriparesis form part of the major symptoms in 6 children with atlanto-axial chordomas [5] [see Table **2**]. Similarly, a slow-growing antero-lateral neck mass causing dysphagia is also a common presenting feature [6-8] (Tables **1** and **2**). Facial pain and nasal obstruction can occur in the uncommon event of tumour encroachment on the nasopharynx: adults [4] and children [9] are likewise affected. Dysphonia from tumour compression on the posterior pharynx is infrequent in adults [10], and none among the current case series have this complaint. Symptoms of upper cervical cord compression such as progressive quadriparesis are predominant in 3 young children while one other presents with hemiplegia. The studies by Sibley *et al.* [11] and Scimeca *et al.* 1996 [12] each illustrate a setting of rapid clinical deterioration. The first concerns a 2-year-old girl [11] who succumbed within 3 months to secondary pulmonary deposits from an undifferentiated chordoma compressing the cord at the clival-axial level. The second relates to a girl of similar age [12] in whom an MRI depicted a large enhancing facial mass extending into the foramen magnum. She died within a few months from disseminated metastasis. In recounting the third case, Chavez *et al*. [13] call attention to the swift development of quadriplegia in another 2-year-old girl whose 2x3cm-diameter craniocervical chordoma revealed anaplastic features. In describing the 4th and final patient, Guillonnet *et al*. [14] highlights the odd presentation of right hemiplegia in a 4-year-old whose medulla oblongata is displaced posteriorly by a clival-axial tumour. Additionally, 3 others [6, 15, 16], show MRI features of cord compression although their prime symptomatology ranges from neck to shoulder pain. In contrast, the case-report by Wajchenberg *et al*. [17] is distinctive in that a 19-year-old girl was found with an asymptomatic swelling in the posterior oral cavity during tonsillectomy. The lesion turns out to be a chondroid chordoma.

3.2. Radiological Characteristics

3.2.1. Computed Tomography (CT)

Vertebral body erosion characterises cervical chordomas. Increased bone density or sclerotic change, though a recognised feature even on plain radiographs [18] has not been mentioned in the current series. Neither have the authors of all 11 case-reports noted tumour calcification. Occasionally, there is moderately dense enhancement not specific of chordoma. But lesional characterisation is reliant more on the excellent soft tissue resolution of MRI (Tables **1** and **2**). Yet in our current literature review, CT is the preferred modality in assessing enlargement of the affected neural exit foramina. On evidence of CT the differential diagnosis rests with nerve sheath tumour, lymphoma or a solitary secondary deposit. Although considered an invaluable and safe diagnostic tool amongst adult patients for many decades, CT guided percutaneous aspiration needle biopsy is now commonly used as a therapeutic work-up among paediatric patients [5, 7, 17, 19]. One minor drawback of CT relates to the presence of surgical implants causing artefacts in the calculation of dosage for radiotherapy. Correction of such errors however can be done manually [20] or with the application of computer software.

3.2.2. Magnetic Resonance Imaging (MRI)

All authors in the case-reports are unanimous in the value of contrast enhanced MRI in defining the margins and extent of chordomas. Chordomas show a spectrum of enhancement with mild to moderate being the commonest in children [6, 21], adolescents and young

Table 1: Summary of Case Reports on Paediatric Cervical Spine Chordomas since 1987

Author	Sex/ Age	Clinical Features	Imaging Findings	Pathology	Surgery	Radiotherapy	Follow-Up / Comments
Sibley *et al*. 1987 [11]	F/2½	Neck pain. Torticollis for 2 weeks	CT: lytic lesion clivus, odontoid, lateral mass of C1 with cord compn; CXR: pulmonary infiltrates	Lung biopsy – undifferentiated malignant T	Nil	Nil	DOD 3 months later from pulmonary MET
Karakida *et al*. 1996 [21]	M/6	Pain and stiffness of neck x 3 months. ↓ tendon reflexes Rt UL	MRI: C3 to C5 Rt extra-dural paravert mass with cord compn – poorly enhancing	Conventional CH; Gelatinous T	Lamin C3 – C5 and excision	Nil	N/S
Zhou *et al*. 2009 [24]	F/11	Pain in Cx Sp - 12 months; Lt UL weakness 1 month	Lt paravert T C2 to C4 extraosseous on CT; N/C MRI: Cord compn septation within T suggest CH; D/D neurogenic T	Classical CH	Intra-lesional excision only as no bone involvement	Nil; patient declined	Minor residual disease at 6 months
Guillonnet *et al*. 2012 [14]	M/4	Progressive Rt hemiparesis – 1 month	MRI: mildly enhanced T lower clivus to C2; compn medulla and upper Cx cord	Classical CH	N/S	N/S	N/S A case for discussion: D/D; lymphoma chondrosarcoma; solitary MET
Storm *et al*. 2007 [15]	F/16	Known tuberous sclerosis. Worsening Rt shoulder pain several months. Decreased biceps reflex	N/C T2WI MRI shows large high intense mass in Cx canal with cord compn, extending through Cx foramen. Rt C4 to C6	Classic CH	C3 – C6 lamin initially. Then C4 – C6 corpectomy with GTR of T	Declined proton beam therapy	Tumour free at 1 year
Currier *et al*. 2003 [16]	F/13	Progressive Rt UL pain and weakness. Neck pain x 2 years	N/C MRI: extradural high intensity mass on T2WI; cord compn marked. D/D possible neurofibroma	Physaliferous cells identified: consistent with CH	Initially laminoplasty. Then C3 and C4 corpectomies; fibular grafts C2 – C5	High dose conformal photon – proton	No residual disease at 2 years
Bianchi *et al*. 1989 [8]	M/4	Nasal obstruction progressive difficulty swallowing 12 months. Pharyngoscope: ovoid Lt lateral pharyngeal swelling to C5 level	Enhanced CT: confirmed extent of T from SB to C5. Little enhancement T retro-pharyngeal space. No bone involvement	Classic CH	Lateral Cx incision accesses T in retrostyloid region. Strong adhesions to prevertebral structures. T completely excised	6,000 rads. Other details N/S	ALNW at 5 years
Choi *et al*. 2010 [6] 2 cases	(a) M/10	Palpable Lt neck mass and dysphagia 2 weeks	CT: dumb-bell shaped T widening Lt neuroforamina C2 to C4 levels. Lt verta. Compn. MRI: nil enhancement of paraspinal T from C2 to C4. Disc spaces spared	Classic CH	STR and Lt hemi-lamin C2 to C4	Tomotherapy 54.4Gy 20 fractions at high risk planning volume. Adjuvant proton beam dose N/S.	Residual T at 12 months

Table 1 continue…

Author	Sex/ Age	Clinical Features	Imaging Findings	Pathology	Surgery	Radiotherapy	Follow-Up / Comments
	(b) M/7	Posterior neck pain 2 months	Slightly enhancing dense T encasing Lt verta. Well defined enhancing mass infiltrating C2, C3, C4 vertebrae; widened neural foramen; cord compn	Classic CH	(i) Lamin C2, C3 attempted total removal. (ii) Then removal of residual T along Lt verta	N/S	Slow and gradual onset of pain typical due to bone destruction nerve root compressn
Chavez *et al*. 2014 [13]	F/2	Rapid progressive quadriplegia 1 week	N/C MRI: extradural mass 2x3.1x1.8cm arising from C1 and C2 with marked cord compn mildly enhancing	Poorly differentiated (anaplastic) CH	Resection: extent N/S	N/S	Not classic of CH. Dx partly based on Brachyury positive and loss of SMARCB 1/INI-1 expression
Wajchenberg *et al*. 2015 [17]	F/19	Incidental discovery increased volume Rt Postr oral cavity at tonsillectomy	N/C MRI: T2WI - Hi intense Rt paravert extra-osseous T from C2 to C4 enlarging neural foramina; cord compn T partly cystic. Rt verta "encapsulated"	Trans-oral biopsy: Chondroid CH	Two stage Sx for total excision 2 weeks after emboln of Rt verta	Nil	ALNW at 15 years. MRI: no recurrence. Authors argued chondroid CH had better prognosis
Scimeca *et al*. 1996 [12]	F/1½	Enlarging large Rt neck mass 2 weeks	MRI: Enhancing Rt Postr Cx T. Compn Cx and medulla	Malignant CH	Nil	Nil	Only Chemo: Ifosfamide; doxorubicin. DOD few months later from METS

Abbreviations

ALNW = Alive and well; CH = chordoma; Compn = Compression; Cx = cervical; D/D = differential diagnosis; DOD = Died of disease; Dx = diagnosis; emboln = embolisation; F/U = follow=up; GTR = gross total resection; Lamin = laminectomy; Lt = left; MET = Metastasis; N/C = non-contrast; N/S = none stated; Paravert = Paravertebral; Postr = posterior; Prevert = prevertebral; Rt = right; SB = skull base; Sl = slight; Sp = spine / spinal; Sx = surgery; T = tumour; T2WI = T2-weighted image; UL = upper limb; Verta. = vertebral artery.

Table 2: Summary of Paediatric Series on Cx Spine Chordomas

Authors	No. of Patients	Level	Clinico-Radiological Features	Surgery / Tumour Type	DXR Dose	Follow Up / Comments
Benk V *et al*. 1995 [36]	3 of 18 had Cx CH			Laminectomy Sx resections incomplete all 3 cases		
	(a) F/17	N/S	Neck and shoulder pain	2 procedures / non-chondroid / T Volume 149 cc	71.96 CGE	Had distant MET
	(b) M/18	N/S	Neck and shoulder pain	2 procedures non-chondroid - T Volume 282 cc	70.60 CGE	ALNW at 100 months
	(c) F/16	N/S	Neck and shoulder pain	1 incomplete Sx excision – non-chondroid	68.00 CGE	DOD – local recurrence and distant MET
Yadav *et al*. 2014 [9]	F/2 - 1 of 8 cases – clival and1 nasal CH age range 10 – 18	1 upper cervical 1 nasal	Neck/facial pain; T extends to para-vertebral/carotid and nasopharynx spaces	Nil - atypical	Not given	Expired a week after presentation; MIB-1 Li= 4%

Coffin *et al*. 1993 [7]	3 Cx CH in series of 12 cases					
	(a) F/2.5	Clival and C1 – C2	Torticollis, neck pain, fever, pulmonary nodules	Palliative; atypical	N/S	DOD; MET to lungs 3 months
	(b) F/17	C6 – C7	Cx and epidural mass	Partial resection; atypical	N/S	DOD; MET to lungs and bones
	(c) M/2.5	C7 – T1	Neck mass, brachial palsy and myelopathy	Resection (extent N/S); classic	N/S	DOD; MET to lymph nodes
Habrand *et al*. 2008 [29]	1 Cx and 12 with SB extension to Cx Sp. age range 6 – 17 years	N/S	All 5 patients with local recurrence had pain initially	Incomplete trans cervical resection in 5 Cx CHs / Classic	Proton beam total dose 68.4 CGE	4 of 5 SB with Cx extension failed locally. Mean F/U 26.5 months. Risk of neuro-psychological disorders post DXR
Rutz *et al*. 2008 [20]	2 Cx Sp of 6 CHs age range 10 – 20 (median 16-years) – all post surg					Local control maintained 73 months. Good results proton spot-scanning minimal risk for treatment induced secondary cancer. Local control 38 months
	(a) F/10	N/S	N/S – residual T Vol = 0	Classic	Proton 74 CGE	
	(b) F/14	N/S	Residual T Vol.=0 (?un-detected by imaging)	Classic	Proton 74 CGE	
Rombi *et al*. 2013 [28]	5 Cx Sp CHs in series of 26 CH. Age range: 5 – 21 years (median 13 years)	N/S	CT and MRI for treatment planning			Mean F/U = 46 months. Actuarial 5-year OS=89% considered excellent outcome.
	(a) M/3.7	C-C junction	Presented with pulmonary MET at diagnosis	NIL / de-differentiated	Proton 73.8 CGE and chemo for mets	Alive at 39 months with local progression of disease.
	(b) ?/?	N/S	Cx pain	3 x surgery / N/S	N/S	DOD – local recurrence.
	(c) ?/?	N/S	Recurrent local disease	N/S	Yes 74 Gy	Died of local failure.
Menezes *et al*. 2014 [5]	5 cranio-axial CHs of 23 children with C-C junction T.					
	(a) M/13	C2 – C3	Neck pain; quadriparesis	Pre-op Lt verta embolisation – total resection / Classic	Proton beam	ALNW at 7 years
	(b) M/14	C2	Neck pain; limited motion; CT expanded C2 body and para-spinal extension	Trans-oral resection and fusion; classic	Proton beam	ALNW at 6 years
	(c) F/8	C1	Neck pain; difficulty swallowing; lateral mass C1 and C-C junction	Trans-oral resection and fusion; classic	Proton beam	ALNW at 16 years
	(d) F/6	C2	Neck pain; torticollis; mass C2 body and pre-vertebral space	Lateral extra-pharyngeal T resection; classic	N/S	ALNW at 2 years
	(e) M/7	Clivus to C1 and C2	Quadriparesis; ventral C1 – C2 mass	Trans-oral resection and dorsal fusion; classic	Given: but dose N/S	Alive at 3 years; symptoms improved

Table 2 continue...

Authors	No. of Patients	Level	Clinico-radiological Features	Surgery / Tumour Type	DXR Dose	Follow Up / Comments
Ridenour *et al*. 2010 [41]	7 CHs in mob. Sp out of 35 cases – age range 8 – 25 1 Cx CH - M/16	C6 vertebra	N/Ss	GTR / dedifferentiated	Probably proton beam	Recurrence and died of MET. The only failure following GTR out of 7 others with atypical histology and aggressive behaviour? genetic factor
Yin *et al*. 2011 [43]	3 of 5 CHs in mob. Sp; others in clivus; age range 0.8 to 19 years; mean 9.2 years	Cx level N/S	N/S	3/8 had GTR; 4/8 had STR Anaplastic in 3/8 cases	Yes	Pts with MIB-1 staining 40% and absent INI-1 protein expression; tested positive in 3 with anaplastic histology. All DOD within 1.4 years
Saad *et al*. 2005 [44]	8 with clival CHs; 1 had MET to Cx Sp M/13	Clival and Cx sp	N/S; 6 months	Yes – STR	Yes	DOD 23 months; High MIB-1 Li correlate with T recurrence; expression of percentage E-Cadherin by T cells correlate with recurrence and low survival rate

Abbreviations

ALNW = Alive and well; C-C = Cranio-cervical junction; CGE = cobalt Grey equivalent; CH = Chordoma; Chemo = Chemotherapy; Cx = Cervical; D/D = Differential diagnosis; DFS = disease free survival; DOD = Died of Disease; DXR = Radiotherapy; F / U = follow up; GTR = Gross total resection; Imhisto = immumohistochemistry; MET = Metastasis; Mob = mobile; Ner = nerve; N / S = none stated; OS = Overall survival; PFS = Progressive Free survival; Pts = patients; Recur = recurrence; SB = Skull base; Sp = spine; STR = Subtotal resection; Sx = Surgery; T = Tumour; Verta. = vertebral artery.

Table 3: Summary of Adult Series with Paediatric Cases

Authors	No. of Cases and Sex and Age	Levels	Clinico-Radiological Features	Surgery	Tumour Type	Radiotherapy	Follow Up/ Comments
Wang *et al*. 2012 [27]	F / 17 One of 14	C2 – C3	Progressive neck and shoulder pain	Subtotal resection	N/S	70 Gy	DOD local recurrence 8-months post-surgery
Zhou *et al*. 2014 [19]	F / 18 One of 21	C1 – C2	Moderate motor impairment – 2 months	N/S	N/S	Not given	OS x 1 month ? expired
Neo *et al*. 2007 [32]	M / 19 One of 2	Clivus to C2 – C3	Large retropharyngeal T - adherent to C1	Two staged procedure - complete removal	Classic CH	60 Gy	ALNW 5 years post-surgery
Barrenechea *et al*. 2007 [30]	(a) F / 10	C3 – C4	Rt hand weakness and hemiparesis	Intra-lesion excision	Classic	Proton beam – dose N/S	ALNW at 23 months
	(b) F / 6 Two of 6	C2 – C5	Neck pain	Intra-lesion excision	Dedifferentiated	Proton beam and chemo	DOD at 7 months
Fagundes *et al*. 1995 [40]	One 7 year old of 18 with recurrent Cx sp T	N/S	Neck pain	Type of Sx N/S	Non-chondroid	Median dose of 70 CGE	Further F/U N/S
Yasuda *et al*. 2012 [3]	Five of 6 cases aged <25	C–C junction	N/S	Intra-lesion or complete excision at C-C junction and SB	N/S	N/S	Younger than 25 - poorer outcome esp. PFS. Possible biologically aggressive

Table 3 continue...

Authors	No. of Cases and Sex and Age	Levels	Clinico-Radiological Features	Surgery	Tumour Type	Radiotherapy	Follow Up / Comments
Wippold II *et al*. 1999 [22]	3 of 10 patients adolescent age (a) F/15	C2 – C3	MRI: enhancing neck mass Vertebral collapse C2 and C3 – cord compression	N/S	Classic	N/S	N/S
	(b) M/11	C2 – C3	Rt arm paraesthesia – intensely enhanced T invading C2/C3 and exit foramen compressed VA	N/S	Classic	N/S	Resembled nerve sheath T
	(c) F/11	C5 – C6	Lt arm weakness – MRI epidural mass; cord compression	N/S	Classic	N/S	N/S
Smolders *et al*. 2003 [23]	?/12 One of 6 with Cx CH	N/S	MRI: Dumbbell appearance (axial images) moderate enhancement. Inter-vertebral discs uninvolved	N/S	Classic	N/S	N/S D/D = benign notochordal T lymphoma, neurogenic.
Colli *et al*. 2001 [4]	One 8-year old of 6 Cx CHs in series of 53 adults. Six others: extension from clivus to Cx spine.	Possibly at C1 – C3 level	All had MRI in pre and post-operative periods	Treatment philosophy: to perform the most extensive resection possible	N/S	Proton beam therapy.	Histological pattern and patient age no influence on prognosis. Higher recurrence among abnormal Karyotypes

Abbreviations

ALNW – Alive and well; C-C = Cranio-cervical; CGE = cobalt Grey equivalent; CH = Chordoma; Chemo = Chemotherapy; Cx = Cervical; D/D = Differential diagnosis; F/U = follow up; Lt = left; N/S = none stated; OS = Overall survival; PFS = Progressive Free survival; Rt = right; SB = Skull base; Sx = Surgery; T = Tumour.

adults [22]. On the other hand Smolders *et al.* [23], have found occasional dense and heterogeneous enhancement in a cohort of mainly adults. They suggest that a mix of mucinous contents and tumour lobules have given rise to this appearance. In the studies by both Wippold *et al.* [22] and Smolders *et al.* [23], the T2W low intensity intratumoural fibrous septations, that typify a chordoma, have been unaccountably rare. They reiterate value of the "collar button" sign on sagittal T2W images as distinctive for upper cervical cord compression by this class of tumour. Smolders *et al.* [23] and Zhou *et al.* [24] state that a chordoma has to be differentiated from a notochordal remnant. The former group of investigators also suggest that notochordal harmatoma is a possibility if the lesion is intraosseous, larger and not eroding bone. On MRI these benign lesions show intermediate intensity on T1W sequences while their T2W images are bright; significantly they do not show contrast enhancement. Zhou *et al.* [24] give a brief description of the probability of a benign notochordal tumour (BNT) in the rare event a lesion is paravertebral in position. But most BNTs are intraosseous and situated in the lumbo-sacral spine [25]. In their collection of 16 spinal lesions arising from 8 patients, Iorgulescu *et al.* [25] find BNTs to be more common among adults and only occasionally originate at the cervical spine. The youngest in their series is a 12-year-old who had her small sacral lesion excised on the insistence of her parents. As a BNT shows almost similar MRI signal characteristics as a chordoma, Yamaguchi *et al.* [26] have argued it can, over time, transform into a chordoma.

Of the three surgical articles, two on children [5, 6] and the other on adults [27], the value of MRI in presurgical planning and postsurgical follow-up is stressed. In addition, the initial reports by Colli *et al.* [4] and later those by Rutz *et al.* [20] and Rombi *et al.* [28] have used MRI and CT in their pre-radiotherapy planning in which the gross tumour volume is calculated. Rombi *et al.* [28] also use both modalities to map out tissues at risk, the prime target being the high cervical cord. MRI is imperative in monitoring clinical progress post-therapy. The presence of residual tumour is a critical prognostic indicator [20, 28, 29].

In a study of 7 patients that includes 2 of paediatric age, Barrenechea *et al.* [30] regard MRI as indispensible in defining the extent of vertebral artery involvement preoperatively. In up to 50% of the current case-reports [6, 17, 19, 21], the tumours have pre- and para- vertebral extensions causing at least partial encasement of the vertebral artery (Table **1**). Menezes *et al.* [5] have an almost similar experience in the frequency of partial tumour encasement of that vessel. Among adult patients the incidence of vertebral artery involvement, comprising encasement and displacement, varies from 30% [19] to 70% [27]. At surgery it may be necessary to mobilise this vessel in the process of clearing the tumour tissues. There is scant literature on the role of diffusion weighted (DWI) MRI in distinguishing paediatric chordomas from other morphologically similar conditions. In relating their experience of using DWI MRI in evaluating cranial base chordomas in adults, Yeom *et al.* [31] found that the lower mean ADC value in classic chordomas serves to differentiate them from chondrosarcoma. The same authors also state that where a chordoma's T2 weighted intensity is lower than that of grey matter, this is an indication that the tumour has undergone dedifferentiation.

3.2.3. Cerebral Angiography

To minimise bleeding, Menezes *et al.* [5] advocate pre-operative embolisation of the vertebral artery in selected cases. The case study by Wajchenberg *et al.* [17] illustrates this point: they found significant tumour encapsulation of the right vertebral artery and embolised this vessel, having established by conventional cerebral angiography that the main supply to the posterior cranial fossa was from the left vertebral artery. However, Neo *et al.* [32] have described an equally large prevertebral tumour extending from the skull base to C3 without resorting to vascular intervention, as the vertebral artery is uninvolved. Furthermore, Barrenechea *et al.* [30] caution vascular interventionists that they must be certain the proposed vertebral artery for embolisation is not the sole supply to the posterior inferior cerebellar artery or anterior spinal artery.

3.3. Therapeutic Strategies

3.3.1. Surgery

Surgical treatment for children, especially the very young, is delicate and fraught with potential complications because of the proximity of the vertebral arteries, spinal nerves and cervical cord [19, 27, 33]. This applies especially to tumours at the cranio-cervical junction [3, 5, 27] where the vasculature is rich and fine [34]. The prime indication for preoperative embolisation is to reduce intra-operative bleeding. In the case of pre- and para-cervical chordomas the vertebral artery is embolised/or ligated to facilitate tumour clearance on the affected side [5, 27]. Menezes *et al.* [5] have done so safely and effectively on children. Only rarely, would surgeons request a super selective preoperative embolisation of the tumours' arterial feeders. Nevertheless, Kalish *et al.* [35] did successfully embolise the anterior and deep cervical arteries prior to excision of a C3 to C6 chordoma. In accordance with the excellent paper by Hacein-Bey *et al.* [34] super-selective cannulation of the ascending pharyngeal artery to occlude branches to the rich odontoid arcade is a possibility, but would be difficult to perform on a child.

Although gross total resection (GTR) is the treatment of choice, this is not easily accomplished whether in either adults [27] or children [5]. Wang *et al.* [27] are especially aware of the life-threatening blood loss in the latter instance. A paper by O'Toole *et al.* [33] focuses on children's physical limitations to withstand radical surgery. They also state that surgical reconstruction with bone grafts and metallic fixatures on the growing spine is intricate. On the other hand intralesional resection has its advocates [5, 27] of whom Barrenechea *et al.* [30] have performed this procedure with success. There are also those who practise 2-staged procedures should the tumour be large and spreading from the clivus to the occipital condyles and retro-pharynx. In one of the largest series on cranio-cervical chordomas affecting adults and children, Colli and Al-Mefty [4] had performed two-staged operations successfully.

3.3.2. Radiation Therapy

Proton beam radiotherapy uses the Bragg peak effect at which the effective dose is delivered to the

lesion while sparing the adjacent organs at risk (OAR) [3]. Benk *et al.* [36] are among one of the first to use photon-proton beam irradiation to treat post-surgical cranial and cervical chordomas in children (age range: 4 to 18). The mean dose in their series amounts to 70.8 CGE. No significant difference in outcome is present in a cohort of 18 patients with tumour volumes ranging between 13.9 and 282 cc. They achieve a five-year disease free rate of 63% in a median follow-up of 72 months. Benk *et al.* [36] also report location as a statistically significant prognostic factor; survival rate for patients with cervical chordomas are worse than that in the skull base. However, others [28, 29] have not supported this thesis.

Rutz *et al.* [20] use proton beam spot-scanning, a technique that dispenses with field specific hardware. Other recent publications [28, 29] also regard this regime as the adjuvant radiotherapy of choice in paediatric skull base and cervical spine chordomas. In their series of 25 patients, 20 with skull base and five with cervical lesions, Rombi *et al.* [28] report an overall actuarial survival of 89% using spot-scanning proton therapy. Of the five with cervical spine lesions [28], two have died; one from progressive disease, while the other from local failure having received three additional surgeries. Therefore for those with local failure after surgery and radiotherapy, even the use of additional proton beam therapy may not be able to control disease [3].

Unfortunately, stray radiation dose secondary to proton beam carries a possible risk for the child to develop a second cancer [20, 29, 37]. Habrand *et al.* [29] are cognisant of the fact it can bring a psychological burden on the child and anxiety to the family. The most efficient shielding is required to minimise exposure to organs at risk (OAR). Even so, 3 adolescent patients in our current case reviews [15, 17, 19] have nominated not to receive radiation therapy. For one of them [17] it is on the grounds that tumour excision had been complete: significantly no recurrence is evident at follow-up 15 years post surgery.

In using proton spot scanning to treat children with residual disease, Rutz *et al.* [20] have concluded the best outcome is achieved by administering a high dose. A dose of 68 to 74 Cobalt Gray Equivalent (CGE) is within the non-toxic range, being similar to that for adult patients treated for extracranial chordomas [38]. Although the potential for cervical cord toxicity is low with proton spot scanning, other factors require attention. The paper by Marrucci *et al.* [39] evaluates cervical cord tolerance to high dose 3D proton photon irradiation in 85 patients treated for cervical vertebral tumours. Dose constraints to the cord surface range from 67-70 CGE while the mean prescribed dose is 76.3 CGE [39]. They regard such dose constraints appropriate for conformal radiotherapy but point out that at this dose level the supportive muscular skeletal tissues and vascular supplies are important factors to consider. Significantly such toxicity is related to the number of surgical procedures performed prior to irradiation.

3.4. Prognostication

The seven main factors that influence prognosis are listed in Table **4**.

Incomplete surgical excision invariably leads to local recurrence that has an unfavourable outcome. Surgery for recurrent disease is technically more difficult resulting in a higher incidence of residual tumour [27, 40]. Fagundes *et al.* [40] reinforce the notion that local relapse is the predominant type of treatment failure, reiterating the importance of a combined approach between experienced surgeons and oncologists at the commencement of therapy.

In their studies on the paediatric spinal chordomas, Coffin *et al.* [7] and Ridenour *et al.* [41] identified a special subset with atypical and dedifferentiated features that show an adverse outcome. In studying histopathological risk factors such as necrosis, mitosis and dedifferentiated features, Ridenour *et al.* [41] have found cytological atypia to be the only parameter to reach statistical significance. Rapid vertebral and paravertebral invasion and a high incidence of distant metastasis are the hallmarks of the clinical aggressiveness in this tumour subgroup.

The cytopathology of the physaliferous cells can play a role in predicting the biological behaviour of chordomas. In their study of this easily-identified large “foamy cell”, pathognomonic of chordoma, Crapanzano JP *et al.* (2001) [42] have observed an increase in pleomorphism, nuclear inclusions and bi- or multi-nucleation in 2 of 11 lesions of the spinal axis. Their follow-up reveals cellular dedifferentiation to sarcoma in 1 of the 2 cases. Yadav *et al.* [9] have noted physaliferous cells to be few or absent in 4 of their cases with documented cellular atypia; a fifth shows spindling tumour cells resembling poorly differentiated sarcoma.

Table 4: Summary of Prognostic Factors in Paediatric Cervical Spine Chordomas

	Factor	Reasons	Selected References	Comments
1.	Surgical: Incomplete resection leads to recurrence	Limited physical reserves in the very young: difficult pre-op embolisation	Wang 2012 [27] Coffiin 1993 [7]	Surgery for recurrent disease difficult; higher incidence residual T.
2.	Histopathology: Atypical	A subset with histology atypical and de-differentiated features	Ridenour 2010 [41] Coffin 1993 [7] Yin 2011 [43]	Increase incidence of MET in this group
3.	Patient's Age: 5 years old and younger	High incidence of atypical histology cause early death. Disseminated METS.	Coffin 1993 [7] Ridenour 2010 [41] Yin 2011 [43] Sibley 1987 [11]	Widespread MET cause of death. Spread to lungs, lymph nodes, liver and bones
4.	Affected Level: C-C Junction	Complex vasculatures: increase network of arteries and Cx nerves. Sx difficulties.	Yasuda 2012 [3] Menezes 2014 [5]	Fine vascular structures at SB and upper Cx Sp not easily defined on MRI.
5.	Abnormal imaging feature: Not specific	Features not specific to CHs; Cx Sp neural T and lymphoma can mimic CHs. Must consider benign notochord T.	Smolders 2003 [23] Zhou 2009 [24]	CT guided percutaneous biopsy determines results.
6.	Biomarkers / abnormal Immunohistochemistry: Identify tumour aggression	(1) Increased MIB-1Li and increased expression of E-Cadherin correlate with increase recurrence and low survival (b) Absence/deletion of SMARCB1/INI-1 indicative of T aggression in very young patients	Yadav 2014 [9] Yin 2011 [43] Saad 2005 [44] Chavez 2014 [13]	
7.	Radiotherapy (1) Under dose (2) Side effects	Artefacts caused by hard ware mask real extent of residual T. in planning. Margin of error important as dosage similar to adults is reached.	Rombi 2013 [28] Marucci 2004 [39] Habrand 2008 [29]	MSK support tissues and vascular supply factors to consider at this dose level. Neuropsychological burden on child.

Abbreviations

C-C = Cranio-cervical; CHs = chordomas; Cx = Cervical; MET = metastasis; SB = skull base; Sp = spine; T = tumour.

Irrespective of the spinal level affected, a child's age has a significant bearing on survival. The series by Yin *et al.* [43] reveal that very young children with clival tumours have a high incidence of anaplastic histology, with greater possibilities of recurrence, metastasis and death. In the paper by Coffin *et al.* [7] two of three cervical chordomas at two and a half years of age succumb to the disease within 12 months of initial diagnosis: the first depicts classic features while the second shows atypical histology. In a similar vein, the reports by Sibley *et al.* [11] and Scimeca *et al.* [12] share a common ground where malignant chordomas in the foramen magnum region had caused death within a few months of initial presentation. Contrarily, Ridenour *et al.* [41] have demonstrated that, over an average follow-up period of 129 months (range 1 to 501 months), the mortality rate is 36%, a figure more favourable than some series on adult patients.

In their studies of C-C junction chordomas, Yasuda *et al.* [3] have concluded this tumour subgroup have a less favourable outcome in comparison with those at the clivus. It is also their observation that patients at 25 years of age and younger shows a poorer prognosis than those in middle age. They postulate that natural tumour aggression at a young age might be responsible. In addition the complex vasculatures and neural structures at the cervico-medullary junction make complete excision difficult in all age groups with the prospects of recurrence. The experiences of Zhou *et al.* [19] and Wang *et al.* [27] also support this concept.

There are limitations to imaging when it comes to establishing a firm diagnosis for chordoma as it shares similar MRI features with other neoplasms arising from the cervical spine. Therapeutic strategies for a lymphoma or solitary secondary deposit are dissimilar, but a CT guided percutaneous aspiration biopsy will establish a final diagnosis [42].

Estimating the levels of some common biomarkers is essential in predicting the clinical course of paediatric

chordomas. One of those frequently used is SMARCB 1 INI-1, a tumour suppressor gene in which a decrease in level correlates positively with an increased rate of recurrence and an unfavourable outcome. The other relates to MIB-1Li expression where an over-expression of this marker is predictive of recurrence in those with a history of previous surgery and radiotherapy. Both of these markers are indicators of tumour aggression especially in the very young [9, 43]. The third commonly used biomarker is E-Cadherin that is also a tumour suppressor gene. In their paper evaluating the prognostic indicators for paediatric chordomas, Saad *et al.* [44] put emphasis on the level of expression of E-Cadherin: significantly a raised level correlates positively with increased recurrence and low survival rates [44].

In treating spinal canal tumours with irradiation there is a remote possibility of under-dose to the gross tumour volume (GTV) from artefacts generated by cord shielding. With the use of an iso-centric gantry and spot-scanning Habrand *et al.* [29] are able to avoid such technical deficiencies. Based on the experience in their recent studies of radiation effects on disease-affected children, Rombi *et al.* [28] have given an assurance that low-grade late toxicities such as unilateral hearing impairment, partial hypopituitarism and otitis media are related to therapy to the skull base rather than the cervical spine. In another paper focussing on the use of proton beam to treat paediatric intracranial tumours and craniocervical cancers, Seneja *et al.* [45] state that symptoms of acute toxicities such as nausea and anorexia can arise at a median dose of 5,400 cGy (RBE).

4. DISCUSSION

If there were a weakness in this review, it would be the small number case-reports and the very few paediatric case examples cited in the adult patients series. A sum total of 41 cases, ranging in age from 2 to 25 years, would appear inadequate to categorise paediatric cervical chordoma as a separate entity. But the argument in favour of such concept is the uniqueness of this tumour. It possesses great variations in clinical presentation compounded by interesting morphological mimics: this is exemplified by an excised “neurogenic tumour” that shows physaliferous cells at microscopy [16]. Consider the neural and vascular complexities at the C-C junction, towards which clival and cervical-nasopharyngeal lesions might spread. The rare yet important conditions to be differentiated would include chondrosarcoma, aneurysmal bone cyst and chondroblastoma [5]. The list is incomplete without reiterating the unusual instance of an upper cervical spine lesion, spreading through the pre-cervical fascia into the nasopharyngeal, and peri-carotid spaces to deny a frail child definitive treatment [9].

Apart from the work of Coffin *et al.* [7] and Menezes *et al.* [5] the other investigators in this review tend to frame their work more for the consumption of their specialist colleagues, which from a practical standpoint has been beneficial to us. The surgical papers are educational with good correlation between radiological and operative findings. Yin *et al.* [43] and particularly Yadav *et al.* [9] have given us valuable insights in predicting the biological behaviour of chordomas in the young. The bleak outcome of those less than five years of age leads Yadav *et al.* [9] to hypothesise there are epigenetic events involved. They speculate that molecular alterations in childhood chordoma are different from that of adults, a theory that explains the ominous prognosis of the former. Of late, Almefty *et al.* [46] have highlighted the impact of cytogenetic abnormalities on management of skull base chordomas. They note in the worst scenario, 95% of adults with tumour progression harbour aberrations in chromosome 3 and /or 13. Where both anomalies are present the median survival time of these patients is 4 months. However, there have not been substantiated views on such aberrations on cervical chordomas in the paediatric age as most current research in molecular genetics is on adults. In one of the most recent studies, Sun *et al.* [47] quoted, from a reliable source, the presence of aberrations in chromosome 1p36, 1q25, 2p13 and 7q33 in seven primary chordomas and similar aberrations in eleven recurrent tumours. On a more pragmatic basis, mutations of the suppressor genes TSC1 and TSC2 are the known cause of development of chordomas among patients afflicted with tuberous sclerosis although these tumours arise predominantly from the sacrum [15, 48].

Guiu *et al.* [49] make use of a chordoma’s soft and jelly-like texture in performing an intratumoural injection of carboplatin into a patient with recurrent disease at the cervical spine. Their success and absence of complications of the procedure strongly indicate chordomas are not vascular. In their radiologic-pathological correlation paper, Maclean *et al.* [50] further support this concept by stating eleven lesions in their series are shown to be non-vascular at microscopy. Bleeding therefore depends on the scale of the surgery, such as performing gross resection of multilevel intraosseous lesions. Dissecting an

encapsulated dominant artery free of tumoural adhesions can cause oozing of blood as the extensive pre and paravertebral venous plexus is breached [5, 27].

CONCLUSION

We have dealt with the aberrant molecular genetics and abnormal histopathology that are causative factors of the unfavourable prognosis in a subset of young patients. Apart from these, the clinico-radiological features, therapeutic strategies and overall prognostication of cervical chordomas in both adult and children are near to similar. Our understanding of the biological behaviour of chordomas is incomplete. The only clinical course we know, as keenly expressed by George *et al.* [51], is that some patients would succumb to the disease within 2 years despite receiving optimal therapy while others will survive free from disease progression for 10 years or more. Nevertheless, our attitude and approach towards a child with chordoma must be one of utmost compassion because such a situation has a profound emotional impact on the whole family.

CONFLICT OF INTEREST

We declare that this review paper has no conflict of interest.

ACKNOWLEDGEMENT

We express great appreciation to Ms Pam Dougan for her excellent work in executing her duty as our Research Assistant.

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Received on 05-05-2016 Accepted on 11-05-2016 Published on 15-07-2016

DOI: http://dx.doi.org/10.12974/2311-8687.2016.04.01.1