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The Role of Irradiation in the Treatment of Chordoma of the Base of Skull and Spine

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1. Introduction

Chordoma is an uncommon neoplasm of the bone arising from embryonic remnants of the notochord. The overall age-adjusted incidence is about 8 per 10 million, but this figure is dependent on age, sex, and race (Jemal et al., 2007). This tumor typically occurs in the axial skeleton mainly involving the sacrococcygeal region and the base of the skull (Mirra et al., 2002). The natural history of such malignancy is of a slow but progressive growth ultimately translating into a local aggressive behaviour. Overall, five-year survival rates are near 60% to 70%, although 10-year survival drops to 35% to 40% (Dorfman, 1998). The rate of distant metastases (to lung, bone, soft tissue, lymph nodes, liver, and skin) varies in a range between 0% and 40% (Chambers et al., 1979) even though usually late detected with most patients succumbing to their local disease. Based on these considerations the control of primary disease remains the major therapeutic challenge.

Given the rarity of this tumor, data on efficacy and safety of the treatments are limited and mainly based on few, small sized, retrospective series. The standard of care is considered surgery, when feasible, with the aim of establishing a definitive diagnosis and obtaining the maximal debulking of the lesion. Surgical outcomes depend on tumor location and size at diagnosis. Considering the large size of most sacral lesions and the proximity to critical healthy structures of skull base and vertebral chordomas, maximal resection usually entails a relevant morbidity with poor functional outcome in a significant proportion of patients. Therefore, even if local control and survival rates strictly depend on the achievement of negative margins, radical surgery can be rarely obtained (Cotler et al., 1983). In such scenario recurrence rates can approach 70%.

This situation clearly supports the interest for radiation therapy as an adjuvant modality after residual disease even though the irregular and infiltrative nature of this tumor makes it difficult to be targeted.

The role of irradiation either as a postoperative treatment or as a curative measure in inoperable lesions is widely debated. Chordomas have been historically considered radio resistant tumors requiring high doses of radiation (> 60 Gy) to respond best. However, a dose–response relationship has not been clearly reported across all series (Tai et al., 1995) and the doses needed to control the tumor in general exceed the tolerance dose levels of nearby normal structures (Pai, 2001; Slater, 1988).

Several irradiation modalities have been proposed (particle therapy, intensity-modulated radiation therapy, stereotactic irradiation) without a clearly established superiority of one

technique over the others. No randomized studies are reported in the literature on this topic and the current available evidence is based on mono-institutional series using different treatment techniques over a long period of time, thus limiting the strength of the corresponding findings.

Technological progress has made it possible to improve the quality of irradiation in an attempt to safely deliver high doses to the target volume while sparing organs at risk.

Since the seventies, particles (administered either alone or in combination with conventional photon beam therapy) have been used with the aim to improve the clinical results. Thank to the rapid dose fall-off beyond the target and the corresponding sparing of surrounding tissues, proton beam irradiation shows a distinct dosimetric advantage over conventional external beam radiotherapy. Ions can exploit the same physical advantage along with a superior radiobiological effect.

At the same time, the recent development of new radiation delivery modalities (such as intensity-modulated radiation therapy) has improved the use of conventional photon radiotherapy. Stereotactic radiosurgery has been used as an effective adjunct in the management of small tumors. Fractionated stereotactic radiotherapy with the use of micro-multileaf collimators may help to optimize radiation delivery. As a consequence, hadron-based radiation therapy and best photon-based techniques deserve comparative evaluations. To date, current data suggests that the optimal treatment strategy includes maximal safe resection and shaping of residual disease to a very limited volume (if any) in order to optimize postoperative proton or modern external photon beam radiation therapy (Crockard et al., 2001).

The purpose of this chapter is to review the literature and the developments in the multimodal approach to chordoma with particular regard to the role of radiation therapy.

2. Chordoma of the base of the skull

Base of the skull presentation represents about one third of all chordomas. This tumor usually affects younger individuals, even children and adolescents (Tai et al., 2002), and is diagnosed more frequently in males. In adults, skull base chordomas occur close to the spheno-occipital area while craniocervical lesions most often involve dorsum sella, clivus, and nasopharynx. Chordoma is the only tumor that can present with dysfunction of any cranial nerve due to its location. Patients with skull base chordomas can also develop endocrinological dysfunction due to involvement of the pituitary gland within the sella turcica.

The standard treatment is surgery with the aim to assess the pathological diagnosis and to perform the maximal resection even though a radical removal of the lesion is infrequent due to the critical location and the infiltrative pattern of these lesions. Gross total resection is accomplished in three quarter of the patients and 10-year recurrence free survival is about 30% (Tzorzidis et al., 2006). As a consequence, the likelihood of tumor control is low after surgery alone, even after gross total removal (Menezes et al., 1997). For this reasons, in an attempt to accomplish radical resection and improve the overall outcome, advanced microsurgical techniques have been developed and applied into skull base surgery (Scholz et al., 2010). However, the possibility of complete resection, even with modern surgical techniques, has been associated with still high morbidity and mortality rates (Monfared et al., 2007) as well as with the risk of permanent neurological deficits in 25% of patients (Gay et al., 1995).

The tumor can keep stable even after subtotal resection but the patients ultimately experience local recurrence and need to repeat surgery during the course of their disease. Moreover, recurrent tumors are generally more challenging for surgical interventions and have worse overall outcomes.

In order to avoid the potential evolution of the residual disease, the use of conventional photon radiotherapy was introduced in the eighties in the postoperative setting without being able to increase survival rates but showing longer local control in comparison to surgery alone (Table 1).

Author	Year	Pts	TD range in Gy (med)	% OS (years)		% LC (years)		Med F/U in months
				5	10	5	10	
Cummings et al.	1983	10	25-60 (50)	62	28	41 (3.5)		40
Chetiyawardana et al.	1984	14	30-40	45	23	NA		12-240
Raffel et al.	1985	17	36-69.36 (54.54)	70	--	47	--	60
Amendola et al.	1986	11	53.2-66.3 (60)	30	--	40 (3)		48
Fuller & Bloom	1986	13	47-65 (55)	44	17	23	16	31
Forsyth et al.	1993	39	22.93-67.42 (50)	51	35	39	31	99
Watkins et al.	1993	38	50-60	63	59	34	--	84
Catton et al.	1996	20	25-60 (50)	54	20	23	15	62
Zorlu et al.	2000	18	50-64 (60)	35	--	23	--	42
Cho et al.	2008	11	50.4-69.3 (59.4)	72	--	40	--	55

Legend: Pts: patients; Gy: Gray; TD: total dose; NA: not available; OS: overall survival; LC: local control; Med: median; F/U: follow-up.

Table 1. Published studies on photon beam conventional radiation therapy of skull base chordoma

In general, the series using conventional radiotherapy report on a limited number of patients, treated with median total doses between 50 and 60 Gy, far from the needed high dose level to control such a tumor. As a consequence, the rates of long-term response and survival resulted limited.

High doses (in the range of 70-75 Gy) of radiation are considered necessary for treating chordoma, but, unfortunately, nearby critical neurologic structures (spinal cord, brainstem, optic nerves and chiasm) limit the doses that can be delivered with conventional techniques.

Charged particles, alone or in combination with photons, have been used since long time after surgical excision providing adequate support to their use for their peculiar physical/dosimetric advantage (protons and ions) and radiobiological features (ions) over conventional photon radiotherapy. The estimated overall survival rates obtained with protons range between 62% and 80.5% at 5 years and are of 54% at 10 years (see Table 2). Several types of ions (Helium, Neon, Carbon) have been also used with comparable results (see Table 3).

Author	Pts	Rad. type	TD in CGE (range)	% LC at 5 years	% OS at 5 years	Med F/U in months
Hug et al.	33	P	71.9 (66.6-79.2)	59	79	33.2
Munzenrider & Liebsch	169	P + Ph	66-83	73 (10-year: 54)	80 (10-year: 54)	41
Igaki et al.	13	P	72 (63-95)	46	66.7	69.3
Weber et al.	18	P	74 (67-74)	87.5 (3-year)	93.8 (3-year)	29
Noël et al.	100	P + Ph	67 (60-71)	53.8 (4-year)	80.5	31
Ares et al.	42	P (+Ph 4 pts)	73.5 (67-74)	81	62	38

Legend: Pts: patients; Rad.: radiation; P: protons; Ph: photons; LC: local control; OS: overall survival; Med: median; F/U: follow-up; TD: Total dose; CGE: Cobalt Gray equivalent.

Table 2. Series of skull base chordoma treated with protons

Author	Pts	TD in CGE	% LC at 5 years	% OS at 5 years	Med F/U in months
Berson et al.	32	59.4-80	classical Ch 55, chondroid Ch 36	classical Ch 89, chondroid Ch 80	min. 12
Castro et al.	53	60-80 (mean 65)	63	75	51
Schulz-Ertner et al.	96	60-70 (med 60)	70	88.5	31
Tsujii et al.	25	48-60.8	88 (3-year)	86	NA
Mizoe et al.	34	48-60.8	85.1	87.7	53

Legend: Pts: patients; LC: local control; OS: overall survival; med: median; F/U: follow-up; TD: total dose; NA: not available; CGE: Cobalt Gray equivalent; Ch: chordoma; min: minimum.

Table 3. Series of skull base chordoma treated with ions

The debate on the use of this wide set of irradiation techniques is still open in the radiation therapy community (Brada, 2007, Lodge, 2007, Goitein, 2008). Proton therapy is now widely considered the best radiotherapeutic approach but high level of evidence is still lacking. Hence, this treatment modality probably deserves comparative evaluations with the other available conformal technologies in order to optimize the management of the patients, tailoring the radiation treatment to each specific clinical presentation.

From this standpoint, newer methods of delivering photon-based radiation therapy, including fractionated stereotactic radiation therapy, radiosurgery and intensity-modulated radiation therapy have allowed to deliver the dose with better conformity. In particular, despite the limitation concerning the small size of the suitable target, gamma-knife surgery is the most frequently used radiosurgical machine and it has been employed also in the treatment of skull base chordomas. However, data of the most recent literature on this argument (see Table 4) show not consistent results in terms of local control.

Author	Pts	Mean treated volume	Type of radiation treatment	Med dose in Gy	% LC (years) 5 10	% OS (years) 5 10	Med F/U in months
Chang et al.	10	1.1-21.5 mL	5 CyberK, 5 LINAC	19.4	2 PD	NA	4
Crockard et al.	26	40.8 cm^3 (pre-op.)	GK	15	NA	65 -	51
Krishnan et al.	25	14.4 cm^3	GK	15	32 -	88 -	56
Martin et al.	18	9.8 cm^3 (average)	GK	16.5	63 - (+ 10.4)	63 -	88
Hasegawa et al.	30	19.7 mL	GK	14 .0	72 67	80 56	59
Kano et al.	71	7.1 cm^3	GK	15.0	66 -	80 -	60

Legend: Pts: patients; NA: not available; Gy: Gray; LC: local control; med: median; F/U: follow-up; pre-op.: preoperative; GK: gamma knife; CyberK: cyberknife; LC: local control; OS: overall survival; PD: progression disease.

Table 4. Data of patients with base of the skull chordoma treated with radiosurgery

2.1 Pediatric chordoma

The median age at presentation of chordomas is around 60 years; however, such skull base tumors may occur also at a younger age and has been reported in children and adolescents (Tai et al., 1995).

Special techniques such as intensity-modulated radiation therapy, brachitherapy or intraoperative radiotherapy have been introduced in the management of childhood tumors (Saran, 2004). Proton therapy is treating an increasing proportion of patients (DeLaney et al., 2005) and there is a general agreement that protons will play a major role in the future in treating childhood cancer (Wilson et al., 2005) for its peculiar properties in the potential reduction of secondary cancer risk and reducing rates of late side effects (Miralbell, 2002; Schneider, 2008). Table 5 summarizes some data on the use of particle therapy in chordoma presenting during childhood. In general it is possible to observe that patients with cervical chordoma had a significant worse survival than those with base of the skull presentation, that survival in males was significant superior than in females, and that the reported rate of Grade 3-4 late side effects is very low.

Author	Pts	Radiation	TD in CGE	% LC at 5 years	% OS at 5 years	Med F/U in months
Hug et al	10	P	73.7 (70-78.6)	60	60	30
Hoch et al.	73	P	NA	NA	81	86.5
Habrand et al.	26	P + Ph	69.1	77	100	26.5
Rombi et al.	19	P	74.0 (73.8-75.6)	81	89	46
Combs et al.	7	I	60-66.6	1 progression	-	49

Legend: Pts: patients; P: protons; Ph: photons; I: ions; CGE: Cobalt Gray equivalent; LC: local control; OS: overall survival; med: median; F/U: follow-up; TD: Total dose; NA: not available.

Table 5. Series of skull base pediatric chordoma treated with particles

3. Chordoma of the spinal axis

Overall, chordoma of the spine represents more than half of all chordomas. Along the spinal axis, the most common site of origin is the sacrococcygeal region. The distribution of the remaining vertebral group, in a decreasing order of frequency, is cervical, lumbar and thoracic, respectively. Bjornsson et al. did report that 325 chordomas were diagnosed at the Mayo Clinic since 1902 (Bjornsson et al., 1993). One hundred fifty-six patients (48%) had tumors involving the sacrococcygeal region and 44 (13.5%) had chordomas of the mobile spine.

Because of their slow growth rate, the onset of symptomatology is gradual and long lasting with early symptoms differing according to the anatomical location. At the time of diagnosis, most patients experience pain secondary to bone destruction. However, sacral chordomas may cause rectal and urinary dysfunctions as well as deficient motor function of the lower extremities, whereas lesions involving the rest of the spine usually compress the nerve roots, the spinal cord or adjacent organs mainly translating into sensory deficits, motor disturbances or organ-specific symptoms.

The above-mentioned variability according to the anatomical localization of the tumor along the spinal axis also concerns the tumor size at diagnosis. In fact, sacrococcygeal chordomas can grow filling up the pelvic spaces so that they are usually huge, whereas the limited space availability along the mobile spine translate into an earlier diagnosis of smaller lesions.

The treatment mostly advocated in the literature is surgery. However, the impossibility to achieve an oncologically adequate tumor resection at least in a certain amount of patients has increased the use of radiation therapy as well. Unfortunately, because of the low incidence rate of this malignancy only few centers have achieved extensive experience in the management of chordomas. Nevertheless, the relative rarity of chordomas also explains why the patients collected in clinical series were treated over a long period of time and even managed according to different strategies. Overall, such drawbacks hampered the attainment of robust evidence able to lead the therapeutic strategies.

The present section addresses the main issues dealing with each treatment modality and provides an overview of the main clinical series reported in the literature.

3.1 Surgical management

The spine has a very complex anatomy due to its relationship with vessels (e.g. vertebral arteries in the cervical region), joints, nerve roots, and nearby organs. Besides, structural peculiarities featuring each spinal segment itself add further difficulty. Overall, this makes it tough to accomplish an oncologically proper tumor resection and increases the surgical morbidity as well as mortality. Hence, the best surgical care must include an experienced multidisciplinary team with an oncologic orthopedist, a spine surgeon, a plastic one and a vascular surgeon as well. In fact, several authors noted that patients who received their original surgical procedures outside of recognized centres had worse local control (Bergh, 2000, Schwab, 2009) and/or overall survival (Choi et al., 2010), emphasizing the critical role of experience and clinical expertise in managing this rare malignancy.

Early studies on spinal chordomas reported that the very high local recurrence rates following conventional surgical debulking entailed a very poor survival (Eriksson et al., 1981). Clinical outcomes are considerably improved by the means of better surgical techniques that allowed wide resections and complete removal of the tumors (Boriani et al., 2009). From this standpoint, several series with long enough follow-up have demonstrated that radical resection with adequate surgical margins translates into high local control rate, which ultimately prolongs overall survival. So far, patients amenable by wide resection with adequate margins range between 23% (Yonemoto et al., 1999) and 82% (Ozger et al., 2010) mainly depending on tumor location along the spine and size of the lesion. In fact, the number of vertebral chordomas suitable for radical resection is usually smaller than that occurring in the sacrococcygeal area (Sundaresan, 1979, Bjornsson, 1993, Boriani, 2006). Accomplishing this type of surgery contributes to high absolute local control rates that are very consistent and vary mainly between 72% (Kaiser et al., 1984) and 87% (Hsieh et al., 2009). Few series pointed out even the absence of local relapse (Yonemoto, 1999, Osaka, 2006). Concerning overall survival, radical resection can achieve absolute values in the range of even 90-100% even though these values are reported by a very limited number of studies (Hsieh, 2009, Fuchs 2005). It is noteworthy, that while in some series inadequate surgical margins were an adverse prognostic factor for local recurrence (York, 1999, Bergh, 2000) or for both local recurrence and overall survival (Fuchs et al., 2005), other authors pointed out the lack of such a role (Hulen, 2006, Schwab, 2009). However, ensuring adequate margins can be at the expense of relevant surgical morbidity and mortality. In the management of vertebral chordomas, neurologic deficit and early postoperative deaths have been reported till 55% (Bergh et al., 2000) and 12% of the patients respectively (Boriani et al., 2006). In sacrococcygeal surgical procedures, neurologic deficit correlate with the number of sacrificed nerve roots and the rate of bowel, bladder and sexual dysfunctions can score 89%, 74% and 67%, respectively (Schwab et al., 2009). Besides, fatigues fractures can occur up to 20% of the patients (Bergh et al., 2000), ambulatory deficits till 10% (Hsieh et al., 2009) and wound complications up to 50% of the cases (Hulen et al., 2006) while mortality can achieve 18% (Ozger et al., 2010).

Finally, it is proper to remark that despite apparently macroscopic total resection, local recurrence of disease is not a rare event with most series reporting a rate between 20% (Boriani et al., 2006) and 29% (Ozgeret al., 2010).

3.2 Radiotherapy

Local recurrence and progression are inevitable in case of suboptimal surgery. Hence, postoperative adjuvant radiotherapy has been widely employed in the attempt to achieve local control and possibly improving overall survival.

Since the seventies radiotherapy has been applied both as a curative and adjuvant treatment of spinal chordomas. However, for tumors in this location, it is to note that radiation oncologists face the same constraints hampering an adequate surgical excision. In fact, the tolerance dose of most organs nearby the spine is widely below that providing effective treatment.

From this standpoint, it is not surprising that most of the series employing photon radiotherapy (the main series are reported in Table 6) were not able to deliver average doses exceeding 60 Gy. However, the most recent studies pointed out that the evolutionary developments of photon techniques such as three-dimensional conformal radiation therapy and intensity-modulated radiation therapy allowed the delivery of more than 70 Gy though employed only in a limited number of patients.

Author	N. Irr. Pts	Site	Surg	Dose in Gy Mean/Range	Results (%)	Med F/U in months (range)
Conventional photon radiotherapy						
Cummings et al.	11	11 S	2 ST, 9 B	48/24-66	OS 5y 62 10y 28	NR
O'Neill et al.	11	11 S-Cx	3 MT, 8 ST	-/10-60	ST+RT° 5y OS 55 10y OS 20	(12-240)
Fuller & Bloom	12	9 S, 3 SP	5 ST, 7 B	52/30-70	LC° 5y 42 10y 0 OS° 5y 50 10y 0	Min 60
Romero et al.	10	5 S-Cx, 5 SP	8 ST, 2 B	Conv 60/56-65 Hyper 40/30-59	5y PFS° 0 5y OS° 20	Mean 54 (12-102)
Samson et al.	16	21 S	NR	-/50-65	LC° 5y 77 10y 77	Mean 54
Cheng et al.	13	13 S-SP	13 M/I	54/40-70	LC° 5y 72 10y 44 OS° 5y 84 10y 43	Mean 84 (18-288)
York et al.	18	18 S	8 MT, 10 ST	53/30-74	ST+RT Med TtR 25 months	43 (4-408)

Baratti et al.	10	10 S-Cx	10 M/I	-/50-60	Ab. LC 50	71 (15-200)
Atalar et al.	10	10 S-Cx	7 M/I, 3 B	52/50-62	3y LC° 60 3y OS° 78	Mean 65 (7-152)
Boriani et al.	34	34 SP	8 E-b I/C, 16 I, 10 B/P	40-44/-	I surg +RT Ab LC 25 E-b surg +RT Ab LC 50	(3-155)
Stacchiotti et al.	42	42 S-SP	4 W, 13 M, 25 I	79% pts <60 Gy 21% pts ≥60 Gy	LC 5y 52 10y 33 OS 5y 85 10y 58	142 (76-210)
Chen et al.	15	15 S	15 M/I	50/30-60	Cont. DFS 5y 59 10y 42	Mean 74 (16-182)
"High-tech" photon radiotherapy						
Zabel-du Bois et al.	34	34 S	4 R0, 4 R1, 16 R2, 10 B	PTV1 -/40-66 PTV2 -/60-72	5y LC 27 5y OS 70	54 (4-109)

Legend: N.: number; irr.: irradiated; pts: patients; surg.: surgery; Gy: Gray; med: median; F/U: follow-up; S: sacral; Cx: coccygeal; SP: spinal; MT: macroscopically total resection; ST: subtotal resection; B: biopsy; M: marginal; I: intralesional; W: wide; C: contamined; P: palliative; E-b: en bloc; R0: complete resection; R1: microscopic residual tumor; R2: macroscopic residual tumor; conv: conventional fractionation; hyper: hyperfractionated regimen; PTV: planning target volume; RT: adjuvant radiotherapy; OS: overall survival; LC: local control; y: year; TtR: time to recurrence; ab.: absolute; cont.: continuous; DFS: disease-free survival; °: data from article's graphics; NR: not reported; min: minimum.

Table 6. Main series concerning vertebral chordomas treated with photon radiotherapy

The analysis of the results dealing with photon radiotherapy shows that there was a great variability among the radiation regimens in terms of both total dose and dose per fraction. Probably, this feature can explain why data are not consistent. Overall, the use of a postoperative dose usually less than 60 Gy improved local control compared to subtotal resection only (Cummings, 1983, O'Neill, 1985, Fuller, 1988, Romero, 1993). However, such a dose level does not provide long lasting results. The resulting 5-year local control is only 42% (Fuller & Bloom, 1988) and 10-year overall survival ranges between 0% (Fuller & Bloom, 1988) and 28% (Cummings et al., 1983). At the same time, there are also some series providing better results. Probably, this is because these studies delivered a slightly higher dose to most patients. The corresponding 5-year local control varied between 50% (Baratti et al., 2003) and 77% (Samson et al., 1993) while 10-year overall survival increased up to 43% (Cheng et al., 1999). However, data on long-term local control appear still disappointing especially in comparison with the results of wide radical resection.

It is to note that two authors (Cheng, 1999, Baratti, 2003) pointed out no significant differences in terms of local control and overall survival comparing patients with positive margins treated with adjuvant radiotherapy with those having negative margins who did

Author	N. Irr. Pts	Site	Surg.	Dose in CGE Mean/Range	Results (%)	Med F/U in months (range)
Nowakowsky et al.	12	12 SP	NR	He-Ne +/- Ph 72/-	3y LC 33 3y OS 48	28 (18-89)
Schoenthaler et al.	14	14 S	4 MT, 8 ST, 2 B	He +/- Ne-Ph 75/70-80	LC 5y 55 10y 23 OS 5y 85 10y 22	Mean 65 (22-164)
Breteau et al.	12	11 S Cx	2 B; 10 ID	N + Ph -/55-65 N only -/10 and 17.6	4y LC 54 4y OS 61	NR
Munzenrider & Liebsch	85	85 SP	NR	Ph + P -/66-83	LC 5y 69 10y 48 OS 5y 80 10y 33	36 (1-172)
Hug et al.	14	8 S, 6 SP	4 MT, 8 ST, 2 B	Ph + P 75/67-82	5y LC 53 5y OS 50	Mean 38 (6-136)
Schulz-Ertner et al.	16	8 S, 8 SP	NR	C +/- Ph Ovrl med 68	Ab. LC 87 Ab. OS 87	NR
Park et al.	27	27 S	5 NM, 16 PM, 6 B/ID	Ph +/- P 72/59-84	LC 5y 72 10y 57 OS 5y 82 10y 62	Mean 91 (26-261)
Rutz et al.	26	7 S-Cx, 19 SP	18 MT, 8 ST	P +/- Ph -/59-74	LC 3y 86 5y 69 OS 3y 84	35 (13-72)
Wagner et al.	25	25 S-SP	NR	P, Ph, P + Ph -/70-77	5y LC 73 5y OS 64	32
Imai et al.	95	95 S	95 ID	70/53-74 (70 CGE in 90% of pts)	5y LC 88 5y OS 86	NR

Legend: N.: number; irr.: irradiated; pts: patients; surg.: surgery; CGE: Cobalt Gray equivalent; S: sacral; SP: spinal; Cx: coccygeal; NR: not reported; MT: macroscopically total resection; ST: subtotal resection; B: biopsy; ID: inoperable disease but pathologically proved; NM: negative margins; PM: positive margins; He: helium ions; Ne: neon ions; Ph: photons; N: neutrons; P: protons; C: carbon ions; ovrl: overall; y: year; LC: local control; OS: overall survival; ab.: absolute.

Table 7. Main series concerning vertebral chordomas treated with particle radiotherapy

not receive adjuvant irradiation. Finally, the only series reporting the use of intensity-modulated radiation therapy (Zabel-du Bois et al., 2010) highlighted that dose higher than 60 Gy significantly improved local control and overall survival as well as the radiation delivery at the time of initial diagnosis. The disappointing local control rate reported in this study could be explained considering the wide range of dose delivered to the gross tumor volume with only a limited number of patients receiving 72 Gy.

The significant advantage related to the different energy deposition in tissues supported the use of charged particles (protons, ions, neutrons) also in spinal chordomas. As above mentioned, protons do not have a significant biologic advantage over conventional photon irradiation and only their physical properties make attractive this treatment modality. Conversely, concerning ions, the favorable physical features coexist with a radiobiological advantage that could further increase the tumor control probability.

Such evolutionary technique has been applied to vertebral chordomas only recently. Therefore, only a limited number of studies are reported in literature (main series are summarized in Table 7).

Likewise to photon radiotherapy, mainly mono-institutional retrospective series enrolling a limited number of patients over many years are reported. However, most series employing particle radiotherapy were able to deliver average doses exceeding 70 Gy as well as total doses even higher than 80 Gy.

Therefore, analyzing the results, it is not surprising that they are generally better than those registered in photon radiotherapy series. The 5-year local control ranged between 53% (Hug et al., 1995) and 72% (Park et al., 2006) in the studies employing protons and between 55% (Schoenthaler et al., 1993) and 88% (Imai et al., 2011) in those using ions. The corresponding 5-year overall survival rates varied between 50% (Hug et al., 1995) and 82% (Park et al., 2006) in the proton series and between 85% (Schoenthaler et al., 1993) and 88% (Imai, 2011) in studies using ions. Disappointing results were reported only in one study (Nowakowsky et al., 1992). Almost all these series have not enough long follow-up. Hence, it is fair wondering whether such results are long lasting. With this regard data are not consistent and actuarial 10-year local control varied between 23% (Schoenthaler et al., 1993) and 57% (Park et al., 2006). Concerning overall survival, the actuarial rate at 10 years ranged between 22% (Schoenthaler et al., 1993) and 62% (Park et al., 2006). However, if the best results will be confirmed at adequate follow-up they will be consistent with data reported in patients treated by wide radical resection. This scenario could offer a new standard of care: a function-preserving surgery followed by high-dose radiotherapy (particle or mixed particle/photon). It is worth of note that results pointed out by Imai et al. (Imai et al., 2011) concern only inoperable patients even suggesting the possibility to avoid surgery. Finally, three authors (Nowakowsky, 1992, Schoenthaler, 1993, Park, 2006) pointed out the improvement of local control delivering the irradiation at the time of initial diagnosis.

In summary, radical tumor resection with adequate margins can achieve optimal results in terms of local control and overall survival even though at the expense of relevant peri-operative morbidity suggesting that such surgical procedures could be reserved for patients with a high cure possibility. The functional consequences should be clearly discussed preoperatively with the patient as well as the nature of the disease.

Radiation therapy, when positive surgical margin or residual tumor is present can improve the local control. Long lasting results in terms of local control can be achieved only delivering doses higher than 70 Gy. Such a strategy could also translate in high long-term overall survival rates. In order to optimize the outcome, adjuvant radiotherapy should be applied preferably at the time of initial diagnosis rather than at relapse.

Similar to skull base chordomas management, a function-preserving surgery followed by high-dose radiotherapy could represent a new standard of care.

4. Conclusion

Chordomas are rare primary bone tumors with a high risk for local recurrence and modest propensity for distant metastasis. Optimal therapy of chordoma is a combined approach of maximal safe surgical resection followed by proton beam irradiation for residual disease.
In our review, radiation therapy demonstrated to be a valuable modality for the achievement of durable local control in the postoperative setting, particularly with the advent of charged particle radiotherapy. The use of protons has shown better results in comparison to the use of conventional photon irradiation, with favourable long-term outcome and relatively few significant complications considering the high doses delivered.

5. References

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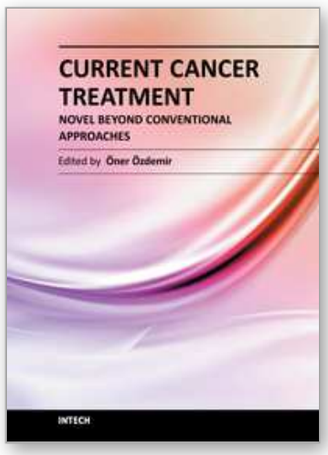

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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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