



Building a global consensus approach to chordoma: a position paper from the medical and patient community

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Chordomas are very rare bone malignant tumours that have had a shortage of effective treatments for a long time. New treatments are now available for both the local and the metastatic phase of the disease, but the degree of uncertainty in selecting the most appropriate treatment remains high and their adoption remains inconsistent across the world, resulting in suboptimum outcomes for many patients. In December, 2013, the European Society for Medical Oncology (ESMO) convened a consensus meeting to update its clinical practice guidelines on sarcomas. ESMO also hosted a parallel consensus meeting on chordoma that included more than 40 chordoma experts from several disciplines and from both sides of the Atlantic, with the contribution and sponsorship of the Chordoma Foundation, a global patient advocacy group. The consensus reached at that meeting is shown in this position paper.

Introduction

Chordomas are rare cancers, which have long been in need of more effective treatments. Innovative treatment approaches have been developed in the past 20 years, but evidence generated by available studies is weak. Therefore, the degree of uncertainty in selecting the most appropriate treatment remains high and adoption of the new treatments remains inconsistent across the world, which results in suboptimum outcomes for many patients.

In December, 2013, the European Society for Medical Oncology (ESMO) convened a consensus meeting to update its clinical practice guidelines on sarcomas, with one aim being to expand the chordoma section. Recognising the special need for a global consensus around the management of patients with chordomas, ESMO hosted a parallel meeting that included chordoma experts from several disciplines and from both sides of the Atlantic, with the contribution and sponsorship of patient advocacy group the Chordoma Foundation.

Quality of existing evidence

At present the quality of evidence available for more common tumour types is considerably stronger than for chordoma. No phase 3 randomised clinical studies and only a few phase 2 trials are available, and most reported clinical evidence is based on retrospective case series. Thus, a degree of uncertainty needs to be accepted when considering regulatory matters and clinical decision making. The approval of imatinib by the US Food and Drug Association and the European Medicines Agency for the similarly rare dermatofibrosarcoma protuberans on the basis of a retrospective case series (and subsequently, 5 years afterwards, a single phase 2 study) should provide a relevant precedent.¹

In this report, we grade levels of evidence from I to V and use grades of recommendation from A to D adapted from the system used by the Infectious Diseases Society of America-US Public Health Service Grading System² (panel).

Epidemiology

Chordoma is a bone tumour with an annual incidence of 0.1 every 100 000 individuals and prevalence of less than

one every 100 000.³ Chordoma is a tumour showing notochordal differentiation. The notochord disappears in human beings at about 8 weeks in the fetal development, and evidence suggests that chordoma develops from persistent notochordal elements. Sites of origin are the sacrum (50%), skull base (30%), and mobile spine (20%).⁴ Extraskeletal cases have also been described but are very rare.⁵

The median age at diagnosis is 60 years, with skull base presentations generally affecting a younger population, including children. The median time from initial symptoms to diagnosis is longer than 2 years, with a clinical presentation at onset that varies according to tumour site of origin. A small number of familial cases of chordoma have been reported, which suggests the potential for genetic predisposition.⁶

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See Online for appendix

Panel: Level of evidence and grade of recommendation

- I Evidence from at least one large randomised control trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomised trials without heterogeneity
- II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
- III Prospective cohort studies
- IV Retrospective cohort studies or case-control studies
- V Studies without control group, case reports, and experts' opinions
- A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (including adverse events and costs), optional
- D Moderate evidence against efficacy or for adverse outcome, generally not recommended
- E Strong evidence against efficacy or for adverse outcome, never recommended

To distinguish prospectively planned studies from retrospective case series, we assigned the level of evidence V followed by “*” to single-group prospective trials

The guidelines were adapted from the Infectious Diseases Society of America-US Public Health Service Grading System.²

Chordoma is typically a low-grade but locally invasive malignancy. More aggressive, so-called dedifferentiated cases can infrequently occur (in around 5% of patients).⁴ Between 30% and 40% of patients have metastases, typically late in the course of their disease, and usually after evidence of local recurrence. Metastases can occur in the lung, liver, bone, sub-cutis, lymph nodes, and other sites. Overall, the effect of the disease is more a function of its local aggressiveness than its potential to metastasise.⁴

Need for initial multidisciplinary joint investigation

Optimum care of chordoma needs a specialised, multidisciplinary approach. Patients should be treated in referral centres or within reference networks with access to facilities with disease-specific, multispecialty skills, including sarcoma or bone pathology, radiology, surgical specialties and subspecialties (general surgery, orthopaedic surgery, neurosurgery, and ear, nose, and throat surgery), radiation oncology, medical oncology, and palliative care. All members of the team should have substantial experience in the treatment of tumours of the skull base or spine, as appropriate.

When a chordoma is suspected radiologically, patient management (including the analysis of biopsy samples) outside of a referral centre should be avoided. All cases should be discussed in the referral centre's tumour board before and after every step of treatment.

Pathology

A pathological review is essential if the first diagnosis was made outside of a referral centre. Immunohistochemistry for brachyury, a transcription factor associated with notochord differentiation, is strongly recommended to substantiate the diagnosis.⁷

Morphology

Macroscopically, chordomas are grey to bluish-white tumours with a glistening intersection-area, which often show a pseudocapsule. Microscopically, they show a lobular architecture with fibrous strands composed of densely packed spindle-shaped fibroblast-like cells, which encapsulate groups of highly vacuolated (physaliphorous) epithelioid tumour cells. Physaliphorous cells are loosely packed and are embedded in a unique and complex stromal extracellular matrix. Necrosis is frequently noted. Chordomas are classified into four histopathological subtypes: conventional, chondroid, dedifferentiated, and sarcomatoid.⁴ Conventional chordoma, also called classic chordoma, forms most cases. Chondroid chordoma is characterised by a matrix mimicking hyaline cartilaginous tumour. Dedifferentiated chordoma contains areas of conventional chordoma next to highly undifferentiated spindle cells or cells resembling osteosarcoma. The dedifferentiated component does not express brachyury.⁴ The characteristic epithelioid cells are largely replaced

with spindle cells in the sarcomatoid subtype but brachyury expression persists.⁴

Immunophenotype

Chordoma are immunoreactive for low molecular weight cytokeratins; however, epithelial membrane antigen and S100 expression is variable.⁴ Brachyury has been recognised as the diagnostic hallmark for chordoma and is helpful for distinction of chordoma from histological entities with similar morphological or immunophenotypic features.⁸ Brachyury is also positive in benign notochordal tumour. Dedifferentiated chordomas lose expression of brachyury, cytokeratin, and other markers.⁶

Imaging

Tumour assessment

The initial investigations should include imaging of the primary tumour site and the whole spine to rule out spine metastases. MRI is the recommended modality for primary tumour assessment⁹⁻¹¹ because it allows for delineation of the different soft-tissue components of the tumour and adjacent structures. MRI is also the best modality to assess for spinal metastases. CT should be used in addition to MRI in case of diagnostic doubt.¹¹

Before surgery, CT with bone window setting is necessary for surgical strategy planning. When involvement of the vertebral or carotid artery is suspected, the intracranial vascular distribution should be assessed by MR-angiography or CT-angiography. After resection, MRI or CT imaging should be undertaken to assess any residual tumour.

MRI studies should always include three axis images. Unenhanced T1-weighted spin-echo sequence, T2-weighted fast spin-echo sequence with fat presaturation or short T1 inversion recovery sequence, and gadolinium contrast-enhanced spin-echo T1-weighted fat suppression should be practised at 1–2 mm section thickness. After the injection of gadolinium-based contrast-medium, most chordomas show minimum to moderate heterogeneous enhancement. Chordomas are hyperintense on diffusion sequence.

CT is practised in most cases with a large field of view. Standard slice thickness is 1 mm to assess bone. Contrast-enhanced CT allows better visualisation of the tumour soft-tissue component.

Few data are available on [¹⁸F]-fluorodeoxyglucose PET in chordoma. Its role in tumour assessment, staging, and response assessment is still to be defined.

Differential diagnosis

Chordoma should be differentiated from benign notochordal cell tumours, chondrosarcoma, giant-cell tumour of the bone, sacral schwannoma, and other tumours of the vertebral body and skull base.

Previously called giant notochordal rests or notochordal hamartomas, benign notochordal cell tumours are benign lesions within the vertebral bodies believed to be

precursors to chordoma. Very small benign notochordal cell tumours are present in the spine of up to 20% of the population,¹² but are only rarely large enough to be detected on imaging examination. Benign notochordal cell tumours typically arise centrally within a vertebral body with healthy cortex and soft tissues surrounding the tumour. They seem sclerotic on CT, and on MRI have high T2 and low T1 signal without any uptake after injection of contrast medium. If radiological appearances are typical of benign notochordal cell tumours, taking a biopsy is not recommended unless the lesion changes.¹³ Presumed benign notochordal cell tumours should be re-imaged periodically to monitor for growth.

Chondrosarcoma can be indistinguishable from chordoma on imaging studies. Diffusion MRI could be useful because apparent diffusion coefficient values are higher in chondrosarcoma.¹⁴ Additionally, chordomas are more often located within the midline. When located in the sacrum, both chordoma and giant-cell tumour of the bone display locally aggressive characteristics. These tumours are more likely to be eccentric, located in the upper sacrum, and affect sacroiliac joints. They can also have an incomplete bony shell, polycystic areas, and fluid levels.¹⁵

Sacral schwannomas arise from the sheath of the sacral nerve roots, and are characterised by pressure bone erosion instead of bone destruction, large and central cystic areas, and absence of adjacent muscles or sacroiliac joint involvement.¹⁵ Other tumours of the vertebral bodies and skull base include other bone sarcoma (eg, osteosarcoma, Ewing's sarcoma), myxopapillary ependymomas,

lymphoma, and multiple myeloma. Finally, metastatic lesions are often multiple, with a patient clinical history usually positive for malignant diseases.¹¹

Localised disease: primary tumour, treatment

A preoperative biopsy sample should ideally be taken, although at sites like the skull base this biopsy can be omitted. The best approach for taking a biopsy sample should be planned with the surgeon. To minimise the chance of seeding, the biopsy track should be included in the surgical resection, although the need to include it in the radiotherapy field is controversial (level of evidence V, recommendation C).

Quality of surgery is crucial for post-surgical outcomes for chordoma at all sites (level of evidence IV, recommendation B).

The chance of long-term survival after local relapse is low, and local control is rarely achieved.

Table 1 summarises the post-surgical outcome in major published series of chordoma of the skull base or cervical spine, and table 2 of the sacrum and thoracolumbar spine. These data are difficult to compare because of their retrospective nature and because the length of follow-up and investigated endpoints vary widely. Length of follow-up is important because of the potential for tumour recurrences more than 5 years after treatment.

According to the wording of the American Joint Committee on Cancer/Union for International Cancer Control residual tumour classification,³¹ we suggest the following definitions of R0, R1, and R2 margins: R0 for

	Number of patients	Skull base, cervical spine, or craniocervical junction	Quality of margins	Number of patients receiving radiotherapy	Follow-up (months)	5-year estimates %			10-year estimates %		
						OS	LRFS	DMFS	OS	LRFS	DMFS
Sen et al (2010) ¹⁶	71	Skull base and craniocervical junction	R1=59 R2=41	44 (62%)	66 (median)	75%	NR	98%	NR	NR	NR
Wu et al (2010) ¹⁷	106	Skull base	R1=78 R2=22	40 (38%)	64 (mean)	68%	47%	100%	60%	12%	100%
Choi et al (2010) ¹⁸	97	Craniocervical junction	NR	97 (100%)	50 (mean)	55%	NR	NR	36%	NR	NR
Wang et al (2012) ¹⁹	14	Cervical spine	R1=5 R2=9	14 (100%)	59 (mean)	86%	50%	100%	NR	NR	NR
Yasuda et al (2012) ²⁰	40	Skull base, craniocervical junction, and cervical	R1=17 R2=23	30 (75%)	57 (median)	70%	NR	87%	NR	NR	NR
Di Maio et al (2012) ²¹	95	Skull base	R1=67 R2=28	33 (35%)	38 (mean)	74%	56%	NR	NR	NR	NR
Ouyang et al (2014) ²²	77	Skull base	R1=57 R2=9	22 (29%)	60 (mean)	71%	45%	NR	46% (8 years)	18% (8 years)	NR
Rachinger et al (2014) ²³	47	Skull base	R1=15 R2=81 Biopsy: 4	30 (64%)	62 (median)	83%	NR	100%	NR	NR	NR

Series were published over the last 5 years. R1=marginal resection. R2=intralesional resection. OS=overall survival. LRFS=local recurrence-free survival. DMFS=distal metastasis-free survival. NR=not reported.

Table 1: Post-local treatment outcome in major series of chordoma of the skull base or cervical spine

negative microscopic margin of 1 mm or greater of normal tissue surrounding the tumour; R1 for microscopic margin of less than 1 mm, but no evidence of macroscopic tumour left behind; R2 for macroscopic tumour left behind or tumour spillage in the intraoperative field. However, the specific locations of these tumours often make it difficult to obtain a margin of more than a few millimetres.

En-bloc R0 resection is the recommended treatment when feasible and sequelae are accepted by the patient. The expected 5-year relapse-free survival after R0 resection is in excess of 50% (tables 1, 2; level of evidence IV, recommendation B). If en-bloc R0 resection seems unfeasible on the basis of location, or the patient does not accept the surgical morbidities, other options should be considered. Salvage of nerve roots might be possible at the expense of a microscopically positive margin. Additionally, tumour extension into the spinal canal precludes a wide margin.

Adjuvant radiotherapy should always be considered for skull base and cervical spine chordomas, and for sacral and mobile spine chordoma if microscopic positive margins (R1) are noted in the final pathological examination and the tumour has not been spilled during surgery, while taking a biopsy sample, or decompression.^{32,33} Moreover, definitive radiotherapy alone (eg, without debulking) is an alternative to surgery (level of evidence V, recommendation C). However, patients need to be informed about the risk of late toxic effects from the increased dose radiotherapy, which have to be weighed against the more immediate sequelae of surgery in some anatomical sites (level of evidence IV,

recommendation B).^{34,35} Supportive care should be incorporated in treatment from the beginning.^{24,25}

Skull base or cervical spine

Biopsy

Whereas a preoperative histological diagnosis is recommended in principle, preoperative biopsy can be avoided in selected cases of suspected skull base chordoma if reaching the tumour site would be problematic or when the risk of unrecoverable seeding is felt to be high (level of evidence V, recommendation C).

Surgery

Surgery should be practised in referral centres or networks with substantial experience in skull base and upper cervical spine surgery by a multidisciplinary team trained in median and lateral approaches, and equipped for microscopic and endoscopic surgery (level of evidence V, recommendation A).

Other specialties and means that might increase surgical efficacy and safety should be available—ie, endovascular team and intraoperative doppler, and neuronavigation and neuromonitoring are suggested. Particularly, neuromonitoring of cranial nerves is suggested to prevent serious comorbidity (level of evidence V, recommendation A).

Surgery should aim towards maximum tumour resection combined with preservation of neurological function and quality of life.^{20,21,35,36} R0 resection can rarely be done at these sites and tumour spillage is unavoidable (figure 1). R1 resection should be the goal of surgical treatment in all cases not amenable to R0

	Number of patients	Sacrum/mobile spine	Quality of margins	Number of patients receiving radiotherapy	Follow-up (months)	5-year estimates			10-year estimates		
						OS	LRFS	DMFS	OS	LRFS	DMFS
York et al (1999) ²⁴	27	Sacrum=27 Mobile spine=0	R0/R1=15 R2=12	13 (48%)	43 (median)	NR	NR	NR	NR	NR	NR
Bergh et al (2000) ²⁵	30	Sacrum=30 Mobile spine=9	R0=17 R1=5 R2=17	7 (23%)	97 (mean)	84%	66%	72%	64%	NR	NR
Fuchs et al (2005) ³⁶	52	Sacrum=52 Mobile spine=0	R0=21 R1/R2=31	None	85 (mean)	74%	59%	63%	52%	46%	46%
Park et al (2006) ²⁷	27	Sacrum=27 Mobile spine=0	R0=16 R1/R2=5	27* (100%)	106 (mean)	83%	61%	72%	63%	49%	58%
Boriani et al (2006) ²⁸	52	Sacrum=0 Mobile spine=48	R0/R1=10 R2=32	34 (65%)	NR	54%	NR	NR	21%	34%	NR
Stacchiotti et al (2010) ²⁹	130	Sacrum=108 Mobile spine=22	R0=48 R1=35 R2=47	42 (32%)	142 (median)	78%	52%	86%	54%	33%	72%
Clarke et al (2012) ³⁰	30	Sacrum=30 Mobile spine=0	R0=0 R1=28 R2=2	10 (33%)	45 (median)	67%	NR	NR	NR	NR	NR

R0=wide resection. R1=marginal resection. R2=intraleisional resection. OS=overall survival. LRFS=local recurrence-free survival. DMFS=distant metastasis-free survival. NR=not reported. *Six patients received definitive radiotherapy without surgery

Table 2: Post-surgical outcome in major published series of chordoma of the sacrum and thoracolumbar spine

resection (figure 2). When dissection of neural structures is impossible, or an associated vertebral artery cannot be sacrificed because of absent collateral flow, surgery should aim to decompress the brainstem and optic pathway and reduce tumour volume to enhance effectiveness of subsequent radiotherapy (level of evidence V, recommendation A).^{23,37–39} If early MRI shows residual tumour in an easy to reach area, then whether direct re-operation should be done is debatable.

Surgical plans should be made with the input of a multidisciplinary team, including a radiation oncologist and should take into account the effect of surgery on radiotherapy plans. Particularly, titanium reconstructive implants should be discussed upfront in view of their possible interference with postoperative radiotherapy (level of evidence V, recommendation C). Cross-links should be avoided in the tumour site. Pituitary function should be checked before surgery.

Intradural extension should be assessed to plan for dural reconstruction and possible cerebrospinal fluid leak management. Fast imaging using steady state acquisition or constructive interference in steady state MRI sequences are very useful for this purpose because they can sometimes help to identify a very thin remaining layer of dura or small intradural tumour extensions. Association of the cavernous sinus should not be deemed an absolute contraindication to surgery. When the vertebral artery is associated, preoperative assessment of the intracranial vascular distribution can be helpful in deciding whether to sacrifice the artery on one side if necessary.

Median approaches should be used for midline extensions (eg, endoscopic endonasal or transoral approaches).²² Endoscopic endonasal approaches can provide a powerful means for tumour removal. Although chordomas are mainly extradural and originate on the midline, lateral extensions often can be effectively accessed with endoscopic endonasal approaches, rather than transfacial approaches (level of evidence IV, recommendation A).^{20,23} Lateral approaches (eg, transpetrosal, far lateral) are necessary for substantial lateral extensions.^{16–19} Use of standard intradural approaches (eg, pterional, retrosigmoid) without the help of an endoscope to merely decompress the neural structures is deemed debatable when the tumour is mainly extradural (level of evidence V, recommendation C).¹⁷

Radiotherapy

After macroscopic complete surgery, adjuvant radiotherapy is recommended (level of evidence V, recommendation B; figure 1). For inoperable patients, radiotherapy after biopsy is the treatment of choice (level of evidence V, recommendation B; figure 3)

Before radiation, MRI and CT tests are necessary to detect intraosseous extension with osteolytic destruction and extraosseous extension. Preoperative

and postoperative CT and MRI with at least T2-weighted sequence should be available in Digital Imaging and Communications in Medicine format. These approaches are valid for all other tumour sites and will therefore not be repeated in subsequent sections. Additionally, a baseline examination including cranial nerves, visual acuity, visual field assessment, and audiometry and pituitary gland function, should be undertaken to assess treatment side-effects (level of evidence V, recommendation A).

The primary clinical target volume (CTV1) should encompass all volumes at risk for microscopic disease, including areas of preoperative tumour extension, and a second volume (CTV2) receiving a higher boost-dose of radiation should encompass any residual microscopic disease in the tumour bed after surgery, followed in some

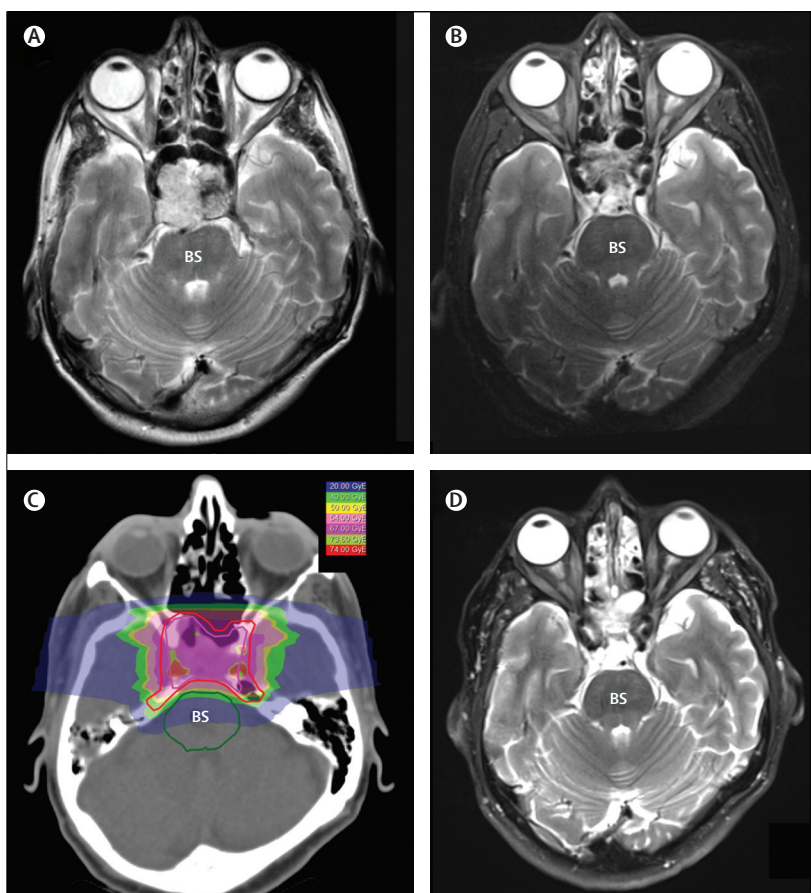


Figure 1: Primary localised skull base chordoma in a 66-year-old man given macroscopic complete surgery followed by high-dose radiotherapy

(A) T2 weighted MRI, axial view, showing a clivus chordoma, compressing the brainstem. Patient underwent a macroscopic complete surgical excision with endoscopic trans-naso-sphenoidal approach followed by proton therapy 74 Gy (radio biological efficacy [RBE]) in 37 fractions in 7 weeks. (B) T2-weighted MRI taken after surgery shows no macroscopic residual disease and brainstem decompression. (C) Radiotherapy plan. Isodoses of proton therapy plan 2 Gy (RBE) x 37 fractions (purple line shows high dose volume, red line shows low dose volume, and green line shows brainstem). (D) T2-weighted MRI taken 16 months after treatment shows no evidence of disease. At the end of treatment patient had grade 1 erythema, whereas the pituitary and visual field deficit present at baseline were unchanged. At 15 months, a worsening of the pituitary failure was detected needing corticosteroids, testosterone, and diuretics. BS=brainstem.

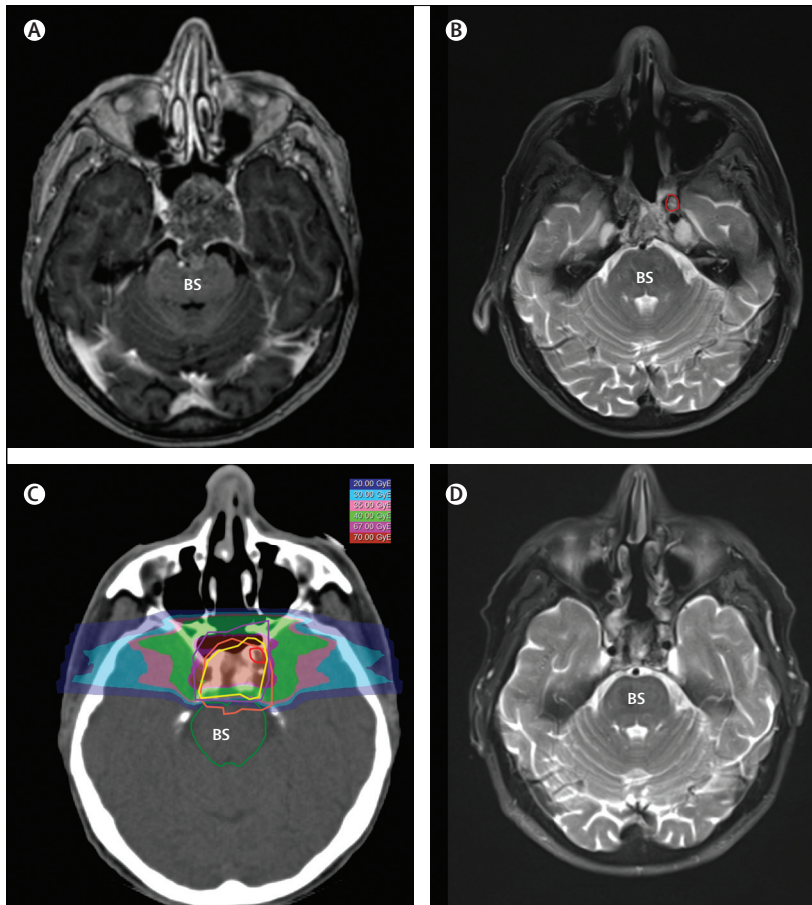


Figure 2: Primary localised skull base chordoma in a 72-year-old woman treated with macroscopic incomplete surgery followed by high-dose radiotherapy

(A) T1 weighted contrast enhanced MRI, axial view, showing a clivus chordoma, compressing the brainstem and infiltrating the cavernous sinus. Patient underwent a macroscopic incomplete surgical excision with endoscopic trans-naso-sphenoidal approach and neuronavigation. (B) T2-weighted MRI showing brainstem decompression and residual disease in cavernous sinus (outlined in red). Surgery was followed by carbon ion radiotherapy, 70.4 Gy (radio biological efficacy [RBE]). (C) The radiotherapy treatment: isodoses of carbon ion radiotherapy plan 4.4 Gy (RBE) $\times$ 16 fractions in 4 weeks (red line shows residual disease, yellow line shows high-dose volume, violet line shows low-dose volume, orange line shows preoperative gross disease, and green line shows brainstem). (D) T2-weighted MRI taken 15 months after treatment shows no evidence of disease. At the end of treatment the patient had grade 1 dysphagia. 15 months after the end of radiotherapy treatment, no toxic effects were reported. BS=brainstem.

cases by a third volume (CTV3) to any sites of residual gross disease (level of evidence V, recommendation A).^{38–42} An image fusion of a planning CT with preoperative and postoperative MRI is necessary to define the CTVs (level of evidence V, recommendation A). Furthermore, a detailed description of the surgical procedure and initial symptoms should be considered when planning the CTV. These general ideas apply to spinal and sacral tumours too.

When prevertebral long muscles are infiltrated, the CTV1 should be extended to include this area (level of evidence V, recommendation B). If evidence of cranial nerve association is noted, volumes should be adjusted accordingly to spare nerves (level of evidence V, recommendation A).

Tumour seeding and recurrence along the surgical pathway for skull base chordoma is reported in less than 5% of cases.^{43,44} To include the entire surgical access path in CTV1 remains controversial (level of evidence V, recommendation C). The inclusion of the retropharyngeal space in the target volume definition as a possible site of recurrence remains controversial too.

Because chordomas are radioresistant, a dose of at least 74 GyE should be delivered to CTV2 and CTV3, using conventional fractionation (1.8–2 GyE) for photon and proton therapy (level of evidence V*, recommendation A).^{37,39–41,45–48} Moderate hypofractionation with 16–22 fractions of 3–4.2 GyE per fraction to CTV2 and CTV3 (66–67.6 GyE total dose) and at least 36 GyE to CTV1 is feasible using carbon ions (level of evidence V*, recommendation B).^{38,49}

During treatment planning, organs at risk such as brainstem, temporal lobes, and optic pathway should be contoured to avoid unacceptable damage. The risk of side-effects have to be discussed individually with every patient (level of evidence V, recommendation A). Dose constraints should be derived from formal analysis of measured clinically relevant toxic effects if available (level of evidence V, recommendation A). For many organs, constraints have to be extrapolated from the general radiotherapy experience. Table 3 summarises recommended dose constraints specifically derived from treatment of chordoma with particle therapy.

The published series show better local control and survival with particle therapy compared with conventional radiotherapy techniques.^{21,38–41,43–46,49,50} Very conformal photon irradiation can offer a viable alternative, but should only be used when similar dose uniformity within the target volume and dose to the organs at risk can be achieved (level of evidence V, recommendation B). This general statement is valid for all the tumour locations.^{28,50–54}

In some situations, mixed beams (particles and photons) enable the development of a more robust plan.⁴⁶ Protons are now being compared with carbon ions in clinical trials (NCT01182779).

Dose uniformity within the gross tumour volume is a prognostic factor for local control even though the most appropriate dose-volume histogram profile is debateable. Inadequate dose at the coolest 5 cm³ (D_{5cc}) of the target volume has been associated with poor local control (level of evidence V, recommendation A).^{46,55}

Daily image guidance is necessary for all types of radiotherapy at all tumour sites to avoid excessive irradiation to adjacent critical organs (level of evidence V, recommendation A).

Sacrum Surgery

Preoperative trocar CT-guided biopsy is recommended. The site of biopsy should be posterior and possibly along the midline.

Surgery should include the biopsy track and be aimed at achieving complete en-bloc resection because this is the most important determinant of long-term outcome (level of evidence IV, recommendation A). Intralesional surgery followed by radiotherapy should not be regarded as an alternative to en-bloc resection, if en-bloc resection is feasible (level of evidence V, recommendation A). Tumour rupture must be avoided because it inevitably results in locoregional seeding and subsequently in locoregional recurrences, which are difficult to salvage (level of evidence IV, recommendation E).

Unfortunately, apparent, adequate margins are only achieved in roughly 50% of cases (figure 4);^{26,29,30} however, several steps should be taken to increase the chance of achieving adequate margins. For example, the anterior resection plane should not fall just beyond the sacral fascia because the likelihood of it being infiltrated is high (level of evidence V, recommendation B). Resection should include the mesosigmoid or mesorectum to keep the tumour covered by healthy tissue (figure 4). Additionally, segmental resection of the rectum can be considered at times (figure 5) and, when done, protected by colostomy to avoid bone infection from colorectal fistula (level of evidence V, recommendation C). However, segmental resection is rarely needed unless a biopsy sample was inappropriately taken through the rectal wall. The tumour might extend laterally to the gluteal muscles or along the sacro-tuberous ligaments. Careful preoperative planning of resection margins should be done to include all these extensions and avoid contamination of the surgical field. Intraoperative CT navigation can be of help to optimise the extent of resection and surgical margins (level of evidence V, recommendation C).

Omentoplasty should also be considered when tumour resection results in a large bone and soft tissue loss (level of evidence V, recommendation C). Similarly, plastic surgery (ie, a rectus muscle myocutaneous flap) should be planned at the time of initial surgery to reduce complications.

Although crucial for the achievement of long-term tumour control, en-bloc resection can result in substantial perioperative morbidity, including bowel, bladder, and motor impairment, which can largely be predicted according to the level of sacral amputation. When planning treatment, these sequelae should always be taken into consideration and balanced against the desire to obtain negative margins.

For tumours arising from S4 and below, surgery should definitely be offered as the first choice to patients (figure 4) (level of evidence IV, recommendation A). For tumours originating from S3, surgery is the standard treatment, especially if preservation of S2 roots is possible because the surgery could result in some neurological recovery (40% of the cases) (level of evidence IV, recommendation A).^{34,56} For tumours originating above S3, surgery always results in important neurological sequelae and the chance of obtaining an R0 resection is lower compared to

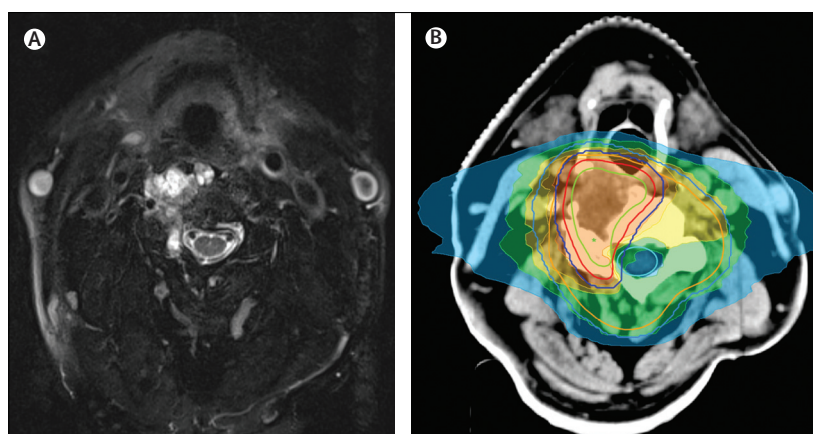


Figure 3: Primary locally advanced cervical spine chordoma in a 77-year-old man given definitive radiotherapy (A) T2 weighted MRI, axial view, showing a chordoma located to C3–C5. Patient underwent carbon ion radiotherapy, total dose 66 GyE carbon ion (45 GyE + 21 GyE Boost) in 22 fractions (dose per fraction 3 GyE), 6 fractions per week, corresponding to 82.5 Gy (2 Gy dose per fraction and α/β value of 2: 82.5 Gy; radio biological efficacy is included in the 66 GyE). (B) The radiotherapy treatment (the green line shows the gross tumour volume, the red line the clinical target volume [CTV], the dark blue line the planning target volume [PTV], the orange line the CTV-primary plan, the light blue line the PTV primary plan). At the end of treatment he had grade 2 mucositis and dysphagia.

chordoma arising below S3 (figure 5). Therefore, the risks and benefits of surgery versus radiation alone should be discussed with the patient (level of evidence IV, recommendation B).⁵⁶ Patients should be informed that local control rates with radiation alone seem to be slightly lower than with surgery and radiation. However, patients who have intact neurological function and do not want to accept the neurological results of a high sacral resection might prefer to accept this slightly higher risk of recurrence. Nevertheless, patients should be made aware that high-dose definitive radiotherapy (level of evidence IV, recommendation C) has a risk of late toxic effects too. For tumours arising from S1, surgery has substantial morbidity. Therefore, definitive radiotherapy should be regarded as a valid alternative to surgery in patients with intact neurological function (level of evidence V, recommendation C) (figure 6).^{34,53}

In all cases, a final treatment plan should be made only after discussion among many specialists, taking into account the unique situation of the patient, and offering all possible alternatives (level of evidence V, recommendation A).⁵¹

Radiotherapy

The general concepts regarding radiation volumes are detailed in the section about radiotherapy of the skull base or cervical spine, although one centre has reported outstanding results with a combination of preoperative and postoperative radiotherapy for mobile spine and sacral chordomas.⁴² The CTV1 should account for the high-risk of lateral diffusion in the gluteal muscles, piriform muscles, iliac wings, quadrilateral lamina, and for the initial extension of the disease, including at least one to two vertebral bodies rostral to detectable tumour

	Clinical endpoint	Dose (GyE) constraints for standard fractionation	Dose (GyE) constraints for hypofractionation with carbon ions
Optic pathway (chiasm and each optic nerve to be regarded separately)	Visual loss	$D_2 < 60$ (level of evidence V, recommendation A)	$D_2 < 40$ (level of evidence V, recommendation A)
Brainstem	Any measurable toxic effects	$D_{\text{surface}} < 63$ (level of evidence V, recommendation C) $D_{\text{centre}} < 50$ (level of evidence V, recommendation B)	$D_{\text{max}} < 40$ (level of evidence V, recommendation C)
Temporal lobe	Necrosis visible on MRI	$D_2^* < 71$ (level of evidence V, recommendation B)	$D_{\text{maxV-1cc}} < 68.8$ (level of evidence V, recommendation B)
Cauda equina/sacral nerve roots/peripheral (sciatic nerve)	Pain/sensorimotor deficit	Total dose < 70.2 (level of evidence V, recommendation A)	$D_{10 \text{ cm sciatic nerve}} < 70$ (level of evidence V, recommendation A)
Skin	Skin necrosis, need of skin grafting	No specific data	$D_2 \text{ cm}^2 < 60$ (level of evidence V, recommendation A)
Spinal cord	Any clinical symptoms	Cervical spine $D_{\text{surface}} 67$ (level of evidence V, recommendation A) $D_{\text{centre}} 55$ (level of evidence V, recommendation A) Lumbar or thoracic spine $D_{\text{surface}} 63$ (level of evidence V, recommendation A) $D_{\text{centre}} 54$ (level of evidence V, recommendation A)	No specific data

For level of evidence and grade of recommendation see Panel. D_2 =dose to the 2% of the volume. D_{surface} =dose to the surface of the brainstem. D_{centre} =dose to the centre of the brainstem. D_{max} =maximum dose. $D_{\text{maxV-1cc}}$ =maximum dose received by the organ after subtracting from its volume the cubic centimetre that receives the highest dose. $D_{10 \text{ cm sciatic nerve}}$ =dose to 10 cm of the sciatic nerve. *Dose at 2 mL.

Table 3: Recommended dose constraints for organs at risk

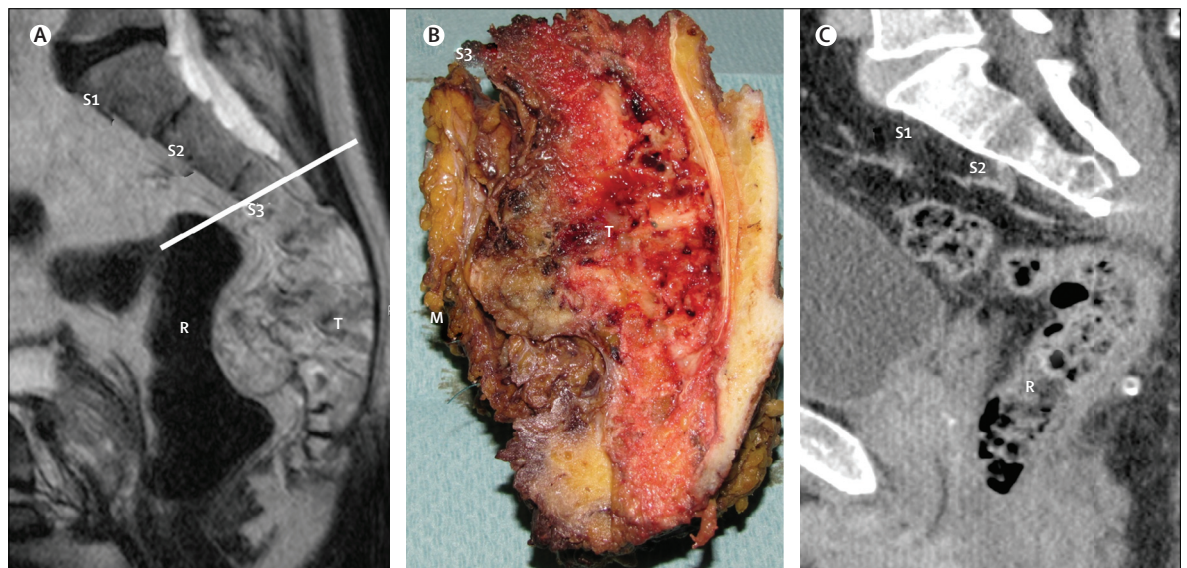


Figure 4: Primary localised sacral chordoma arising below S3, in a 55-year-old man who had surgery

(A) contrast enhanced T1 weighted MRI, sagittal view, showing a low sacral chordoma, involving S4–S5. The cut level is shown by the white line. (B) Surgical specimen cut along a sagittal plane. The anterior surface of the tumour is covered by mesorectum. Microscopic margins are negative. (C) Postoperative CT scan, sagittal view, showing the sacral stump. Bladder and sexual intestinal functions were fully recovered in 6 months. S1=first sacral vertebra. S2=second sacral vertebra. S3=third sacral vertebra. R=rectum. T=tumour. M=mesorectum.

(level of evidence V, recommendation A). In case of R1 resection, CTV2 needs to include the area of positive resection margin, as reconstructed by description of surgery and pathological changes report (level of evidence V, recommendation A). After R2 resection, CTV2 needs to include areas of microscopic disease followed by a further cone down to CTV3 to include visible tumours plus reduced margins (level of evidence V, recommendation A). After R0 resection, the

role of a reduced volume boost on a CTV2 is still controversial (level of evidence V, recommendation C).⁴²

In case of macroscopic residual disease, high-dose radiotherapy (more than or equal to 74 GyE) with conventional fractionation (photons and protons) has to be delivered to the CTV2, and at least 50–54 GyE to the wider CTV1. In case of R1/R0 resection, the dose to high-risk volume can be limited to 70 GyE (level of evidence V, recommendation A).^{27,42,52,56,57} In case of macroscopic

disease, moderate hypofractionation is feasible (3–4·4 GyE per fraction, in 22–16 fractions with carbon ions) with the wider CTV1 receiving at least 36 GyE (level of evidence V*, recommendation A).⁵³

The general principles regarding organs at risk are detailed in the skull base and cervical spine radiotherapy section above. The cauda equina, sacral nerve roots, rectum, sigmoid colon, small bowel, and skin need to be contoured and respected during treatment planning. The risk of side-effects should be discussed with every patient (level of evidence V, recommendation A).

The general approach described for skull base chordoma applies to sacral chordoma too. Carbon ion or proton-beam radiotherapy should be used for definitive treatment after biopsy only in patients who do not want surgery (level of evidence V*, recommendation A).⁵³

Thoracolumbar

Surgery

Taking a preoperative, trocar, CT-guided biopsy is recommended. The approach should be posterior (track always through the pedicle) (level of evidence V, recommendation B).^{58,59}

Surgery should be practised following the same principles applied to that for sacral tumours. Thoracic vertebral bodies are those most suitable to resection with acceptable morbidities. When en-bloc resection is feasible, surgery is the recommended primary treatment (level of evidence IV, recommendation B). Resection of lumbar vertebral bodies is inevitably followed by major functional sequelae at least to one lower limb. If feasible, R0 resection remains the primary approach (level of evidence IV, recommendation B), but it should always be discussed in the context of other alternatives (level of evidence V, recommendation B). Transection of the posterior elements to accomplish vertebrectomy might unavoidably pass through the tumour; adjuvant radiotherapy is to be used in such cases.

When tumour extension into the neck, the thorax or mediastinum, or the retroperitoneum prevents an R0 resection, a combination of radiotherapy and surgery can be considered (level of evidence V, recommendation B).

Definitive radiotherapy has to be considered when the disease is not resectable or if the patient does not accept surgery-related neurological impairment (level of evidence V, recommendation A). In selected cases preoperative or postoperative radiotherapy (to avoid the difficulties of metal implant artifacts) can be used if there was risk that surgery would result in incomplete resection (level of evidence V, recommendation B).^{21,34,42} In selected cases, intraoperative dural brachytherapy can be used in combination with external beam radiotherapy (level of evidence V, recommendation A).^{60,61}

Definitive radiotherapy in operable patients is a controversial issue and could be considered within clinical studies, especially for the cervical and lumbar

spine (level of evidence V, recommendation C). The role of postoperative radiotherapy in case of R0 resection is still controversial (level of evidence V, recommendation C). Simple laminectomy and surgical debulking of intracanal tumour without metal implant insertion can be done to help with radiotherapy, if en-bloc resection is not feasible (level of evidence V, recommendation C). The potential effect of spine-stabilising metal implants should be discussed by the surgeon and the radiation oncologist before surgery.^{30,54}

Radiotherapy

The general approach to radiotherapy technique is described in the skull base or cervical spine radiotherapy section. CTV1 should include one vertebral body, both cranial and caudal to the detectable tumour and paraspinal muscles. Dose and fractionation are identical to those applied to skull base chordoma (level of evidence V, recommendation A).^{21,34,42,57}

The general principles regarding organs at risk are detailed in the skull base or cervical spine radiotherapy section. Spinal cord, nerve roots, skin, and where relevant, small bowel, kidneys, lungs, oesophagus, and heart have to be contoured and avoided during treatment planning. Potential side-effects have to be discussed individually with every patient.

The general approach described for skull base tumours applies likewise to thoracolumbar chordoma. If artifacts from metal implants prevent adequate dose delivery with particles, advanced photon radiotherapy might be preferable (level of evidence V, recommendation A). In selected cases dural plaque intraoperative brachytherapy can be considered for a boost dose (level of evidence V, recommendation A).^{62,63}

Locoregional relapse

Patients who recur locally are unlikely to be cured by any local salvage treatment. Treatment choice can include surgery, radiotherapy, and systemic treatment, balancing morbidity and quality of life.⁶² Detailed recommendations about the management of recurrences are not within the scope of this publication and will be the subject of a subsequent consensus meeting and publication.

Advanced disease (metastatic and locally advanced not amenable to surgery or radiation)

Surgery

Surgery, radiofrequency ablation, or stereotactic radiation of metastases can be considered in selected cases as palliative treatment.^{62–65} Nonetheless outcome data following these procedures are sparse and no recommendations can be made.

Drug therapy

At present, no drugs are approved for the treatment of advanced chordoma. Cytotoxic chemotherapy is generally inactive. The only chemotherapy that has been

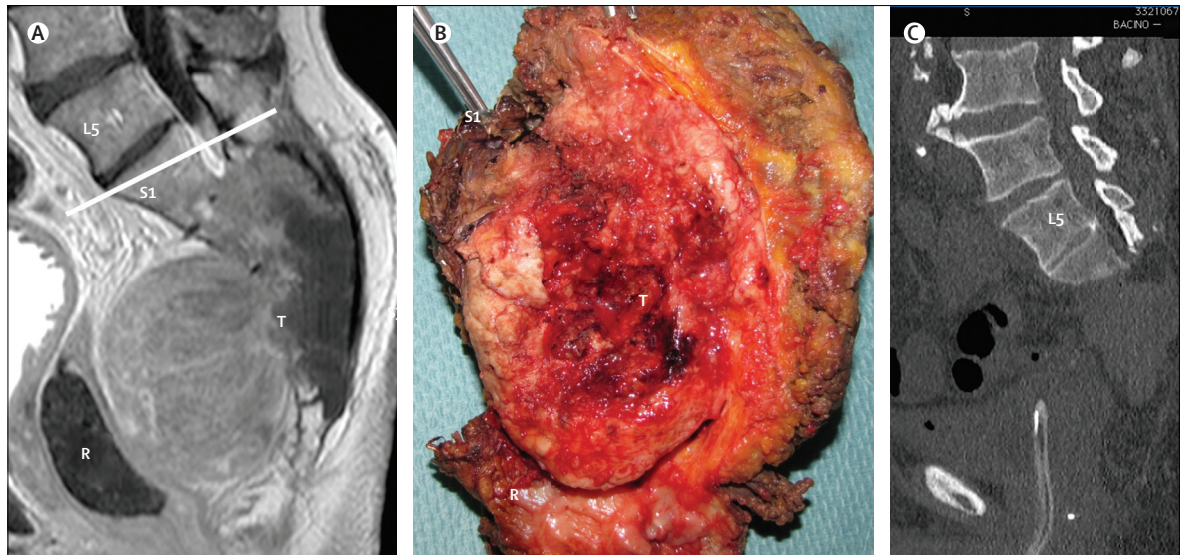


Figure 5: Primary localised sacral chordoma involving S2, in a 72-year-old man who had surgery

(A) Contrast enhanced T1 weighted MRI, sagittal view, showing a high sacral chordoma, involving S2-S4. The cut level is shown by the white line. (B) Surgical specimen cut along a sagittal plane. The anterior surface of the tumour is covered by the rectum. Microscopic surgical margins are close at the sacral stump. (C) Postoperative CT scan, sagittal view, showing the sacral stump. The operation is followed by definitive faecal incontinence, sexual impotence, and urinary retention, but no functional impairments to the lower limbs. L5=fifth lumbar vertebra. S1=first sacral vertebra. R=rectum. T=tumour.

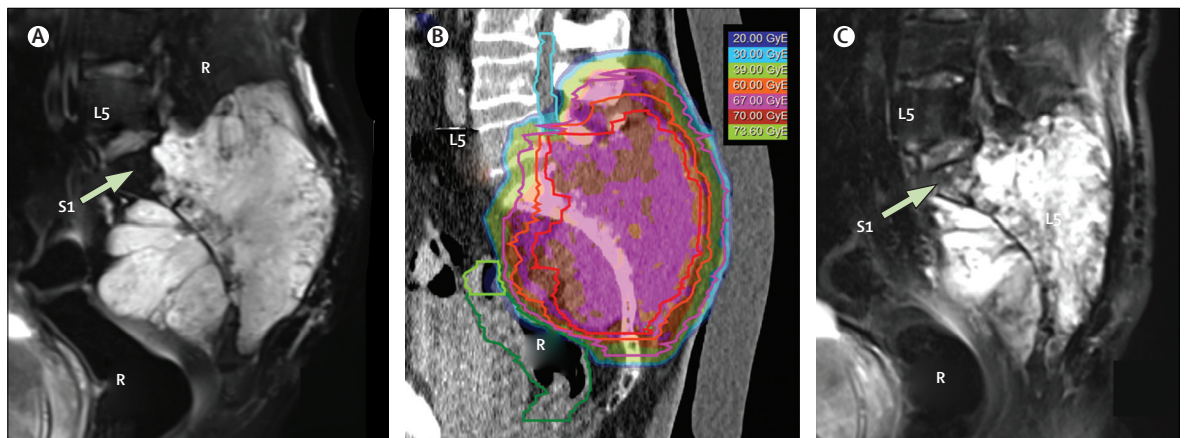


Figure 6: Primary locally advanced sacral chordoma in a 67-year-old man given definitive radiotherapy

(A) T2 weighted MRI, sagittal view, showing a 13 cm chordoma involving S1 and L5, iliac wings and the surrounding soft tissues. Surgery was excluded and patient was given definitive radiotherapy. He received carbon ion radiotherapy, 73.6 Gy (radio biological efficacy [RBE]) in 16 fractions of 4.6 Gy (RBE) each in 4 weeks. Radiotherapy plan is depicted in (B) (red line shows macroscopic disease, orange line shows high-dose volume, purple line shows low dose volume, green lines show rectum, and sigmoid light blue line shows cauda-equina). (C) T2-weighted MRI, 10 months after treatment shows initial tumour shrinkage. At the end of radiotherapy treatment no signs of toxic effects were detectable. 10 months after end of treatment patient reported a grade 1 hypo-paesthesia, grade 1 skin hyperpigmentation, improvement in pain and walking impairment present at baseline, and the complete resolution of urinary incontinence. S1=first sacral vertebra. L5=fifth lumbar vertebra. R=rectum.

tested in a phase 2 trial is irinotecan, which resulted in one out of 15 treated patients having an objective response, and median 6-month progression-free survival of 33% for all treated patients (level of evidence V*, recommendation D).⁶⁶ Anecdotal reports exist of responses to anthracyclines, cisplatin, alkylating agents, and etoposide, in high-grade dedifferentiated and paediatric cases.⁵⁸ Overall, not enough evidence is available to recommend chemotherapy for chordoma (level of evidence V, recommendation D).

Some potentially relevant therapeutic targets have been identified in chordoma, including mTOR, β -type platelet-derived growth factor receptor (PDGFRB), EGFR, and MET.⁴ Inhibitors of several of these targets have shown slight activity in the disease. Most notably, in a multicentric, non-randomised, phase 2 study of imatinib in patients with advanced chordoma⁶⁷ the objective response was achieved in one (2%) of 50 patients according to the Response Evaluation Criteria in Solid Tumors,⁶⁸ whereas a minor response

	Trial registration number	Treatment modality	Clinical setting	Country
Phase 3 trial of proton versus carbon ion radiation therapy in patients with chordoma of the skull base (HIT-1)	NCT01182779	Radiotherapy	Skull base, localised, primary	Germany
Phase 2 study of high-dose intensity modulated proton radiation treatment with or without surgical resection of sarcomas of the spine, sacrum and skull base	NCT01346124	Surgery + radiotherapy	All sites, localised, primary	USA
Phase 1 study on nilotinib with radiation for high-risk chordoma	NCT01407198	Medical therapy + radiotherapy	All sites, localised, primary	USA
Phase 1 safety study of intratumoral injection of <i>Clostridium novyi</i> -NT spores to treat patients with solid tumours that have not responded to standard therapies	NCT01924689	Locoregional medical therapy	..	USA
Phase 1 study to assess the safety and tolerability of GI-6301 (whole heat-killed recombinant yeast modified to express brachyury protein) in adults with solid tumours	NCT01519817	Medical therapy	Advanced phase	USA
Phase 2 study on imatinib in combination with everolimus in advanced chordoma	EUDRACT 2010-021755-34	Medical therapy	Advanced phase	Italy

Table 4: Clinical trials in progress

(ie, less than a 30% maximum diameter decrease) was achieved in an additional 20% of patients. Median progression-free survival was 9 months. A PET response at 3 months was reported in 39% of assessable patients. Symptomatic improvement evaluated by the Brief Pain Inventory score⁶⁹ was consistent with the response assessment (level of evidence V*, recommendation B). Efforts are needed to make imatinib accessible for patients with advanced disease. Additionally, a retrospective study⁷⁰ showed that the mTOR inhibitor sirolimus in combination with imatinib could be more active than imatinib alone. A phase 2 study of imatinib plus everolimus in advanced chordoma is in progress (EUDRACT-2010-021755-34).

In another trial, 44% of patients with chordoma treated with sunitinib achieved stable disease for at least 16 weeks (level of evidence V, recommendation C).⁷¹

Several case reports noted activity of EGFR inhibitors (cetuximab, erlotinib, and gefitinib),⁷²⁻⁷⁴ and as a result a phase 2 study of lapatinib was run in EGFR-positive advanced chordoma. However, lapatinib showed only slight activity (level of evidence V*, recommendation C).⁷⁵

Follow-up

For the first 4 to 5 years after diagnosis, MRI of the primary tumour site and the area at risk of tumour implantation should be done every 6 months. Thereafter, if no disease progression is observed, MRI should be done yearly for at least 15 years (level of evidence V, recommendation C). The appropriate frequency of imaging for other sites of metastatic disease is still to be determined.

Ongoing studies and future directions

At present, surgery and high-dose radiotherapy are the treatment mainstays for localised chordomas, both of which have a curative potential. Studies randomly assigning patients between the two approaches or combinations thereof have not been done and probably

will not take place in the future because of ever-evolving technologies, differences across presentations, and the duration of follow-up needed to assess definitive endpoints. Even so, prospective studies assessing and refining available techniques should be a priority. Table 4 summarises clinical trials that are in progress.

With regard to drug therapy, further prospective studies are needed. Drugs have been identified that show activity in preclinical models of chordoma, creating rationale for upcoming clinical trials. However, the design of clinical trials is complicated by the rarity of the disease and difficulty of defining reliable and valid surrogate endpoints. With new targeted therapies, response often does not result in a change in tumour size, but substantial changes in tumour tissue characteristics (eg, tumour density by CT scan, contrast enhancement by MRI, and max standardised uptake value by PET scan) have been documented. Therefore, new tumour response criteria are needed. Potential alternatives include the growth modulation index (a comparison of progression-free survival before and after treatment),⁷⁶ PET response, changes in tumour contrast uptake, and circulating tumour DNA. Quality-of-life outcomes need to be investigated in all studies.

The rarity of chordomas makes high-power randomised clinical trials challenging, and as such uncontrolled studies, case series analyses, and even case reports

Search strategy and selection criteria

We searched abstracts in PubMed, ASCO, and ASTRO for articles in English with the terms "chordoma", and "incidence", "diagnosis", "biology", "brachyury", "radiology", "surgery", "radiotherapy", "protons", "carbon ion", "chemotherapy", "drug therapy", "tyrosine-kinase", "prognosis", "relapse", "metastasis", "radiofrequency", "out-come", "palliative care", "review". We included papers published between Jan 1, 1990, and May 15, 2014.

should be regarded as contributing to the available evidence. Observational studies merit attention in the disease because they have the ability to provide external controls for future uncontrolled studies. To this end, a European patient data registry is being developed.

Contributors

SS planned and organised the consensus event, chaired the consensus meeting, and contributed to scientific literature review, drafting of the report, and final approval. JS organised the consensus event, and contributed to scientific literature review, drafting of the report, and final approval.

Declaration of interests

SS reported grants, personal fees and other from Novartis, grants and personal fees from Pfizer, grants from GlaxoSmithKline, grants from Bayer, grants from Roche, outside the submitted study. JS declares no competing interests.

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