Best practices for the management of local-regional recurrent chordoma: a position paper by the Chordoma Global Consensus Group


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Chordomas are rare, malignant bone tumors of the skull-base and axial skeleton. Until recently, there was no consensus among experts regarding appropriate clinical management of chordoma, resulting in inconsistent care and suboptimal outcomes for many patients. To address this shortcoming, the European Society of Medical Oncology (ESMO) and the Chordoma Foundation, the global chordoma patient advocacy group, convened a multi-disciplinary group of chordoma specialists to define by consensus evidence-based best practices for the optimal approach to chordoma. In January 2015, the first recommendations of this group were published, covering the management of primary and metastatic chordomas. Additional evidence and further discussion were needed to develop recommendations about the management of local-regional failures. Thus, ESMO and CF convened a second consensus group meeting in November 2015 to address the treatment of locally relapsed chordoma. This meeting involved over 60 specialists from Europe, the United States and Japan with expertise in treatment of patients with chordoma. The consensus achieved during that meeting is the subject of the present publication and complements the recommendations of the first position paper.

Key words: chordoma, sarcoma, relapse, radiotherapy, surgery, chemotherapy

Introduction

Chordomas are rare, malignant bone tumors of the skull-base and axial skeleton [1]. Loco-regional recurrence is a common event following initial treatment of chordoma patients, and represents a major clinical challenge, which these recommendations seek to address. Loco-regional recurrence is defined as tumor relapse or progression after surgery and/or RT of the primary tumor at the same site and/or contiguous spreading of tumor from the primary site to adjacent areas. This includes progression of treated primary lesions, lesions recurring usually at, or near surgical margins, lesions that develop as a result of iatrogenic seeding along a biopsy or surgical tract, as well as skip metastases in the immediate vicinity of the tumor. In most cases, spread of the tumor is mediated by direct physical contact rather than dissemination via lymphatic, circulatory or subarachnoid routes. As such, cases with lymph node involvement are considered to have metastatic disease and are thus not addressed in these recommendations.

Published case series reporting post-surgical outcomes for chordoma indicate that loco-regional recurrence affects >50% of patients treated with macroscopic complete resection with or without RT (Tables 1–3). Notably, a high proportion of recurrences occur late (after 5 and 10 years), requiring long-term follow-up [2, 3]. Limited data are available about long-term recurrence-free survival (RFS), but all available long-term survival projections do not plateau, even after optimal local therapy. In particular, RFS or local control (LC) of skull-base chordomas at 5 and 10 years is 47–76% and 42–71% [3, 4], respectively, while observed even at 15 years.

Major determinants of local control in primary chordomas at all sites include tumor size, extent of resection, quality of surgery, quality of RT (e.g. dose, volume, timing and dose inhomogeneity) and patient age [2, 7–9]. The experience of the treatment center may also play a role in the likelihood of recurrence.

Patients whose tumors recur/progress locally are challenging to control in the long-term and only a minority can be cured. Hence, every effort is needed to maximize the chances for long-term control of tumor with optimal management of the patient at the time of initial treatment. Nevertheless, with optimal treatment, long-term disease control and good quality of life (QOL) may still be possible for some patients. Thus, defining evidence-based best practice to manage this disease state is of utmost importance in order to improve patient outcomes.

Methods, level of evidence and grade of recommendation

To generate the recommendations summarized herein, a consensus group meeting was organized in Milan in November 2015 by ESMO and the Chordoma Foundation (CF). Representatives from the all the disciplines involved in care and treatment of patients with chordoma participated, including specialists in pathology, radiology, neurosurgery, ENT surgery, orthopedic surgery, general surgery, radiotherapy (RT), medical oncology, and palliative care (PC). A representative from main European, United States and Japanese RT centers with protons/carbon ions facilities and with experience in chordoma joined the meeting. Additional participants included patient representatives, statisticians, and molecular biologists. Prior to the meeting a literature search was conducted (details in the supplementary Appendix 1, available at Annals of Oncology online) to elucidate data upon which to base consensus recommendations. During the meeting, representatives from 14 of the participating institutions presented unpublished clinical data on patients treated with surgery and/or RT for recurrent chordoma from 2005. Based on these data and the literature review, the group reached consensus about key aspects of the management of patients with loco-regional recurrence, reported in this position paper. The present article is aimed at complementing the recommendations of the first position paper, published in 2015. To avoid repetition, this text contains several cross references to it [2].
We chose to grade level of evidence (LOE) 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 System 2 (Table 4). When published evidence was scarce but a strong consensus was present, we recorded the LOE as V. Points for which consensus among participating experts was not achieved are acknowledged herein.

While strong evidence would be desirable in many areas, we recognize the inherent difficulty of generating such data for rare cancers like chordoma, and, thus, accept that a higher degree of uncertainty must be tolerated for purposes of guideline development to avoid depriving rare cancer patients and those who care for them of much needed guidance [10].

### Treatment strategy

Figure 1 summarizes the recommended treatment strategy for patients with loco-regional recurrence.

### Table 1. Outcome of patients with recurrent skull-base and cervical spine chordoma and treated with surgical re-resection

<table>
<thead>
<tr>
<th>Series (REF)</th>
<th>Year</th>
<th>N. of patients$^*$</th>
<th>Location</th>
<th>Resection rate (%)</th>
<th>Complications %</th>
<th>Median follow-up (years)</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colli [45]</td>
<td>2001</td>
<td>19</td>
<td>Skull-base</td>
<td>T: 31</td>
<td>NA</td>
<td>3.2</td>
<td>74</td>
<td>NA</td>
<td>32</td>
<td>NA</td>
</tr>
<tr>
<td>Samii [47]</td>
<td>2007</td>
<td>23</td>
<td>Skull-base</td>
<td>ST: 48</td>
<td>CSF: 0 (0, 12)$^c$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sen [49]</td>
<td>2010</td>
<td>12</td>
<td>Craniovertebral junction</td>
<td>GT: 33</td>
<td>NA</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Chibbaro [52]</td>
<td>2014</td>
<td>22</td>
<td>Skull-base</td>
<td>GT: 30</td>
<td>NA</td>
<td>2.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Boari [53]</td>
<td>2016</td>
<td>13</td>
<td>Clivus</td>
<td>GT: 40</td>
<td>NA</td>
<td>6.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Gui [54]</td>
<td>2016</td>
<td>91</td>
<td>Skull-base</td>
<td>GT: 11</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
</tr>
</tbody>
</table>

Data on the outcome at a longer follow-up are frequently not available since primary and recurrent cases are not analysed separately.

$^*$Total number of patients with evidence of recurrent chordoma, including those not operated at latest follow-up or dead for disease progression.

$^b$Reported for reoperations (first and subsequent).

$^c$In brackets, complication at second and third reoperation.

N of patients, number of patients with chordoma undergoing surgery after initial treatment; REF, reference; N, number; GT, gross total; ST, sub-total; D, death; NA, not available; CS, cavernous sinus.
### Table 2. Outcome of primary and locally recurrent mobile spine and sacrum chordoma patients treated with surgery plus or minus RT

<table>
<thead>
<tr>
<th>Series (REF)</th>
<th>Year</th>
<th>No. pts</th>
<th>Sacrum/mobile spine</th>
<th>Quality of margins</th>
<th>No. pts. receiving RT/surgery</th>
<th>Median FU (years)</th>
<th>OS rate primary</th>
<th>OS rate recurrent</th>
<th>LR rate primary</th>
<th>LR rate recurrent</th>
<th>Prognosticators for LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park [55]</td>
<td>2006</td>
<td>27</td>
<td>Sacrum=27/Mobile spine=0</td>
<td>R0=5, R1/R2=16, R2=30</td>
<td>27 (100%)/21/78%</td>
<td>8.8 (mean)</td>
<td>93% at 10 years</td>
<td>44% at 10 years</td>
<td>9% at 10 years</td>
<td>81% at 10 years</td>
<td>R1/R2 margins, Recurrent tumor</td>
</tr>
<tr>
<td>Boniani [56]</td>
<td>2006</td>
<td>48</td>
<td>Sacrum=0/Mobile spine=48</td>
<td>R0/R1=18, R2=30</td>
<td>34 (65%)/48/100%</td>
<td>NR</td>
<td>23% overall</td>
<td>44% overall</td>
<td>53% overall</td>
<td>89% overall</td>
<td>R1/R2 margins, Recurrent tumor</td>
</tr>
<tr>
<td>Stacchiotti [9]</td>
<td>2010</td>
<td>130</td>
<td>Sacrum=108/Mobile spine=22</td>
<td>R0=48, R1=35, R2=47</td>
<td>42 (32%)/130/100%</td>
<td>11.8</td>
<td>54% at 10 years</td>
<td>26% at 10 years</td>
<td>67% at 10 years</td>
<td>69% at 10 years</td>
<td>Large tumor size, R1/R2 margins, Recurrent tumor</td>
</tr>
<tr>
<td>Zabel Du Bois [57]</td>
<td>2010</td>
<td>34</td>
<td>Sacrum=34/Mobile spine=0</td>
<td>R0=4, R1=10, R2=3</td>
<td>34 (100%)/24/71%</td>
<td>4.5</td>
<td>76% at 5 years</td>
<td>76% at 5 years</td>
<td>53% at 5 years</td>
<td>76% at 5 years</td>
<td>No radiation therapy, R1/R2 margins, Recurrent tumor</td>
</tr>
<tr>
<td>Staab [58]</td>
<td>2011</td>
<td>40</td>
<td>Sacrum=12/Mobile spine=29</td>
<td>R0/R1=21, R2=19</td>
<td>40(100%)/40(100%)</td>
<td>3.6</td>
<td>80% at 5 years</td>
<td>NR</td>
<td>38% at 5 years</td>
<td>NR</td>
<td>No pre-RT surgical stabilization, Recurrent tumor</td>
</tr>
<tr>
<td>DeLaney [59]</td>
<td>2014</td>
<td>29</td>
<td>NR/Mobile spine=56</td>
<td>R0=7, R1=10, R2=3</td>
<td>29(100%)/20(69%)</td>
<td>7.3</td>
<td>NR</td>
<td>NR</td>
<td>0% at 5 years</td>
<td>50% at 5 years</td>
<td>Recurrent tumor</td>
</tr>
<tr>
<td>Xie [8]</td>
<td>2015</td>
<td>54</td>
<td>Sacrum=54/Mobile spine=0</td>
<td>R0=13, R1=34, R2=7</td>
<td>NR/54(100%)</td>
<td>7.8</td>
<td>82% at 5 years</td>
<td>56% at 5 years</td>
<td>51% at 5 years</td>
<td>NR</td>
<td>R1/R2 margins, Recurrent tumor</td>
</tr>
<tr>
<td>Rotondo [60]</td>
<td>2015</td>
<td>126</td>
<td>Sacrum=71/Mobile spine=56</td>
<td>R0=34, R1=57, R2=30</td>
<td>126 (100%)/126(100%)</td>
<td>3.4</td>
<td>81% at 5 years</td>
<td>78% at 5 years</td>
<td>32% at 5 years</td>
<td>51% at 5 years</td>
<td>R1/R2 margins, Recurrent tumor</td>
</tr>
<tr>
<td>Uhl [61]</td>
<td>2015</td>
<td>56</td>
<td>Sacrum=49/Mobile spine=7</td>
<td>R0/R1=13, R2=19</td>
<td>56(100%)/32(57%)</td>
<td>2.1</td>
<td>100% at 2 years</td>
<td>100% at 2 years</td>
<td>100% at 2 years</td>
<td>53% at 2 years</td>
<td>Recurrent tumor, Female patients</td>
</tr>
<tr>
<td>Imai [62]</td>
<td>2016</td>
<td>188</td>
<td>Sacrum=188/Mobile spine= 7</td>
<td>R0=13, R2=19</td>
<td>188(100%)/0(0%)</td>
<td>5.1</td>
<td>69% at 10 years</td>
<td>52% at 10 years</td>
<td>52% at 10 years</td>
<td>68% at 10 years</td>
<td>R1/R2 margins</td>
</tr>
<tr>
<td>Radaelli [8]</td>
<td>2016</td>
<td>99</td>
<td>Sacrum=99/Mobile spine=0</td>
<td>R0=46, R1=43, R2=10</td>
<td>19 (19%)/99(100%)</td>
<td>8.7</td>
<td>92% at 5 years</td>
<td>92% at 5 years</td>
<td>92% at 5 years</td>
<td>92% at 5 years</td>
<td>Large tumor size, R1/R2 margins, Recurrent tumor</td>
</tr>
</tbody>
</table>

*One patient had synchronous lumbar and sacrococcygeal chordoma.*

*pts, patients; RT, radiotherapy; FU, follow-up; OS, overall survival; LR, local recurrence; NR, not reported; R0, wide resection; R1, marginal resection; R2, intralesional resection.
<table>
<thead>
<tr>
<th>Series (REF)</th>
<th>Year</th>
<th>N. pts</th>
<th>Type of RT</th>
<th>Dose and fractionation</th>
<th>Mean FU (years)</th>
<th>Oncological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull base</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munzenrider [63]</td>
<td>1999</td>
<td>290</td>
<td>Surgery + protontherapy (passive fields) + photon RT</td>
<td>66–83 CGE, Protons 4 fx/week (1.92 CGE), Photons 1 fx/week (1.8 Gy)</td>
<td>3.4</td>
<td>5-year LRFS 73% chordoma</td>
</tr>
<tr>
<td>Noel [64]</td>
<td>2005</td>
<td>88</td>
<td>Surgery + protontherapy (passive fields)</td>
<td>Median dose 67 CGE with standard fractionation</td>
<td>2.6</td>
<td>2-year LC 86%</td>
</tr>
<tr>
<td>Ares [65]</td>
<td>2009</td>
<td>41</td>
<td>Surgery + protontherapy (active spot scanning)</td>
<td>Median total dose 73.5 Gy (RBE) with standard fractionation</td>
<td>3.2</td>
<td>5-year LC—81%</td>
</tr>
<tr>
<td>Mizoe [66]</td>
<td>2009</td>
<td>33</td>
<td>Surgery + carbon ions (passive fields)</td>
<td>Dose escalation 480, 528, 576, and 608 Gy in 16 fractions</td>
<td>4.4</td>
<td>5-year LC—85% 10-year LC—64%</td>
</tr>
<tr>
<td>Uhl [61]</td>
<td>2014</td>
<td>155</td>
<td>Surgery + carbon ions (active spot scanning)</td>
<td>Median total dose 60 Gy RBE, 3 Gy RBE per fraction</td>
<td>6</td>
<td>5-year LC—72% 10-year LC—54% Overall LC 48% 5-year PFS 35.2%</td>
</tr>
<tr>
<td>Choy [67]</td>
<td>2016</td>
<td>57</td>
<td>Surgery + stereotactic radio surgery (SRS) or stereotactic radiotherapy (SRT)</td>
<td>Median total dose 75 Gy (RBE) with standard fractionation</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Bugoci [68]</td>
<td>2013</td>
<td>12</td>
<td>Surgery + fractionated stereotactic radiotherapy</td>
<td>Median dose 66.6 Gy with standard fractionation</td>
<td>3.5</td>
<td>5-year PFS 37.5%</td>
</tr>
<tr>
<td>Kano [69]</td>
<td>2011</td>
<td>71</td>
<td>Surgery + Gamma Knife stereotactic radiosurgery (SRS)</td>
<td>Median margin dose 15.0 Gy (range 9–25 Gy)</td>
<td>5</td>
<td>5-year LC 66%</td>
</tr>
<tr>
<td>Chang [70]</td>
<td>2001</td>
<td>10 (8 skull base, 2 cervical spine)</td>
<td>Surgery + LINAC stereotactic radiosurgery</td>
<td>Mean radiation dose 19.4 Gy</td>
<td>4</td>
<td>Gross LC 80%</td>
</tr>
<tr>
<td>Zorlu [71]</td>
<td>2000</td>
<td>18</td>
<td>Surgery + 3D photons RT</td>
<td>Median 60 Gy with standard fractionation</td>
<td>3.6</td>
<td>5-year PFS 23%</td>
</tr>
<tr>
<td>Foweraker [72]</td>
<td>2007</td>
<td>12 (10 clivus, 2 cervical spine)</td>
<td>Surgery + photons radiotherapy</td>
<td>Median 65 Gy in 39 fractions</td>
<td>3.2</td>
<td>Gross LC 92%</td>
</tr>
<tr>
<td>Sacrum and spine</td>
<td></td>
<td></td>
<td>Exclusive carbon ions (passive fields)</td>
<td>Median 67.2 GyE in 16 fractions</td>
<td>5.2 (median)</td>
<td></td>
</tr>
<tr>
<td>Imai [62]</td>
<td>2016</td>
<td>188</td>
<td>Exclusive carbon ions (passive fields)</td>
<td>Median 66 GyE</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Uhl [61]</td>
<td>2015</td>
<td>56 (41 primary tumors, 15 recurrent tumors)</td>
<td>Carbon ions (active scanning) or photons RT and carbon ions (active scanning) ± surgery (10 R0/R1 resection 11 R2 resections 20 biopsy only, 15 recurrences)</td>
<td>Median 66 GyE</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Mima [73]</td>
<td>2014</td>
<td>23</td>
<td>Exclusive carbon ions or exclusive protontherapy</td>
<td>Median 70.4 GyE in 16 fractions or 32 fractions</td>
<td>3.2</td>
<td>3-year LC—94%</td>
</tr>
<tr>
<td>Rotondo [60]</td>
<td>2015</td>
<td>126 (71 sacrococcygeal, 40 lumbar, 16 thoracic)</td>
<td>Surgery + protontherapy</td>
<td>Median 72.4 Gy RBE with standard fractionation</td>
<td>3.5</td>
<td>Primary tumor 5-year OS 81% 5-year LC 68% Recurrent tumor 5-year OS 78% 5-year LC 49%</td>
</tr>
</tbody>
</table>
### Table 3. Continued

<table>
<thead>
<tr>
<th>Series (REF)</th>
<th>Year</th>
<th>N. pts</th>
<th>Type of RT</th>
<th>Dose and fractionation</th>
<th>Mean FU (years)</th>
<th>Oncological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holliday [74]</td>
<td>2015</td>
<td>19</td>
<td>Surgery+protontherapy</td>
<td>Median 70 Gy RBE with standard fractionation</td>
<td>32.9</td>
<td>2-year LC—58%</td>
</tr>
<tr>
<td>DeLaney [59]</td>
<td>2014</td>
<td>29 (23 primary, 6 recurrent)</td>
<td>Surgery+protontherapy</td>
<td>77.4 Gy RBE with standard fractionation</td>
<td>7.3</td>
<td>Primary tumor 5-year LC 100% 8-year LC 92% Recurrent tumor 5-year LC 50% 5-year LPFS 79.8%</td>
</tr>
<tr>
<td>Chen [75]</td>
<td>2013</td>
<td>24 (19 sacrum, 2 cervical, 1 thoracic, and 2 lumbar spine)</td>
<td>Exclusive protontherapy (passive fields)</td>
<td>77.4 Gy RBE (range 71.6–79.2 Gy RBE) with standard fractionation</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Staab [58]</td>
<td>2011</td>
<td>40 (32 primary, 8 recurrent) (21 adjuvant RT, 19 macroscopic disease)</td>
<td>Protontherapy spot scanning±radical surgery</td>
<td>72.5 Gy RBE with standard fractionation</td>
<td>3.6</td>
<td>5-year OS 80% 5-year LC 62%</td>
</tr>
<tr>
<td>Dhawale [76]</td>
<td>2014</td>
<td>21 (sacrum)</td>
<td>Surgery+ (18) – (3) 3D conformal RT or IMRT</td>
<td>Mean dose 56 Gy with conventional fractionation</td>
<td>5.8</td>
<td>Gross LC 60%</td>
</tr>
<tr>
<td>Zabel-du Bois [57]</td>
<td>2010</td>
<td>34</td>
<td>First diagnosis: surgery+adjacent IMRT (13) or IMRT alone (4) Recurrent tumor Surgery+adjacent IMRT (11) or IMRT alone (6)</td>
<td>Mean dose 66 Gy with conventional fractionation</td>
<td>4.5</td>
<td>Primary tumor 5-year OS 76% 5-year LC 47% Recurrent tumor 5-year OS 76% 5-year LC 24%</td>
</tr>
</tbody>
</table>

There is no paper specifically reporting the outcome of relapsed chordoma treated with RT. Most series include both first line RT and salvage treatments.

N, number; pts, patients; RT, radiotherapy; FU, follow-up; CGE, cobalt gray equivalent; LRFS, local recurrence-free survival; LC, local control; RBE, relative biological effectiveness; Gy, Gray; PFS, progression-free survival; GyE, Gray equivalent; OS, overall survival; IMRT, intensity-modulated radiation therapy; LINAC, linear accelerator; R0, wide resection; R1, marginal resection; R2, intralesional resection.

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### Table 4. Level of evidence and grade of recommendation

Adapted from the Infectious Diseases Society of American-United States Public Health Service Grading System.

Level of evidence:
I. Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomized trials without heterogeneity
II. Small randomized trials or large randomized 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

Grade of recommendation:
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.
Patients who experience LR should be evaluated by a multidisciplinary team including at least a medical oncologist, radiotherapist, surgeon, pathologist, radiologist and PC specialist with expertise in chordoma. This recommendation is consistent with best practice for managing musculoskeletal neoplasms [11].

The presence/absence of symptoms should be factored in the decision-making algorithm. It is important to involve the patient when deciding which treatment to pursue.

The ‘extent of local disease’ should be determined using intravenous contrast-enhanced MRI. In addition, restaging with total body computed tomography (CT) and whole spine MRI with a thorough clinical examination should complement local-regional assessment to rule out distant metastases and/or subarachnoid spread.

‘Histological confirmation’ of recurrent disease is needed when there is diagnostic uncertainty, or when there is the suspicion of tumor dedifferentiation (e.g. unusually fast growth), or of a secondary malignancy. In cases where a tumor relapse is uncertain, a period of observation and re-imaging is an appropriate alternative to histologic assessment. A biopsy can be considered in selected cases for directing medical therapy.

‘Salvage’ treatment choices with curative intent can include surgery and/or RT, balancing morbidity, QOL and expected disease control. Surgical and RT strategy should be guided by the nature and extent of the previous procedure(s), the location of the recurrence, tumor restcatbility, deliverability of RT and the expected added morbidity of each procedure. Other relevant factors to consider include age, comorbidity, performance status (PS), and status of the surrounding tissues including the skin. The choice between surgery alone, surgery + RT, and RT alone must be based on individual case assessment; to date, there are no specific data to back generalized recommendations. A period of observation and re-imaging may help select best candidates for resection/RT or both. In particular, postponing active therapy can be considered in case of stable disease and/or no progression of symptoms.

The goal of ‘salvage re-section with curative intent’ should be to achieve gross total resection, and, when feasible, en-block resection with negative surgical margins (IV-B). The best candidates for a complete re-resection are patients with isolated disease, a long disease-free interval, good PS (i.e. Eastern Cooperative Oncology Group-ECOG PS ≤ 2) and with a reasonable likelihood of acceptable morbidity. In cases of multifocal disease, a cure is virtually impossible so re-resection with curative intent should not be performed (IV-B); in these cases, only a limited resection should be considered with the goal of preventing the ill effects associated with disease progression whilst preserving function. A prior history of piecemeal resection (except for skull-base tumors where resection may be necessarily piecemeal), prior high-dose RT (in case of mobile spine and sacral chordoma), and/or tumor rupture are obvious exclusion criteria for re-resection with curative intent (IV-B). There is no consensus on how to treat intracanal disease. In patients who have not previously received high-dose RT at the time of primary treatment, pre- and/or post-operative treatment with RT may also be appropriate [12, 13]. This approach is currently the standard treatment strategy in primary disease at some referral centers [14] and may be particularly well suited for treating local recurrences as the chance of achieving a true R0 resection after prior surgical procedures is low. It is currently not possible to make any recommendations regarding the role of adjuvant re-irradiation after macroscopically complete resection of recurrent chordoma.

‘Salvage’ radiotherapy with curative intent should be offered with the same dose and techniques as employed in first-line therapy [2]. Thus, in case of recurrence in patients not previously treated with RT, definitive RT alone (e.g. without debulking) is a
reasonable alternative to surgery plus radiation, although neither is very effective (V-C). Comparative effectiveness data for these approaches are limited and additional research is needed to determine which approach is superior. Patients considering definitive RT need to be informed about the risk of late toxicities from high-dose radiation (IV-B).

In the case of recurrent disease after previous RT, a new course of RT is indicated only when (i) this can be delivered without exceeding the estimated dose constraints on organs at risk (OARs) and (ii) adequate coverage of target volumes can be achieved. If this is not feasible, other treatment modalities are preferable (V-C). Currently, the cumulative dose tolerance for key OARs and the potentially protective role of partial damage repair after the first course of RT are still largely unknown. When complete resection of a recurrent lesion is not feasible, and proximity to critical structures precludes adequate RT coverage of target volumes, debulking surgery may be an appropriate option in order to separate critical structures from the residual tumor, thereby allowing delivery of a tolerable radiation dose.

‘Salvage palliative/supportive treatment choices’ include debulking surgery, low-dose RT, stereotactic body RT (SBRT), including radiosurgery to small volume, radiofrequency ablation (RFA) and other loco-regional approaches (i.e. cryotherapy), systemic therapy, PC and observation. The patient’s symptom burden should guide the selection of an appropriate therapeutic approach as the potential for cure is nil. Care should be taken to avoid aggressive therapies that could cause unnecessary additional morbidity. Maximal debulking surgery should only be considered to alleviate or prevent symptoms related to nerve/cord/brain compression or for separating vital structures from the tumor to allow for radiation of the residual disease (V-C). This type of surgery is indeed only a temporizing measure, as local disease that remains after surgery will regrow in the region. Particular caution should be exercised in performing surgery near prior high-dose RT (IV-C) as the risk of surgical complications is dramatically greater in this setting. Additionally, the oncologic outcome generally deteriorates, and the chance of mortality and serious morbidity increases, with each serial resection (IV-B). Low-dose re-irradiation with palliative intent can be considered in selected case if it can be performed with negligible risk of toxicity (V-C).

‘PC’ should be considered as part of the active management of all patients and should include pain and symptom control, discussion about a patient’s concerns and wishes, a conversation about advanced directives, and evaluation of patient and family psychosocial needs. ‘Salvage palliative anticancer medical therapy’ should be considered to attempt to stop tumor growth and/or alleviate symptoms in cases not amenable to local treatment or when symptomatic relief is needed, taking into consideration the PS, co-morbidities, expected treatment-related side effects, and the patient’s preferences (V*-B).

### Technical aspects of treatment

#### Pre-treatment assessment

**Imaging.** Any relevant imaging studies performed prior to and after treatment of the primary chordoma should be obtained and reviewed. The first post-operative baseline imaging should be evaluated to confirm the initial extent of resection. Likewise, the post-radiation imaging at best response should be evaluated to assess the extent of residual disease. A comparative analysis of the imaging from first diagnosis to recurrence is important to distinguish recurrent disease from treatment sequelae and for assessing areas at high-risk of microscopic infiltration.

Although MRI is the modality of choice, CT may be a useful ancillary imaging modality, particularly to assess the bone involvement and when surgical implants or hardware limit MRI reliability. Myelo-CT can be useful to visualize peridural spaces when chordoma tissue invades the spinal canal. Furthermore, CT is a helpful tool in assessing stability of the spinal column.

For patients with skull-base tumors, assessment of internal carotid artery (ICA) and/or vertebral arteries with angi-CT can be needed for surgical planning. If curative surgery is considered, formal angiography with balloon test occlusion can be considered if ICA involvement is a limiting factor for tumor resection.

FDG-PET may be used in combination with other modalities in certain cases to exclude distant relapse and/or to evaluate tumor activity when tumor dedifferentiation is suspected or if a lesion is not clearly recurrent tumor.

**Pathology.** At the time of recurrence, the primary excised chordoma sample, including immunohistochemistry for brachyury and cytokeratin, should be reviewed and confirmed by an expert pathologist. The diagnosis should be based on the World Health Organization (WHO) Classification [1].

Tumor biopsy of recurrent disease, when warranted, must be performed with every attempt to limit the risk of tumor seeding [2]. A percutaneous core-needle biopsy is the preferable approach.

If a biopsy is obtained, it should be compared with the primary tumor to assess whether the tumor has changed or dedifferentiated over time. Dedifferentiated chordoma can show a deletion of INI1, which is a potentially targetable molecular alteration [15, 16].

**Baseline patient evaluation.** Prior to treatment, a complete physical examination and neurological assessment should be performed. For skull-base chordomas, endocrinological, ophthalmological and audiological examination are suggested. The patient’s symptoms and pace of symptom progression should be noted. Pain assessment should be performed using a 0–10 pain assessment scale [17]. Chronic pain secondary to RT or surgery should be distinguished from acute symptoms related to tumor progression for purposes of considering treatment approaches.

The evaluation should also include a detailed review of notes describing prior resections and/or RT, including but not limited to fields, dose and type of RT. The location of previous incisions or biopsies should be noted in relationship to new tumor lesion(s) for purposes of surgical planning.

### Resection of recurrent or progressive disease

For mobile spine and sacral tumors, the goal of salvage surgery with curative intent should be to achieve en-bloc resection with negative surgical margins (IV-B). Particular attention should be paid to avoid tumor rupture, as this is associated with significant risk of tumor seeding. Recurrences in the skull-base or neck, as
well as in the intrathoracic, intra-abdominal or intra-pelvic areas, are usually not amenable to margin negative/R0 resections, and therefore surgery should be aimed at a gross total resection (IV-B). For skull-base tumors R1 resection should be the goal of surgical treatment in all cases, in order to reduce tumor volume and increase the effectiveness of subsequent RT (V-A).

Debulking surgery should be cautiously considered only in certain rare cases, as it is unlikely to prolong survival. When subtotal resection is performed, every effort should be made to minimize contamination of the surrounding tissues (V-B).

When no prior RT had been delivered, post-operative RT should be considered, especially when microscopic margins were positive/R1. A component of preoperative RT can also be considered [18].

Radiotherapy of recurrence
RT can be delivered both with curative or palliative intent. To achieve local control in recurrent chordoma it is necessary to give a biologically high-dose while limiting the cumulative dose delivered to the critical structures near the target volume (IV-B). The feasibility and utility of RT for patients with recurrent chordoma depends primarily on whether or not the patient received RT to the same area as part of primary management. Thus, recommendations are presented below for two scenarios: patients without and with previous irradiation.

RT in patients without previous irradiation. Salvage RT with curative intent should be offered with the same modality employed for first line therapy (V-C) [2]. Since chordomas are radioresistant, a dose of at least 74 GyE should be delivered, using conventional fractionation (1.8–2 GyE) for photon and proton therapy (V*-A); moderately hypofractionated schedules can be used with carbon ions with dose per fractions ranging between 3 and 4.4 Gy RBE and total doses ranging from 60 and 70.4 Gy RBE [2]. Prior to RT, surgical re-resection should be discussed in all cases. Target volumes should be delineated considering the primary tumor location and its recurrence. The high-dose volume should include any macroscopic disease as well as surgical margins, while the low-dose volume should encompass areas at risk of microscopic spread, skip metastases, or seeding due to surgical procedures. In selected cases, a radio-surgical approach to gross disease may be appropriate, although there is no consensus as of yet about the criteria for recommending it.

RT in patients with previous irradiation. The radiation dose previously received by nearby OARs often limits the dose of radiation that can be safely delivered to the tumor, making local control of recurrences challenging. In general, the dose constraints for re-irradiation to OARs are not clearly established and the degree of recovery from initial radiation is difficult to estimate. However, preliminary data are available regarding tolerance to re-irradiation of the spinal cord, brain and aorta, which can help guide decision-making [7, 19–22]. If a new course of high-dose RT can be delivered without exceeding the estimated dose constraints on OARs, the patient should be treated with the same intent and approach as a RT naïve recurrence (V-C). Radiation plans must be based on an accurate reconstruction of the previous RT dose distribution, and taking into account expected morbidity of additional radiation (V-C). In case of tumor seeding in the surgical pathway, the site of relapse is often outside the previously irradiated volume and can be adequately treated by radiation [7]. The radiotherapist must exercise professional judgment in developing the radiation plan, as there is currently insufficient data to recommend an optimal dose and fractionation scheme for radiation in this setting. Regardless, particular caution is warranted in re-irradiating the carotid artery as severe, life-threatening complications such as carotid blowout syndrome have been reported in patients treated with re-irradiation for head and neck cancer [23]. If re-irradiation cannot achieve sufficiently high-dose or adequate coverage of target volumes without exceeding estimated dose constraints, then other treatment modalities are preferable. Low-dose re-irradiation with palliative intent can be appropriate in selected cases but only if it can be performed with negligible risk of toxicity. The use of high Linear Energy Transfer (LET) radiation such as carbon ions can be considered especially in case of re-irradiation after an initial course of low LET treatment as it may be more effective against the radioresistant clones that may have been selected by the first treatment.

Metal implants (e.g. for spine stabilization) complicate RT delivery by creating artifacts in CT/MRI images. This can interfere with precise delineation of target and OAR, especially in the spinal canal. Additionally, these artifacts affect range calculation for particle therapy, and, therefore, may result in an additional uncertainty in delivered dose. Consequently, the presence of metal implants may be a key factor in deciding not to deliver curative RT or in deciding to deliver it with photons, which are less sensitive to artifacts, instead of particles (IV-B). If a debulking or a separating surgery is planned, the possibility of modifying, removing or substituting metal implants with carbon fiber devices should be considered to enable radiation with potentially curative intent; however, this is appropriate only in very well selected cases after thorough multidisciplinary assessment.

Other local therapies
Retrospective data suggest that cryoablation and RFA can be safe and useful palliative treatments in recurrent extracranial chordomas with a benefit in pain control [24–26]. However, prospective studies are needed before recommending these procedures in chordoma.

SBRT, including radiosurgery, has been described in retrospective and prospective series as safe and effective salvage strategy for spine tumors that have recurred after prior RT [27]. SBRT has been suggested as a palliative treatment option also in chordoma patients who suffer LR after prior RT [28], nevertheless prospective confirmatory data are necessary to make any definitive recommendations.

In principle, other local therapies such as local microwave hyperthermia and high-intensity focused ultrasound (HIFU) may also offer benefit in a palliative setting; however, currently there are no published data supporting their use.

Medical therapy
Medical therapy is an appropriate palliative option for patients whose disease is actively progressing or who are asymptomatic. A brief observation period may be warranted before starting medical therapy to determine whether, and at what rate, the disease is
progressing. If no progression is detected, it may be more appro-
appropriate to continue with active surveillance.

Currently, medical therapy options are limited and no drugs are
approved for the treatment of advanced chordoma. However, sev-
eral targeted therapies have shown modest activity in patients with
recurrent disease. Imatinib and sorafenib are the agents with the
greatest evidence of efficacy in advanced chordoma and represent
reasonable palliative treatment options to slow disease progression
or alleviate symptoms (V*-B) [29–32]. Access to these drugs varies
widely among countries, posing a challenge for patients in some
areas. In addition, several case reports have noted activity of suniti-
nib and EGFR inhibitors (cetuximab, erlotinib, gefitinib) [33–38].

Cytotoxic chemotherapy is generally inactive, and there is in-
sufficient evidence to recommend it (V-D). However, there are
anecdotal reports of responses to chemotherapy in high-grade/
dedifferentiated chordoma and in some pediatric cases [39].

Although no predictors of response to targeted agents have been
identified in chordoma, molecular profiling of tumors may help
guide selection of experimental therapies. One potentially
relevant biomarker is INI1 loss, which has been reported in dedif-
erentiated chordomas and may confer sensitivity to EZH2 in-
hibitors [15, 16].

A more detailed and up to date description of published data
on medical therapy in chordoma is provided in supplementary
Appendix 2, available at Annals of Oncology online.

Table 5. General schema for palliative care application to advanced chordoma patients

<table>
<thead>
<tr>
<th>Palliative care domains</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain control</strong></td>
</tr>
<tr>
<td>Pain requires careful assessment and classification: neuropathic pain is common for chordoma patients and should be correctly diagnosed. The source of pain should be identified to help guide pain management, e.g. as a complication of primary disease, as a result of therapy, or as a consequence of relapse and progression (1).</td>
</tr>
<tr>
<td>Pain management guidelines should be applied by oncology team</td>
</tr>
<tr>
<td>Specialized pain management with medical and anesthesiological procedures may be needed in selected cases (2)</td>
</tr>
<tr>
<td>Control of other symptoms</td>
</tr>
<tr>
<td>Common symptoms requiring management include nausea/vomiting, dyspnea/breathlessness, delirium, anxiety/depression, and other complications of disease progression</td>
</tr>
<tr>
<td>Prognostication of short-term survival</td>
</tr>
<tr>
<td>Psychological support</td>
</tr>
<tr>
<td>Family-oriented interventions and social support</td>
</tr>
<tr>
<td>End-of-life decisions and palliative sedation</td>
</tr>
</tbody>
</table>

**Clinical care pathways and integration with oncology care**

- Shared decision-making on goals of management and care should be considered to help with:
  - Difficult symptom to control
  - Choice of settings of care at the end of life (Hospital, hospice home care) always providing care continuity

**Palliative, supportive and end-of-life care**

PC is part of the active care of patients with advanced illness [40]. A comprehensive PC approach and access to specialized PC are both necessary (Table 5) [41].

Most chordoma patients suffer from both somatic and neuropa-
thic pain that can be difficult to treat. Worsening of pain and/or
of neurologic symptoms can be the first sign of disease relapse/pro-
gression even when this cannot be yet detected radiologically [42].

First-line analgesic therapy should be provided by the oncology
team according to available guidelines [43]. Pain due to the compres-
sion of nervous tissues via epidural compression or radiculopathy
often benefits from steroids (dexamethasone or methylprednisolo-
lone). Difficult pain syndromes poorly responsive to analgesic
pharmacotherapy can benefit from more invasive analgesic tech-
niques such as spinal administration of opioids, ziconotide and adju-
vant drugs [44].

In the terminal phase, the patient’s preferred setting of care
should be identified. Hospice and home-care are valid options
depending on the patient’s and family’s preferences.

**Follow-up**

Currently, there is insufficient data to recommend an optimal rou-
tine follow-up policy for patients with recurrent chordoma. Thus,
follow-up is usually chosen based on the best judgment of the pa-
tient’s care team. However, experts agreed that MRI should be per-
formed every 3–6 months at least for the first 3 years from treatment
of LR/local progression. There is currently no consensus about
whether routine scanning of the rest of the body is beneficial and for
how long follow-up should be continued, though long-term vigil-
ance is warranted as relapses often take place after several years.

**Emerging approaches and future directions**

For those patients who fail surgery and RT, there remains an ur-
gent unmet need for new therapeutic options. To facilitate
patient participation in clinical trials, the CF maintains an up to date list of trials open to chordoma patients (www.chordomafoundation.org/clinical-trials/) and a ‘target dashboard’ (www.chordomafoundation.org/targets/) summarizing published data about therapeutically-relevant targets.

Future clinical trials should be designed considering the rarity and distinctive natural history of chordoma. Due to its rarity, performing randomized trials may not be feasible. Additionally, due to its characteristic slow growth-rate and relatively long expected OS period, determining an OS benefit is likely impractical, thus necessitating the use of surrogate endpoints to assess efficacy. However, because patients often experience prolonged periods of symptomatic disease progression prior to end-stage disease, conventional surrogate endpoints based solely on dimensional response may miss improvements in QOL, and, thus, may be inadequate for inferring clinical benefit. New, and possibly unconventional, approaches are needed for assessing efficacy and facilitate the pathway to drug approval. Meanwhile, patients should be enrolled in prospective registries or observational studies to better understand the natural history of chordoma and identify relevant correlates of outcome that could aid in future trial design and help optimize clinical care.

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References


73. Mima M, Demizu Y, Jin D et al. Particle therapy using carbon ions or protons as a definitive therapy for patients with primary sacral chordoma. Br J Radiol 2014; 87(1033):

