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**CADTH RAPID RESPONSE REPORT:**
**SUMMARY WITH CRITICAL APPRAISAL**

# Carbon Ion Beam Therapy for Chordoma: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines


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## Abbreviations

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| CIRT | Carbon ion beam RT |
| CRT | Conventional RT |
| Gy | Gray units |
| ICER | Incremental cost-effectiveness ratio |
| IMRT | Intensity-modulated RT |
| LC | Local control |
| OS | Overall survival |
| PBT | Proton beam RT |
| PFS | Progression-free survival |
| QALY | Quality-adjusted life-year |
| RBE | Relative biological effectiveness |
| RT | Radiation therapy |
| SRT | Stereotactic RT or stereotactically-guided fractionated RT |

## Context and Policy Issues

Chordomas are low-grade cancerous tumours found along the spine from the skull base to the sacrococcygeal region.[1] In the US, the age-adjusted incidence rate of chordoma is 0.06 to 0.1 per 100,000 people.[2]

*En bloc* surgical resection with wide or marginal margins is the recommended treatment option of choice for chordoma.[1] Resection may be hindered by the presence of osseous structures surrounding the spinal cord and cauda equina, longitudinal muscle compartments, and other unique features of spinal anatomy. Resection may also be challenging under conditions of recurrent or residual disease when tissue planes have been disrupted or tumour seeding has occurred.[1] Specifically, chordomas may be inoperable if they are embedded in locations were resections present an insurmountable risk of morbidity such as bladder and rectal paralysis, chronic neuropathic pain, and sensomotoric deficits.[3] In addition, some patients may reject surgery as a treatment option.[3] To minimize surgery-related morbidity and to accommodate patient preferences, physicians may incorporate radiation therapy or radio-therapy (RT) into treatment plans, either as adjuvant therapy to surgical resection or as primary therapy for patients with chordoma.[1]

RT involves the use of one or more beams of accelerated photons or charged particles to destroy cancerous tissue. RT destroys biological tissue by rapidly depositing stored energy as it penetrates through the tissue.[4] During therapy sessions, the radiation beam is focused so that the peak amount of energy (i.e., Bragg Peak) is deposited at a specific depth (i.e., distance from the point of entry) in a patient's body that coincides with the location of cancerous tissue including a pre-determined margin of healthy tissue.[4] Despite being focused, photon RT inevitably destroys healthy tissue beyond the targeted treatment volume.[4] Unintended radiation to healthy tissue outside the targeted volume could cause harm to patients. Charged particle or hadron therapy is an alternative to photon RT wherein protons (i.e., proton beam therapy [PBT]) or heavy ions such as carbon-12 ions (i.e., carbon ion beam therapy [CIRT]) are used.[4] These ions deposit energy in tissue at a higher rate than photons (i.e., they exhibit higher linear energy transfer) and they deposit energy more precisely.[4] Although CIRT is more precise than photon RT at destroying cancerous tissue, normal tissue damage is expected similar to CRT.[5]

The aim of this report is to summarize the clinical effectiveness and cost-effectiveness, of CIRT as an adjuvant to surgical resection relative to other forms of therapy for chordoma, and to review the relevant evidence-based guidelines.

## Research Questions

1. What is the clinical effectiveness of carbon ion radiation therapy in patients with any stage of chordoma?
2. What is the cost-effectiveness of carbon ion radiation therapy in patients with any stage of chordoma?
3. What are the evidence-based guidelines associated with the use of carbon ion radiation therapy in patients with any stage of chordoma?

## Key Findings

Five relevant publications comprising one systematic review and meta-analysis, two non-randomized studies, and two economic evaluations were identified. Given the quantity and limited quality of available studies and the variety of outcomes of interest, the findings are inconclusive. Evidence of limited quality from one meta-analysis and one non-randomized study suggested that post-operative carbon ion beam radiation therapy provided better survival odds than post-operative conventional radiation therapy and similar odds as stereotactically-guided fractionated radiation therapy. Survival odds for CIRT relative to proton beam radiation therapy were similar up to 5 years following treatment but were worse at the 10-year follow-up time point. The evidence on adverse effects was limited, nonetheless the findings reinforce that carbon ion beam radiation therapy presents morbidity risks including sacral insufficiency fractures, hearing problems, cranial nerve deficit, abducent nerve paralysis, and double vision for patients with chordoma.

Two economic evaluations conducted at one facility in Germany, found that post-operative carbon ion beam radiation therapy was cost-effective relative to post-operative conventional radiation therapy over a lifetime time horizon.

No evidence-based guidelines were identified.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published before October 2, 2018.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

## Table 1: Selection Criteria

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| **Population** | Adults and children with chordoma at any stage; chordo-sarcoma |
| **Intervention** | Carbon ion radiation therapy (pre- and post-operative use) alone |
| **Comparator** | Q1-2: Conventional radiotherapy;<br>Stereotactic radiotherapy;<br>Proton beam therapy;<br>Systemic chemotherapy (intravenous [IV], oral);<br>Image-Guided Intensity-Modulated Radiotherapy;<br>Surgery<br>Placebo/sham<br>Q3: No comparator |
| **Outcomes** | Q1: Clinical effectiveness (e.g., but not limited to, tumour size reduction, local tumour control rate, time to progression, progression rate, survival rate (progression-free, overall), quality of life), safety (e.g., toxicity, adverse events, discontinuation of study drug or from study)<br>Q2: Cost-effectiveness (e.g., cost per QALY increase)<br>Q3: Guidelines |
| **Study Designs** | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, guidelines |

QALY = quality-adjusted life-years

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicates or if they were published prior to 2008. Relevant systematic reviews (SRs) were excluded if all of the primary studies were reported in one or more of the other relevant systematic reviews. Relevant randomized controlled trials (RCTs) were excluded if they were reported in an included systematic review.

### Critical Appraisal of Individual Studies

All studies were critically appraised by one reviewer. The included systematic review was critically appraised using AMSTAR 2,[6] the non-randomized studies were critically appraised using the Downs and Black checklist,[7] and the economic evaluations were assessed using the Drummond checklist.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 246 citations were identified in the literature search. Following screening of title and abstracts, 222 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. Eleven potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 35 potentially relevant articles, 30 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[9] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

## Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2, Table 2, Table 3, and Table 4.

### *Study Design*

One systematic review and meta-analysis,[10] two single-centre retrospective non-randomized controlled studies,[3,11] and two cost-effectiveness studies[12,13] were included in this review. The meta-analysis[10] the non-randomized studies[3,11] and one cost-effectiveness study[12] were published in 2018. A predecessor cost-effectiveness study was published in 2007.[13] The non-randomized studies and the cost-effectiveness studies were published out of the Heidelberg Ion Beam Therapy Centre in Germany and had overlapping sets of authors.[3,11-13]

The systematic review included searches of the Cochrane library and Pubmed database from inception to May 2017 and the meta-analysis included 25 single-arm (observational) studies published between 1986 and 2016.[10] The sizes of the study populations ranged from 5 to 155.[10] The authors assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS) for cohort studies.[10]

The economic evaluations assessed the cost-effectiveness of CIRT over CRT for patients with skull base chordoma.[12,13] The more recent study reported from the cost perspective of the University Hospital of Heidelberg, the institution where patients were treated, and the CRT technique was limited to Gamma Knife SRT.[12] The sources of clinical inputs (i.e., pooled 5-year and 10-year survival rates weighted by the numbers of patients treated) were studies conducted by three sets of authors published in 2014, 2015, and 2016. The average total progression-free survival years corresponded to the area under the curve Weibull distribution curves generated from the 5-year and 10-year survival rates. The discounted, average total progression-free survival years was calculated as 10.66 for CIRT and 8.58 for CRT. Therefore, the discounted increase in effectiveness of CIRT over CRT was 2.08 progression-free years. Costs were calculated for a hypothetical patient population who had previously undergone surgical resection. The sources of cost inputs were a systematic cost analysis of 328 tumor treatments (only 48 were skull base neoplasms) conducted at the CIRT facility from January to June 2013, and CE data for Gamma Knife RT for brain metastases from a study published by other authors. The systematic cost analysis included costs for initial consultation with a physician, treatment simulation and planning, and treatment delivery. The total cost of 20 to 22 fractions of CIRT was €31,538.21. After correcting for external financing (i.e., €23,694.66) and the cost of follow-up (i.e., €733.10), the corrected direct cost of CIRT was €18,957.78. Surgical costs and follow-up costs were excluded. The authors assumed a lifetime time horizon extrapolated to 34 years and a discount rate of 3% per year. To account for treatment of recurrent disease, the discounted cost of treating local progression was added to the direct cost of treatment. Patients with recurrent disease were treated with imatinib at a discounted cost of €134,335.97 for those previously treated with CIRT and €148,319.07 for those previously treated with CRT. After adjusting for external financing and follow-up, the corrected direct cost of CIRT was €153,293.75 and that for CRT was €153,019.07. Patients with recurrent disease were not treated with surgery or RT. Based on recommendations from the World Health Organization, the CE threshold of €105,135 per QALY was determined to be three times the annual gross domestic product per capita (i.e., €35,045 per QALY in 2013). Sensitivity

analysis was conducted assuming an uncertainty of 10% for costs, the 95% confidence interval for the 10-year overall survival rate for CIRT, and a deviance of ±10% for the overall survival rate for CRT.

In the original cost-effectiveness study,[13] the perspective was not specified. Both treatment facility costs and third-party reimbursement rates were considered. The sources of clinical inputs (i.e., 5-year local control rates and overall survival rates) were published studies conducted by a subset of the authors between 2002 and 2005. The source of surgical costs and reimbursement for hospitalization were the department of neurosurgery at the University Hospital of Heidelberg. The source of the reimbursement rate for CRT was the common scale of charges and fees for the German health care system. It is unclear what source the authors used to determine the reimbursement rate for CIRT. Costs incurred for diagnosis, nursing, diagnostic follow-up, and post-operative rehabilitation as well as indirect costs associated with loss of economic productivity and treatment of adverse effects of radiation were excluded. The authors assumed a lifetime time horizon extrapolated to 33 years.

All patients had adjuvant RT following surgical resection. The authors assumed 20 fractions of CIRT were administered to each patient, although a scenario with 16 fractions was also evaluated.[13] CRT was the primary adjuvant RT used for recurrent disease. Based on the literature, the authors assumed that the best local control rate achieved with CIRT was 70% while the best local control rate achieved with high precision SRT was 50%. Lower control rates of 60% and 35% were also considered for CIRT and unspecified CRT, respectively. The 5-year overall survival rate was 88.5% following CIRT and 82% following precision CRT. Treatment costs included the third party (i.e., insurance companies) reimbursement for an average of three weeks of hospitalization (i.e., €12,600 at a university hospital), the average reimbursement for surgery (i.e., €11,000 at the University Hospital of Heidelberg) and RT costs. Overall costs for adjuvant RT incorporated the cost of treating primary and a weighted value of the cost of treating recurrent disease. For the treatment of primary disease, the average reimbursement for CIRT was determined to be €20,000 while for CRT planning and delivery the reimbursement was €3,500. This means the overall cost for treating a patient was €43,600 with CIRT and €27,100 with CRT. For recurrent disease, the average overall reimbursement for hospitalization, surgery, and RT for 10 randomly selected patients who presented with recurrent chordoma at the German Cancer Research Center in 2002 and 2003 was calculated and weighted by the probability of recurrence. All of the selected patients had been treated with RT prior to recurrence and had surgery for recurrent disease. Based on medical records, four patients received one adjuvant CIRT session, three patients received two adjuvant CRT sessions, two patients received one CIRT and one CRT session, while one patient received two CIRT sessions and one CRT session. The average treatment cost for 10 patients was €121,770. The final cost for treating recurrent disease was €81,470 or €94,670 after subtracting the cost for treating the primary disease with CIRT or CRT, respectively.

### *Country of Origin*

The systematic review and meta-analysis[10] was published by authors in China while the rest of the studies were published by overlapping sets of authors in Germany.[3,11-13] Three of the observational studies that were included in the meta-analysis[10] were conducted by subsets of authors that conducted the remaining studies that were included in the report.[3,11-13]

### *Patient Population*

The meta-analysis[10] included patients who had undergone surgical resection for chordoma. The mean age of the patients in the studies that were included in the meta-analysis ranged from 13 to 58 years.[10] One non-randomized study enrolled 56 patients aged 34 to 84 years with histologically confirmed sacral chordomas[3] while the other enrolled 101 patients aged 19 to 77 years with histologically proven grade 1 or 2 skull base chondrosarcomas.[11] Both cost-effectiveness studies reported on patients with skull base chordoma.[12,13] In one of these studies, the authors reported that the average age of patients was 47 years and assumed that the patients had already had surgical resections.[12] The cohort of patients was hypothetical.[12] The treatment setting for CIRT was the German Cancer Research Center in Heidelberg and the University Hospital of Heidelberg.[3,11-13] The non-randomized studies had overlapping recruitment periods.[3,11]

### *Interventions and Comparators*

The intervention of interest in all of the studies was CIRT adjuvant to surgical resection or biopsy for the treatment of chordomas.[3,10-13] Four out of 79 patients had a biopsy and did not have a surgical resection.[11] IMRT was added to the treatment regimen of 12 out of 23 patients in the intervention arm of one study.[3] The comparators were CIRT alone,[3] PBT,[10,11] or CRT (including SRT),[10,12,13] The authors of the non-randomized controlled trials referred to Gamma Knife SRT [12] and high precision CRT or high precision stereotactically guided fractionated RT when referring to the comparator group.[13] All comparators were administered adjuvant to surgical resection, except in one non-randomized study where 4 out of 22 patients underwent biopsy and did not have surgical resection.[11]

In one non-randomized study, 23 out of 35 patients in the intervention group received 15 to 24 grays relative biological effectiveness (Gy RBE) of post-operative CIRT in 5 to 8 fractions plus 50 grays (Gy) of IMRT in 25 factions; while the remaining 12 patients received 60 to 66 Gy RBE of post-operative CIRT in 20 to 22 fractions.[3] In the comparator arm, 21 patients received only 60 to 66 Gy RBE of CIRT in 20 to 22 fractions.[3]

In the second non-randomized study, all patients had either partial surgical resection (n = 93) or biopsy (n = 8) prior to RT.[11] Seventy-nine patients in the intervention arm received CIRT with intensity-modulated active raster scan technique and 22 patients in the comparator arm received PBT.[11] A total of 60 Gy RBE of post-operative CIRT was administered in 5 to 6 fractions at a single dose of 3 Gy per week.[11] About 70 Gy of PBT was offered in 5 to 6 fractions at a single dose of 2 Gy per week.[11] Patients who enrolled earlier in the study had CIRT alone while PBT was used more often later on.[11]

In the recent cost-effectiveness study, CIRT was administered at a dose of 45 Gy RBE in 15 fractions, followed by a 15 to 21 Gy RBE boost delivered in 5 to 7 fractions to the initial extent of the tumour.[12] The comparator CRT dose was not disclosed.[12] In the original cost-effectiveness study, the spot scanning beam technique was used to deliver CIRT in the intervention arm and patients in the comparator arm received CRT. The doses of RT were not disclosed.[13]

### *Outcomes*

The outcomes of interest were local control rates,[11] overall survival rates[10,11] adverse effects or toxicity in incidence of sacral insufficiency fractures,[3] or hearing problems, cranial nerve deficits, abducent nerve paralysis, and double vision.[11] Fracture-free survival probability as well as the predictive probability of patient characteristics were also

reported.[11] Local control rates were calculated 1 year, 2 years, and 4 years following treatment.[11] Overall survival rates were calculated at the same time points[11] and also at years 3, 5, and 10.[10] Sacral insufficiency fracture rates were calculated at the 1-, 2- and 5-year time points,[3] while other toxicity rates were calculated 1 year, 2 years, and 4 years following treatment.[11] Sacral insufficiency fractures that were identified by magnetic resonance imaging were confirmed with an additional CT scan of the pelvis.[3] Medical records were reviewed for correlation of insufficiency fractures with associated clinical symptoms.[3] Medical records and responses to questionnaires were consulted to assess toxicity in the second primary study.[11]

The economic evaluations reported on incremental cost-effectiveness ratio (ICER) in € per QALY,[12] in € per year of disease free survival,[13] and in € per 1% increase in overall survival.[13] The ICER (in € per QALY) was calculated as the difference in direct costs (correcting for financing and excluding surgery-related and follow-up costs) divided by the gain in QALYs.[12] The gain in QALYs (i.e., 1.61) was determined by multiplying the difference in discounted average total PFS years (i.e., 2.08) by a published PFS-to-QALYs conversion factor of 0.775.[12] The ICER (in € per year of disease free survival) was calculated as the difference in direct costs associated with treatment planning, delivery, surgery, and hospitalization for primary and recurrent disease, divided by the gain in disease free survival.[13] The calculation of the gain in disease free survival was not described.[13]

## Summary of Critical Appraisal

A summary of the critical appraisal of the studies is summarized below and details are available in Appendix 3, Table 5, Table 6, and Table 7.

### *Systematic Review*

The systematic review[10] was critically appraised using the AMSTAR 2 checklist.[6] The patients, interventions, and comparators were included in the research objectives. The literature search included two databases and listed the keywords. Study selection was performed in duplicate, the inclusion criteria for the review and the included studies were described in adequate detail, reasons for excluding studies were given, and the review authors reported that they had no conflicts of interest. These strengths indicate that consistent criteria were applied when selecting studies and that there were no financially-motivated biases in conducting the study.

Limitations included the lack of clarity regarding whether the authors established review methods prior to conducting the review, literature searches identified all relevant primary studies, post hoc analyses were conducted, or whether there was potential bias from sources of funding. In addition, trial registries and grey literature were not searched, data extraction was not performed in duplicate, and sources of funding for the primary studies were not reported. Sources of heterogeneity and their impact were not discussed. The authors assessed risk of bias of the included studies using the Newcastle-Ottawa Scale (NOS) for cohort studies. All of the included studies had NOS scores of 6 or 7 out of a maximum of 9. The higher scores suggest lower risk of bias, however, the NOS is still under evaluation.[14] Selection bias was indicated in the systematic review because patients in the CRT group were on average older than those in the other groups. The impact is that the survival rate in the CRT group may have been lower than that in the other groups, potentially resulting in the over-estimation of the ICER of CIRT over CRT. There was a potential publication bias given that the CRT studies were more often published earlier than

the CIRT studies. Assuming an improvement in the technology over time, the studies reporting on the use of CRT may have been skewed toward lower survival rates. Finally, the authors reported that CRT was delivered at a lower dose than CIRT, potentially giving patients in the CIRT a survival advantage.

### *Non-randomized Studies*

The non-randomized studies[3,11] were appraised with the Downs and Black checklist.[7] Strengths common to both studies were that the study objective, main outcomes, included patients' characteristics, interventions being compared, and the main findings were described clearly. Patients were treated at the primary treatment facility available in Germany strengthening external validity of the results. Internal validity was bolstered because appropriate statistical tests were used, the main outcome measures appeared to be accurate, and the period between the intervention and outcome was the same for each patient (though they were treated at different times). Finally, patients in the intervention and comparator groups were recruited from the same population.

The studies[3,11] had comparable limitations. Exclusion criteria and potential confounders were not described a priori and the probability values for one main outcome and estimates of the random variability in the data for the main outcomes were not reported. Patients were retrospectively selected in both studies, and it remains unclear whether patients who were included were representative of the entire population from which they were selected. Blinding of patients, outcomes assessors, compliance with the intervention and comparators were not discussed. Patients were not randomly assigned to the intervention and comparators and an account was not given of patients who were lost-to-follow up by means other than death.

### *Economic Evaluations*

The economic evaluations[12,13] were assessed using the Drummond checklist.[8] Common strengths were that the costs and consequences were measured in appropriate physical units, an incremental analysis of costs and consequences was conducted, the type of cost analysis was appropriate, and the discussion of limitations was extensive. Although allowance was made for uncertainty in both evaluations, there were differences in the extent and format of the analysis. The recent evaluation conducted a sensitivity analysis, however results were reported in graphical format and not in text.[12] The original evaluation allowed for uncertainty in local control rates and the number of CIRT fractions using two discrete values, rather than continuous values.[13] As such, estimates of cost-effectiveness ratios at other input values cannot be determined.

Three common limitations were identified. Both evaluations stated their objective but did not define their research question, perspective, or economic model.[12,13] Without this information is challenging to compare the findings in these studies with future studies. Secondly, each study established effectiveness of the intervention and comparators from four studies. The small quantity of studies suggests that the sources of clinical inputs may have been artificially restricted. In fact, none of the studies conducted a systematic review to identify published studies with clinical inputs. Incidentally, the third common limitation was that the authors appeared to select comparator inputs based on convenience or availability of existing data, as such, important comparators were missing. For example, clinical inputs (i.e., 5-year local control rate and 10-year overall survival rate) for the comparator arm were limited to SRT,[13] specifically Gamma Knife SRT,[12] although other forms of CRT such as

IMRT are used more often to treat chordoma. Additionally, the analysis did not account for differences in costs among the various types of CRT.

The recent evaluation was further limited because surgical costs and capital costs were not considered in the analysis.[12] The assumption that there was no role for repeat RT or surgery for patients with recurrent disease was not justified, given that the original evaluation[13] clearly demonstrated that on average these patients had four surgeries and one to three RT sessions. Specific to the original evaluation, capital costs and costs associated with loss of economic productivity and treatment of adverse effects of RT were omitted.[13] A differential in the costs between the intervention and comparator could have an impact on the estimate of the ICER. In addition, although consequences were extrapolated over a lifetime time horizon, the costs were not adjusted for differential timing. The difference between the reimbursement rates for CIRT and CRT will likely narrow over time. The authors highlighted uncertainty in cost estimates due to lack of patient-specific data and information on the charges and fees in the public health care system, as a limitation of their study. Incorporate more accurate data in the future may change the estimate of the ICER.

## Summary of Findings

Appendix 4 presents tables of the main study findings and authors' conclusions. See Table 8, Table 9, and Table 10.

### *Clinical Effectiveness of CIRT for Chordoma*

#### Local control rates

Findings from one of the non-randomized studies suggested that the differences in local control rates for patients treated with CIRT compared to patients treated with PBT were not statistically significant at the 1-year, 2-year, and 4-year follow-up time points.[11]

#### Overall survival rates

In a meta-analysis of 25 single-arm studies, 361 patients treated with CIRT had statistically significantly higher rates of survival relative to 635 patients treated with CRT when data was compared 3 years, 5 years, and 10 years following RT.[10] Relative to patients treated with SRT, there was no statistically significant difference in survival rates at any of the three time points.[10] Relative to patients treated with PBT, those treated with CIRT had a statistically significantly lower survival rate 10 years after treatment.[10] At other time points (i.e., at 3 years and 5 years following treatment), the differences were not statistically significant.[10] Similarly, in a non-randomized study of 79 patients treated with CIRT compared to 22 patients treated with PBT, the differences in overall survival rates were not statistically significant at the 1-year, 2-year, and 4-year follow-up time points.[11]

#### Adverse effects

The difference in the incidence of sacral fractures between a group of 35 patients treated with surgical resection plus CIRT (with or without IMRT) and 21 patients treated with CIRT alone was not statistically significant.[3] This is an important finding as it suggests that over half of patients treated with CIRT will develop fractures, a fraction of which could cause pain or neurologic deficits.[3] The 1-year, 2-year, and 5-year fracture-free survival probability values were reported without reference to statistical significance of the differences between the two groups.[3] The fracture-free survival probability was higher in the post-operative CIRT group at the 1-year time point but became increasingly lower at the 2-year and 5-year time

points.[3] Based on calculations of hazard ratios, patient's age, gender, tumour volume, bone marrow density, radiation dose, and extent of surgical resection were not predictive of sacral insufficiency fractures.[3]

The authors of the second non-randomized study conducted an extensive analysis of toxicity rates for patients treated with post-operative CIRT or post-operative PBT.[11] Outcomes were measured prior to the 1-year time point, between the 1-year and 3-year time points, and between the 3-year and 5-year time points.[11] Compared with patients in the PBT group, a smaller proportion of patients in the CIRT group had hearing problems prior to the 1-year time point and between the 1-year and 3-year time points. A smaller proportion had cranial nerve deficit and double vision at all measurement points, although the differences in the latter were not statistically significant.[11] Abducent paralysis incidence rate was lower up to the 1-year time point, equal between years 1 and 3, and higher between years 3 and 5.[11]

### *Cost-effectiveness of CIRT for chordoma*

**Incremental cost-effectiveness ratio**

For treating primary disease, the ICER of post-operative CIRT relative to post-operative Gamma Knife SRT was €8,855.76 per QALY indicating that CIRT was cost-effective at a willingness-to-pay threshold of €105,135 per QALY.[12] CIRT was also cost-effective in treating recurrent disease with as ICER of €170.61 per QALY.[12] A sensitivity analysis for treating primary disease was conducted but the values were reported in graphical format on a logarithmic scale and not in text format.[12] As such, the results of the sensitivity analysis are not included in this report.

In a cost-effectiveness analysis reported by authors at the same location 11 years earlier, post-operative CIRT was cost-effective compared to post-operative CRT at an ICER of €16,500 per year of disease free survival or €2,539 per 1% increase in overall survival rate (assuming overall survival rates of 88.5% and 82% for CIRT and CRT, respectively).[13] The willingness-to-pay threshold was not reported in this study.

### *Guidelines*

No relevant guidelines on the use of CIRT for chordoma met the report's inclusion criteria.

## Limitations

The body of evidence on the use of CIRT for chordoma has limitations that warrant caution when interpreting the results of the report. A major limitation of this report is the small number of studies on the clinical effectiveness and cost-effectiveness of CIRT. Furthermore, within the body of available evidence, there is a lack of diversity in the sources of clinical and cost inputs. Both non-randomized studies[3,11] and both economic evaluations[12,13] were conducted at the same facilities in Germany. In addition, three observational studies that were conducted in the same facilities informed the meta-analysis[10] and the economic evaluations.[12,13] The non-randomized studies had overlapping recruitment periods although one reported on 56 adults with sacral chordoma[3] treatment while the other reported on 101 adults skull base chordoma treatment.[11] Information from more sources may have improved the generalizability of the findings.

The small size of the body of evidence also limits synthesis of the evidence. For example, even though the economic evaluations were conducted at the same facility, there were important differences in assumptions, clinical inputs and costs inputs that preclude a

comparative evaluation of the results, other than observing that both studies provided evidence in support of CIRT.

Overall, there were noticeable gaps in the available evidence. Data on viable comparators and outcomes of interest were missing. For example, none of the studies reported on the use of neo-adjuvant RT, nor compared CIRT to surgery alone or chemotherapy alone. None of the studies reported specifically on data from children, or on outcomes such as reduction in tumour size, time to progression, progression rate, quality of life measured directly, or termination of treatment due to adverse events in adults. Additional studies on some or all of these factors would contribute to a richer body of evidence on the relative effectiveness of CIRT for chordoma. Additionally, it is unclear whether chordomas located on certain areas of the spine were over or underrepresented within the included studies.

Finally, it is unclear how well findings from cost-effectiveness studies that focused on patients treated in Germany could generalize to the Canadian setting.

## Conclusions and Implications for Decision or Policy Making

Five relevant publications comprising one systematic review and meta-analysis, two non-randomized studies, and two economic evaluations were identified. The findings from this review suggest that there is insufficient evidence to make firm, comprehensive conclusions about the clinical effectiveness and cost-effectiveness of CIRT relative to other forms of therapy for chordoma. Caution must be taken in interpreting the evidence due to the limited quantity of studies available and their respective limitations.

The results from one meta-analysis and one non-randomized study,[11] suggest that post-operative CIRT provides better survival odds than post-operative CRT, similar odds as SRT, and increasingly worse odds relative to PBT.[10] The survival odds relative to PBT were similar at three years and five years following treatment but were worse at the 10-year follow-up time point.[10] The non-randomized study was conducted at the same facility as three observational studies that were included in the meta-analysis. Information from the same non-randomized study also suggested that there was no statistically significant difference in local control rates between post-operative CIRT and post-operative PBT up to four years following treatment.[11] Long-term (i.e., 10-year) local control rates were not reported in the primary studies.

While evidence on adverse effects was also limited in quantity from one non-randomized study involving 56 patients and another involving 101 patients, some of the findings are worth highlighting. The sacral insufficiency fracture rate for patients who were treated with surgical resection and adjuvant high-dose CIRT (with or without IMRT) was statistically the same for patients treated with high-dose CIRT alone.[3] Importantly, the probability of developing sacral insufficiency fractures following high-dose CIRT was 0.84 following surgery or 0.50 without surgery.[3] Morbidity risks of CIRT extend beyond fractures and encompass adverse effects related to hearing problems, cranial nerve deficit, abducent nerve paralysis, and double vision.[11]

Two economic evaluations conducted at one facility in Germany, found that post-operative CIRT was cost-effective relative to post-operative CRT over a lifetime time horizon.[12,13] Although one study included the costs associated with surgical resection and the other did not, both came to similar conclusions regarding the benefits of CIRT over CRT. One of the studies suggested that CIRT was more cost-effective than Gamma Knife SRT at a willingness-to-pay threshold of €105,135 per QALY.[12]

Further research addressing the relative effectiveness of post-operative CIRT to neo-adjuvant RT, surgery alone, or chemotherapy alone may be useful along with more research comparing adverse effects from CIRT to other ion-based RT and CRT. More evidence on outcomes such as reduction in tumour size, time to progression, progression rate, quality of life measured directly, or termination of treatment due to adverse events in adults is needed. Eventually, evidence on children evaluated separately from adults would be instructive in defining age-specific treatment regimen.

Given that Canada does not have a CIRT facility at this time and that none of the studies documents clinical outcomes or costs specific to Canadian patients, the generalizability of the findings to the Canadian health care context cannot be readily assessed. When contemplating whether to offer CIRT in Canada, decision-makers may need to consider, among other things, the rate at which RT technology is changing, the availability of other forms of charged particle therapy that are currently under evaluation, and the differences in chordoma incidence and health care reimbursement rates between Canada and Germany.

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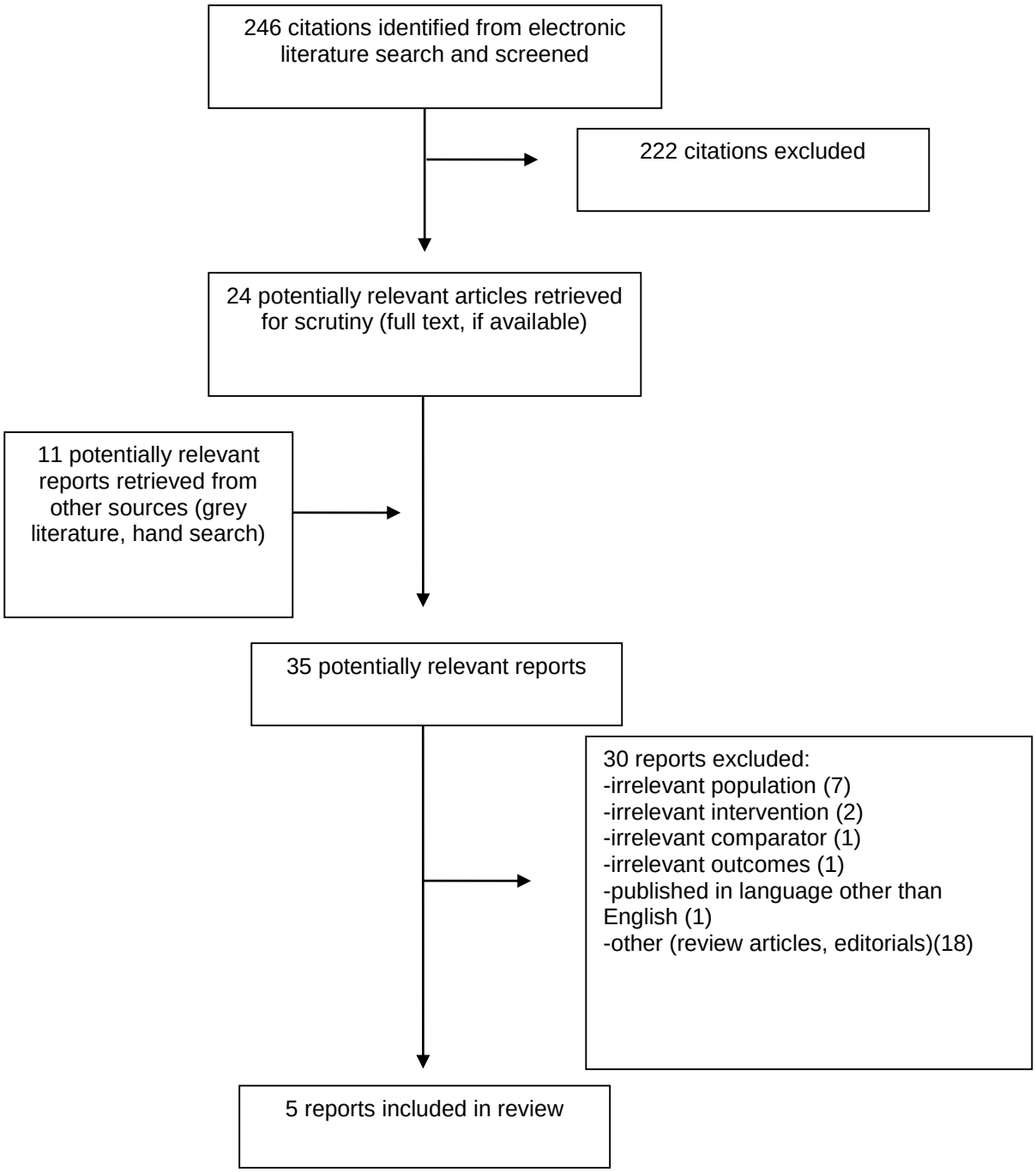
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Systematic Review and Meta-Analysis

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| Zhou, 2018,[10] China | Systematic review of studies in the Cochrane library and Pubmed database and meta-analysis of 25 single-arm (observational) studies published between 1983 and 2016 | 996 patients with prior surgery for chordoma<br><br>Age range: 13 to 58 years | Intervention (n = 361): post-operative CIRT (n = 5 studies)<br><br>Comparator (n = 635): post-operative CRT (n = 4 studies), SRT (n = 7 studies), and PBT (n = 9 studies) | 3-, 5-, and 10-year OS rates |

CIRT = carbon ion beam RT; CRT = conventional RT; OS = overall survival; PBT = proton beam RT; RT = radiation therapy; SRT = stereotactic RT

## Table 3: Characteristics of Included Non-randomized Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| Bostel, 2018,[3] Germany | Single-centre, retrospective non-randomized study | 56 patients with histologically confirmed sacral chordomas, treated between November 2009 and December 2012; 34% female<br><br>Median age: 61 years (range, 34 to 84) | Intervention (n = 35): surgical resection + high-dose CIRT +/- IMRT<br><br>CIRT with IMRT: 15 to 24 Gy RBE CIRT in 5 to 8 fractions + 50 Gy IMRT in 25 fractions (n = 23)<br><br>CIRT without IMRT: 60 to 66 Gy RBE CIRT in 20 to 22 fractions (n = 12).<br><br>Comparator (n = 21): Primary high-dose CIRT<br><br>High-dose CIRT: 60 to 66 Gy RBE CIRT in 20 to 22 fractions | Adverse effects: Incidence of sacral insufficiency fractures; 1-year, 2-year, and 5-year fracture-free survival probability<br><br>Follow-up period (median): 35.5 months (range 2-83 months); 6-8 weeks after RT, every 3 months for a year, every 6 months after |
| Mattke, 2018,[11] Germany | Single-centre, retrospective non-randomized study | 101 adults (≥ 18 years) with histologically-proven grade 1 and grade 2 skull base chondrosarcomas treated between 2009 and 2014; including | Intervention (n = 79; 59.5% women): surgery (n = 75) or biopsy (n = 4) + post-operative CIRT with intensity-modulated active raster scan | 1-year, 2-year, and 5-year LC rate and OS rate, adverse effects (i.e., toxicity rates)<br><br>Follow-up period (median): 40 months |

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | surgery (n = 93) or biopsy (n = 8); 60.4% women<br><br>Excluded: Patients < 18 years or patients with grade 3 chondrosarcoma<br><br>Median age: 44 years (range, 19 to 77 years) at the start of treatment | technique; 60 Gy RBE in 5 to 6 fractions of a single dose of 3 Gy per week.<br><br>Comparator (n = 22; 63.6% women): surgery (n = 18) or biopsy (n = 4) + post-operative PBT with intensity-modulated active raster scan technique; 70 Gy of PBT was offered in 5 to 6 fractions of a single dose of 2 Gy per week. | (range, 0.8 to 78.1 months); 43.7 months for the intervention group and 30.7 months for the comparator group<br><br>CIRT was administered early in the study while PBT was administered in patients who enrolled later on |

CIRT = carbon-ion beam RT; Gy = gray; IMRT = intensity-modulated RT; LC = local control; OS = overall survival; PBT = proton beam therapy; RBE = relative biological effectiveness; RT = radiation therapy

## Table 4: Characteristics of Included Economic Evaluations

| First Author, Publication Year, Country | Type of Analysis, Time Horizon, Perspective | Decision Problem | Population Characteristics | Intervention and Comparator | Approach | Clinical and Cost Data Used in Analysis | Main Assumptions |
|---|---|---|---|---|---|---|---|
| Sprave, 2018,[12] Germany | Cost-effectiveness analysis, lifetime time horizon, institutional perspective | To analyze the cost-effectiveness of CIRT over CRT for patients with skull base chordoma | A hypothetical population of patients with skull base chordomas who had previously undergone surgical resection<br><br>Mean age at treatment: 47 years | Intervention: post-operative CIRT<br><br>Comparator: post-operative Gamma Knife SRT | Model-based analysis | <u>Clinical data</u><br>PFS rates<br><br><u>Cost data</u><br>Direct costs (hypothetical population): initial consultation, treatment simulation and planning, treatment, follow-up including imaging<br><br>Costs for CIRT: | • Lifetime time horizon: 34 years<br>• PFS to QALY conversion factor: 0.775<br>• Discount rate: 3% per year<br>• CE threshold: Three times the annual gross domestic product per capita (i.e., €35,045 in 2013)<br>• Patients with recurrent |

| First Author, Publication Year, Country | Type of Analysis, Time Horizon, Perspective | Decision Problem | Population Characteristics | Intervention and Comparator | Approach | Clinical and Cost Data Used in Analysis | Main Assumptions |
|---|---|---|---|---|---|---|---|
| | | | | | | systematic cost analysis of all tumor entities performed at a single CIRT facility from January to June 2013.<br><br>Excluded financing and follow-up costs<br><br><u>Recurrent disease:</u> Discounted cost of imatinib treatment for local progression | disease were treated with imatinib without RT or surgery<br>• Deviance of OS for CRT: 10%<br>• Disease progressed in every patient |
| Jakel, 2007,[13] Germany | Cost-effectiveness analysis, lifetime time horizon, third-party payer (insurance) perspective | To analyze the cost-effectiveness of CIRT over CRT for patients with skull base chordoma | Patients with skull base chordomas<br><br>Mean age at treatment: 47 years | Intervention: Surgical resection + post-operative CIRT (spot-scanning beam)<br><br>Comparator: Surgical resection + post-operative high-intensity SRT | Trial-based analysis | <u>Clinical data</u><br>5-year LC rates and OS rates<br><br><u>Cost data</u><br>Direct treatment costs: surgical treatment, hospitalization, and RT | • Lifetime time horizon: 33 years<br>• For patients with recurrent disease, CRT was the primary adjuvant RT<br>• CIRT is typically applied in 20 fractions<br>• LC rate of 35% or 50% for CRT and 60% or |

| First Author, Publication Year, Country | Type of Analysis, Time Horizon, Perspective | Decision Problem | Population Characteristics | Intervention and Comparator | Approach | Clinical and Cost Data Used in Analysis | Main Assumptions |
|---|---|---|---|---|---|---|---|
| | | | | | | | 70% for CIRT<br>• 5-year OS rate of 82% following precision CRT and 88.5% following CIRT |

CIRT = carbon ion beam RT; CRT = conventional RT; LC = local control; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RT = radiation therapy; SRT = stereotactically-guided fractionated RT

# Appendix 3: Critical Appraisal of Included Publications

## Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[6]

| Strengths | Limitations |
|---|---|
| Zhou, 2018[10] | |
| • The population, intervention, comparators, and outcomes were described<br>• The review authors explained the process they used to select studies for inclusion<br>• Study selection and data extraction were performed in duplicate<br>• The review authors provided adequate details of the included studies. All included studies were single-arm trials.<br>• The Newcastle-Ottawa Scale for cohort studies was used to assess the quality of the individual studies<br>• The review authors accounted for risk of bias when discussing the results<br>• The review authors declared that there were no conflicts of interest | • An explicit statement that the review methods were established *a priori* was not found<br>• A list of excluded studies was not provided (although reasons for exclusion were listed)<br>• Sources of funding for the individual studies were not included<br>• The review authors did not adequately discuss heterogeneity in the data |

## Table 6: Strengths and Limitations of Non-randomized Studies using the Downs and Black checklist[7]

| Strengths | Limitations |
|---|---|
| Bostel et al., 2018[3] | |
| <u>Reporting</u><br>• The objective, included patients' characteristics, the interventions of interest, and the main findings of the study were clearly described<br>• Adverse events were included as outcomes<br><br><u>External validity</u><br>• Patients were treated at the primary treatment facility available in Germany at the time of the study<br><br><u>Internal validity - bias</u><br>• The statistical tests used to assess the main outcomes were appropriate<br>• The main outcome measures were accurate<br>• Although patients received treatment at different times over a 3-year period, the period between the intervention and outcome was the same for each patient<br><br><u>Internal validity - confounding</u><br>• Patients in both groups were recruited from the same population over a 3-year time period | <u>Reporting</u><br>• Exclusion criteria and potential confounders, were not described *a priori*<br>• Probability values for one out of two main outcomes were not reported<br>• Estimates of the random variability in the data for the main outcomes were not reported<br><br><u>External validity</u><br>• Patients were retrospectively selected. The study did not report the proportion of the source population from which the patients were derived.<br>• It is unclear whether the patients who were included in the study were representative of the entire population from which they were selected.<br><br><u>Internal validity - bias</u><br>• Blinding of patients and outcomes assessors were not discussed<br>• Compliance with the intervention and comparator were not discussed |

| Strengths | Limitations |
|---|---|
| | Internal validity - confounding<br>• Patients were not randomized to intervention groups<br>• An account was not given of patients who were lost-to-follow up by means other than death<br><br>Power<br>• Statistical power was not discussed |
| Mattke et al., 2018[11] | |
| Reporting<br>• The objective, included patients' characteristics, the interventions of interest, and the main findings of the study are clearly described<br>• Adverse events were included as outcomes<br><br>External validity<br>• Patients were treated at the primary treatment facility available in Germany at the time of the study<br>• Although the study was retrospective, all patients treated over a 5 year period were included<br><br>Internal validity - bias<br>• The statistical tests used to assess the main outcomes were appropriate<br>• The main outcome measures were accurate<br>• Although patients received treatment at different times over a 5-year period, the period between the intervention and outcome was the same for each patient<br><br>Internal validity - confounding<br>• Patients in both groups were recruited from the same population over a 5-year period | Reporting<br>• Exclusion criteria and potential confounders, were not described *a priori*<br>• Probability values were reported for one out of five main outcomes<br>• Estimates of the random variability in the data for the main outcomes were not reported<br><br>External validity<br>• Patients were retrospectively selected. The study did not report the proportion of the source population from which the patients were derived.<br>• It is unclear whether the patients who were included in the study were representative of the entire population from which they were selected.<br><br>Internal validity - bias<br>• Blinding of patients and outcomes assessors were not discussed<br>• Compliance with the intervention and comparator were not discussed<br><br>Internal validity - confounding<br>• Patients were not randomized to intervention groups<br>• An account was not given of patients who were lost-to-follow up by means other than death<br><br>Power<br>• Statistical power was not discussed |

## Table 7: Strengths and Limitations of Economic Studies using the Drummond Checklist[8]

| Strengths | Limitations |
|---|---|
| Sprave, 2018[12] | |
| • The study examined costs and effects of post-operative CIRT in comparison with Gamma Knife S RT<br>• Although a perspective was not explicitly stated, the context for decision-making was that of the institution where patients were treated<br>• A comprehensive description of one competing alternative was provided | • Although an objective was stated, a research question was not defined<br>• Important comparators were missing from the assessment. IMRT and other forms of CRT are more often used than Gamma Knife SRT to treat chordomas.<br>• The effectiveness of the interventions was established from four clinical studies, one of which was conducted by some |

| Strengths | Limitations |
|---|---|
| • Costs were measured in appropriate physical units<br>• Adjustments were made to reflect market values by eliminating financing.<br>• Future costs were discounted by 3%<br>• An incremental analysis of the costs and consequences was conducted<br>• The type of cost analysis used was appropriate<br>• Allowance was made for uncertainty in cost variables and the 10-year survival rates through a sensitivity analysis<br>• The authors acknowledged that the perspective taken determined whether the intervention was cost-effective<br>• The discussion of limitations was extensive | of the authors of the economic evaluation<br>• Costs for surgical resection were not included in the analysis<br>• Capital costs were not considered, neither were costs from the patients and societal viewpoints<br>• The consequences (QALYs) were calculated as a function of the progression-free survival rate without justification for using a single reference source to determine the conversion factor<br>• The accuracy of the calculations of costs and consequences was not discussed<br>• It is unclear whether the costs and consequences were credibly valued<br>• It is unclear whether the process used to adjust for market values was appropriate<br>• Justification for the discount rate was not provided<br>• The authors suggested that all patients with recurrent disease were treated with imatinib rather than resection or additional RT<br>• The results of the sensitivity analysis were documented in graphical format |
| Jakel, 2007[13] | |
| • The study examined costs and effects of adjuvant CIRT in comparison with CRT<br>• The effectiveness of the intervention and comparator were established from medical records and other institutional data<br>• Costs and consequences were measured in appropriate physical units<br>• An incremental analysis of costs and consequences was conducted<br>• The type of cost analysis used was appropriate<br>• Allowance was made for uncertainty in local control rates and number of CIRT fractions<br>• The discussion of limitations was extensive | • Although an objective was stated, a research question was not defined<br>• Important comparators were excluded from the assessment. The primary local control rate was for SRT, rather than IMRT or other forms of CRT that are more often used to treat chordoma.<br>• The effectiveness of the interventions was established from four published studies, all of which were conducted by some of the authors of the economic evaluation<br>• The intervention and included comparator were not adequately described<br>• Capital costs were not considered, neither were costs from the patients and societal viewpoints<br>• Follow-up costs were excluded from the analysis<br>• It is unclear whether the costs and consequences were credibly valued. Adjustments were not made to reflect market values. Costs were derived from reimbursement data.<br>• Costs and consequences were not adjusted for differential timing<br>• There was uncertainty in cost estimates due to lack of patient-specific data and information on the charges and fees in the public health care system |

CIRT = carbon ion beam RT; QALY = quality-adjusted life-year; RT = radiation therapy; SRT = stereotactically-guided fractionated RT

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 8: Summary of Findings Included Meta-Analysis

| Main Study Findings | Authors' Conclusion |
|---|---|
| Zhou, 2018[10] | |
| **Post-operative CIRT vs. post-operative CRT**[a]<br>3-year OS rate: 93% (CI, 90% to 95%) vs. 70% (CI, 60% to 81%) *P* < 0.001[b]<br>5-year OS rate: 87% (CI, 84% to 91%) vs. 46% (CI, 36% to 56%); *P* < 0.001<br>10-year OS rate: 45% (CI, 36% to 55%) vs. 21% (CI, 10% to 33%); *P* < 0.001<br>Indicating a statistically significant higher survival rate for patients treated with CIRT at the three time points<br><br>**Post-operative CIRT vs. post-operative SRT**<br>3-year OS rate: 93% (CI, 90% to 95%) vs. 92% (CI, 88% to 96%) *P* = 0.788<br>5-year OS rate: 87% (CI, 84% to 91%) vs. 81% (CI, 75% to 86%); *P* = 0.247<br>10-year OS rate: 45% (CI, 36% to 55%) vs. 40% (CI, 30% to 55%); *P* = 0.474<br>Indicating no statistically significant difference at the three time points<br><br>**Post-operative CIRT vs. post-operative PBT**<br>3-year OS rate: 93% (CI, 90% to 95%) vs. 89% (CI, 85% to 93%); *P* = 0.323<br>5-year OS rate: 87% (CI, 84% to 91%) vs. 79% (CI, 74% to 83%); *P* = 0.093<br>10-year OS rate: 45% (CI, 36% to 55%) vs. 60% (CI, 43% to 77%); *P* = 0.033<br>Indicating a significantly lower survival rate for patients treated with CIRT at the 10-year time point but not at the other time points | *"…results show that particle therapy may be a common therapy for chordoma in the future."* (p52) |

CI = 95% confidence interval; CIRT = carbon ion beam RT; CRT = conventional RT; OS = overall survival rate; PBT = proton beam RT; RT = radiation therapy; SRT = stereotactic RT

a Patients in the CRT group were reported as being older and treated with lower doses of radiation than those in the other groups, however values were not disclosed.

b The number of patients available at each time point was not disclosed

## Table 9: Summary of Findings of Included Non-randomized Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| Bostel et al., 2018[3] | |
| **Surgical resection + post-operative high-dose CIRT +/- IMRT (n = 35) vs. high-dose CIRT alone (n = 21)**<br>Sacral insufficiency fracture rate: 57% (20/35) vs. 43% (9/21); *P* = 0.23; indicating that there was no statistically significant difference between the two groups<br>10 out of 29 patients with fractures suffered from pain that | *"About half of patients undergoing high-dose carbon-ion based radiation of sacral chordomas developed sacral fractures during the further course of their disease, mostly within two years after radiation. However, only one third of those fractures resulted in clinical symptoms such as pain or neurologic deficits."*(p6) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| required strong analgesics with or without intensive care by a pain therapist<br><br>**Surgical resection + post-operative high-dose CIRT +/- IMRT (n = 29) vs. high-dose CIRT alone (n = 18)**<br>1-year fracture-free survival probability: 0.68 (CI, 0.48 to 0.81) vs. 0.63 (CI, 0.37 to 0.80)<br>2-year fracture-free survival probability: 0.43 (CI, 0.24 to 0.61) vs. 0.50 (CI, 0.26 to 0.71)<br>5-year fracture-free survival probability: 0.16 (CI, 0.03 to 0.38) vs. 0.50 (CI, 0.26 to 0.71)<br><br>Age, gender, tumour volume, bone marrow density, radiation dose, and extent of surgical resection were not predictive of sacral insufficiency fractures. Hazard ratios were included were not included in this report. | |
| Mattke et al., 2018[11] | |
| **Surgery or biopsy + post-operative CIRT (n = 79) vs. Surgery or biopsy + post-operative PBT (n = 22)**<br>1-year LC rate: 98.6% vs. 100%<br>2-year LC rate: 97.2% vs. 100%<br>4-year LC rate: 90.5% vs. 100%<br>Cumulative difference: *P* = 0.357<br><br>1-year OS rate: 100% vs. 100%<br>2-year OS rate: 98.5% vs. 100%<br>4-year OS rate: 92.9% vs. 100%<br>Cumulative difference: *P* = 0.384<br><br>**Surgery or biopsy + post-operative CIRT (n = 79) vs. surgery or biopsy + post-operative PBT (n = 22)**<br>**Toxicity rates in years 0 to 1 (time-adjusted rates)**<br>Hearing problems: 43% vs. 68%<br>Cranial nerve deficit: 63% vs. 64%<br>Abducent nerve paralysis: 28% vs. 36%<br>Double vision: 37% vs. 41%<br><br>**Surgery or biopsy + post-operative CIRT (n = 67) vs. surgery or biopsy + post-operative PBT (n = 19)**<br>**Toxicity rates in years 1 to 3 (time-adjusted rates)**<br>Hearing problems: 30% vs. 79%<br>Cranial nerve deficit: 41% vs. 63%<br>Abducent nerve paralysis: 21% vs. 21%<br>Double vision: 24% vs. 37%<br><br>**Surgery or biopsy + CIRT (n = 47) vs. surgery or biopsy + PBT (n = 3)**<br>**Toxicity rates in years 3 to 5 (time-adjusted rates)**<br>Hearing problems: 40% vs. 33%<br>Cranial nerve deficit: 19% vs. 33%<br>Abducent nerve paralysis: 9% vs. 0%<br>Double vision: 21% vs. 33% | *"…particle therapy is a safe and effective therapy for patients with skull base chondrosarcomas. No significant differences between carbon ion–beam and proton-beam treatments could be detected in these first retrospective results in the short term."* (p2043) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| Statistical significance of the cumulative difference for double vision: $P = 0.866$[a] | |

CI = 95% confidence interval; CIRT = carbon-ion beam RT; IMRT = intensity-modulated RT; LC = local control; OS = overall survival; PBT = proton beam therapy; RT = radiation therapy

[a] The statistical significance of the differences in the other adverse effects could not be determined as insufficient or inconclusive documentation was available.

## Table 10: Summary of Findings of Included Economic Evaluations

| Main Study Findings | Authors' Conclusion |
|---|---|
| Sprave, 2018[12] | |
| **Post-operative CIRT vs. post-operative Gamma Knife SRT**<br>Clinical inputs:<br>Discounted average total PFS years: 10.66 vs. 8.58<br>Gain in PFS years: 2.08<br>Gain in QALYs: 1.61 (i.e., 0.775 QALYs/year x 2.08 years)<br><br><u>Primary disease</u><br>Total treatment cost (€): 18,957.78 vs. 4,700.00 (excluding surgery, financing and follow-up costs)<br>ICER (€/QALY): 8,855.76 (i.e., [18,957.76 – 4,700.00]/1.61); indicating that CIRT is cost-effective over CRT for treating primary disease at a willingness-to-pay threshold of €105,135/QALY<br><br><u>Recurrent disease</u><br>Total treatment cost (€): 153,293.75 vs. 153,019.07<br>ICER (€/QALY): 170.61 (i.e., [153,293.75 – 153,019.07]/1.61); indicating that CIRT is cost-effective over CRT for treating primary disease at a willingness-to-pay threshold of €105,135/QALY<br><br><u>Sensitivity analysis</u><br>Uncertainty in costs: ± 10%<br>Range of 10-year OS rates (CIRT): 43% to 65%<br>Deviance of 10-year OS rates (CRT): ± 10%<br>A range of ICERs was reported in graphical format | *"Based on this analysis, CIRT was found to be a highly cost-effective option for the treatment of skull base chordoma."* (p 4857) |
| Jakel, 2007[13] | |
| **Surgical resection + post-operative CIRT vs. surgical resection + post-operative CRT**<br>Clinical inputs:<br>5-year LC rate: 70% vs. 50%<br>5-year OS rate: 88.5% vs. 82%<br><br>Mean individual's total treatment cost (€): 121,770<br><br><u>Primary disease</u><br>Treatment cost (€): 43,600 vs. 27,100 (including surgery, hospitalization, and RT)<br><br><u>Recurrent disease (scenario 1)</u><br>Unadjusted treatment cost (€): 81,470 vs. 94,670 (calculated by | *"…[CIRT] can be more cost-effective in the treatment of some tumors, which are typically treated by a combination of surgery and RT and for which a clear increase of the control rates can be shown, when ion RT is used."* (p137) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| subtracting the primary disease treatment cost from the average individual's total treatment cost)<br>Adjusted treatment cost (€): 24,441 vs. 40,735[a] (based on 5-year LC rates of 70% vs. 50% i.e., recurrence rates of 30% vs. 50%)<br><br>Total treatment cost (€): 68,041 vs. 67,835 (i.e., primary disease treatment cost + adjusted recurrent disease treatment cost)<br>ICER (€/year of disease free survival)[c] = 16,500<br><br><u>Recurrent disease (scenario 2)</u><br>Adjusted treatment cost (€): 32,588 vs. 52,956[b] (based on 5-year LC rates of 60% vs. 35% i.e., recurrence rates of 40% vs. 65%)<br><br>Total treatment cost (€): 76,188 vs. 80,056 (i.e., primary disease treatment cost + adjusted recurrent disease treatment cost)<br>ICER (€/year of disease free survival) = NR<br><br>ICER (€/1% increase in OS rate): 2,539; indicating that adjuvant CIRT is cost-effective compared to adjuvant CRT<br>ICER (€/year): 7,692 (over a lifetime time horizon of 33 years) | |

CIRT = carbon ion beam RT; CRT = conventional RT; ICER = incremental CER; LC = local control; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RT = radiation therapy; SRT = Stereotactic RT

[a] At a recurrence rate of 50% and an unadjusted recurrent disease cost of €94,670, the cost of recurrences would be €47,335

[b] At a recurrence rate of 65% and an unadjusted recurrent disease cost of €94,670, the cost of recurrences would be €61.535.5

[c] The authors defined the term CER as "the additional treatment costs of the new technique weighted by gain in outcome" on page 136. Consequently, the term ICER has been used in this report.

# Appendix 5: Additional References of Potential Interest

## Consensus-based guidelines

The ESMO / European Sarcoma Network Working Group. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals Oncol. 2012 Oct; 23(Suppl 7):vii100–vii109. Available at: https://academic.oup.com/annonc/article/23/suppl_7/vii100/144789

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## Guidelines missing description of the development process

Princess Margaret Cancer Centre Clinical Practice Guidelines: central nervous system: skull base tumours. University Health Network: Toronto (ON); 2018. Available at: https://www.uhn.ca/PrincessMargaret/Health_Professionals/Programs_Departments/Documents/CPG_CNS_SkullBaseTumours.pdf