

Cervical Chordomas: Multicenter Case Series and Meta-analysis

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Abstract

Background

En bloc spondylectomy is the gold standard for surgical resection of sacral chordomas (CHO), but the effect of extent of resection on recurrence and survival in patients with CHO of the cervical spine remains elusive.

Methods

MEDLINE, Embase, Scopus, and Cochrane were systematically reviewed. Patients with cervical CHO treated at three tertiary-care academic institutions were reviewed for inclusion. We performed an individual participant data meta-analysis to assess the overall survival (OS) and progression free survival (PFS) after *en bloc*-gross total resection (GTR) and intralesional-GTR compared to subtotal resection (STR). We then performed an intention-to-treat analysis including all patients with attempted *en bloc* resection in the *en bloc* group, regardless of the surgical margins.

Results

There was a total of 13 series including 161 patients with cervical CHO, including our current series of 22 patients. GTR (*en bloc*-GTR + intralesional-GTR) was associated with a significant decrease in the risk of local progression (pooled hazard ratio (PHR) = 0.22; 95% CI = 0.08–0.59; $p = 0.003$) and risk of death (PHR = 0.31; 95% CI: 0.12–0.83; $p = 0.020$). A meta-regression analyses determined that intralesional-GTR improved PFS (PHR = 0.35; 95%CI = 0.16–0.76; $p = 0.009$) as well as OS (PHR = 0.25; 95%CI = 0.08–0.79; $p = 0.019$) when compared to STR. *En bloc*-GTR was associated with a significant reduction in the risk of local progression (PHR = 0.06; 95%CI = 0.01–0.77; $p = 0.030$), but not a decreased OS (PHR = 0.50; 95% CI = 0.19–1.27; $p = 0.145$). Our intention-to-treat analyses revealed a near significant improvement in OS for the *en bloc* group (PHR: 0.15; 95%CI: 0.02–1.22; $p = 0.054$), and nearly identical improvement in PFS. Radiation data was not available for the studies included in the meta-analysis.

Conclusion

This is the first and only meta-analysis of patients with cervical CHO. We found that both *en bloc*-GTR and intralesional-GTR resulted in improved local tumor control when compared to STR.

Introduction

Chordomas (CHO) are the most common primary malignant spinal bone tumor with an age-adjusted incidence of 0.088 per 100,000 persons per year. [1][2] CHOs of the cervical spine are especially troublesome, as close association or even juxtaposition of critical structures such as the vertebral arteries, esophagus, cervical nerve roots, or the spinal cord itself make surgery a daunting task. Studies have shown that patients with cervical CHOs appear to have worsened overall survival (OS) when compared to patients with CHO of other spinal regions. [3] Intuitively, this should be expected association, as tumor extension toward the aforementioned structures will lead to significantly diminished quality of life and eventual death. Gross total resection (GTR) can be either intralesional, with piecemeal removal of the tumor, or *en bloc*, although there is ample evidence that *en bloc* resection results in improved local control for patients with sacral CHOs [4, 5][6] The *sin qua non* of chordoma management is *en bloc* resection of the tumor, as CHO will nearly inevitably return unless it is resected with clear margins. This can typically be accomplished with tedious pre-surgical planning, using the preoperative imaging as a guide. The Weinstein, Boriani, Biagnini (WBB) surgical staging system classifies the tumors according their zone of infiltration surrounding the spinal cord, and can be useful to describe the location of the tumor. [7] A systematic review found that the WBB staging system accurately predicted the attainment of wide or marginal *en bloc* resection in 88% of primary spinal tumors. [8] While *en bloc* resection is typically feasible in the sacral spine, it is not always possible in most cases of cervical CHOs and therefore intralesional resection is often the standard of care.

With the advent of focused image guided proton-based radiation, there have been reports of increased progression free survival (PFS) for patients with high-dose radiation. [9–12] There has been a surge of interest in the development of novel targeted therapies to combat these tumors, [13, 14] and there now exists an orthotopic animal model of spinal CHO to test these therapies. [15] While CHO is still certainly a surgical tumor, the advancement of adjuvant therapies calls for us as clinicians and surgeons to reassess the benefit to be gained from large, morbid surgeries compared to smaller decompressive surgeries in certain high-risk regions such as the cervical spine. Literature regarding cervical CHOs are predominantly limited to case reports and case series, [16][17][18][19] with no high-level assessment of survival and progression outcomes in this patient cohort. Because any single case series would be unlikely to result in any useful data, a meta-analysis is necessary for this rare but debilitating tumor. In this manuscript, we review our series of patients with cervical CHO at three academic tertiary care institutions, and perform a comprehensive systematic review and meta-analysis of previously published reports to form the highest level of evidence to assess the influence of extent of resection on progression free survival (PFS) and overall survival (OS) for patients with cervical CHO. We hypothesize that there is a significant benefit in PFS and OS by performing GTR in patients with cervical CHO.

Methods

Case Series

All patients with primary cervical CHO treated at three tertiary care academic institutions (Mayo Clinic Florida, Minnesota, and Arizona) were retrospectively reviewed after Internal Review Board (IRB) approval. Inclusion criteria were follows: 1) patients with surgical resection of cervical CHO, 2) histopathological confirmation of diagnosis with typical physaliferous cells, 3) complete records available for extraction, 4) available postoperative magnetic resonance imaging (MRI). Exclusion criteria were as follows: 1) patients with CHO of another location besides the cervical spine that metastasized to the cervical spine, 2) patients with lack of information regarding extent of resection, 3) patients without post-operative imaging, and 4) patients with biopsy but no surgical resection of their tumor. Extent of resection was based on intraoperative reports, post-operative imaging, and pathology reports to determine margins of resection for cases of attempted *en bloc* resection. Patients were noted as having *en bloc*-GTR resection of their tumor, intralesional GTR (intralesional-GTR), or subtotal resection (STR) of their tumors. Patients with attempted *en bloc* resection but violated margins positive for tumor were grouped with the intralesional-GTR group. The pre-operative and post-operative MRIs were used to determine the extent of resection through active contour segmentation. [20] The T2-weighted images were used for this measurement. We collected information regarding age, gender, tumor location, extent of resection, use of radiation, radiation dosage, complications, recurrence, and use of molecular targeted therapy (MTT). For radiation, we counted this variable if the patient had immediate preoperative or postoperative radiation with any radiation modality at the time of their primary surgery.

Systematic Review

Search Strategy

Studies were identified by a medical librarian developing and running searches in the MEDLINE (1946-Present), Embase (1974-Present), Cochrane Central Register of Controlled Trials (1991-Present), and Cochrane Database of Systematic Review (2005-Present) [all via the Ovid interface], Scopus (1823-Present), Science Citation Index Expanded (1975-Present) and Emerging Sources Citation Index (2015-Present) [via the Web of Science interface] and Epistemonikos databases. Grey literature resources were also searched. There were no limits to language or publication date. Filters to remove animal studies were employed. Search terms included database-specific-controlled vocabulary (MeSH, Embase/ Emtree terms) and additional free-text terms/ keywords such as cervical chordoma, surgical resection, radiation, and radiotherapy. All databases and grey literature resources were searched on November 14th, 2020 and the search strategy was performed according to PRISMA guidelines. [21] The full search strategies are available in the appendix.

Study Selection

Inclusion criteria were as follows: 1) Manuscripts including patients who underwent resection of their cervical CHO, 2) retrospective and prospective series. Exclusion criteria were as follows: 1) studies that did not report individual patient data for cervical cases, 2) case reports, 3) case series with fewer than three patients.

Data Extraction and Quality Evaluation

We extracted data regarding patient age, sex, tumor location, extent of resection, use of radiation, complications, local recurrence, metastasis, death, and pathology. For extent of resection, patients were grouped according to extent of resection with groups being *en bloc* resection with negative margins, intralesional-GTR (*en bloc* resection with positive margins + intralesional-GTR), and subtotal resection (STR). *En bloc* resection with positive margins and intralesional-GTR were grouped together as intralesional-GTR. Because the process of attempting an *en bloc* resection is very different from a planned intralesional resection, and there may be a benefit to attempting an *en bloc* resection even if the outcome was violated margins, we also performed an intention-to-treat analysis, and included all patients with attempted *en bloc* resection into the *en bloc* group, regardless of the outcome. For the comparison of upper cervical to lower cervical cases, any tumor that involves the C1 or C2 level was included in the upper cervical group. We assessed quality of evidence using MOOSE Assessment for Quality of Evidence for All Included Studies and Oxford Centre for Evidence-Based Medicine—Levels of Evidence and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. [22] Risk of bias assessment was assessed using the National Health’s Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. [23]

Meta-analysis

Quantitative synthesis of results

In order to quantitatively compare the effect of GTR and STR on PFS and OS, we performed individual participant data meta-analysis of time-to-event outcomes following the recommendations of de Jong et al. [24] We opted for an individual participant data meta-analysis as the studies presented data on an individual participant level, and an individual participant data meta-analysis offers several advantages compared to “classical” meta-analysis based on aggregated data (such as the possibility of better modelling time-to-event outcomes, and the assessment of intervention-covariate interactions at the participant level). Given the low number of participants per primary study, we opted for a one-stage approach with a log-normal frailty and random-effects (so as to account for within-trial clustering of participants). Results are presented as pooled hazard ratio (HR) with 95% confidence intervals (CI). Heterogeneity was assessed by estimating median hazard ratios, corresponding to the median relative difference in the hazard of the occurrence of the outcome variable when two identical participants from two randomly selected different studies are compared. [24] To identify potential sources of heterogeneity, we built models including covariates and intervention-covariate interactions. In particular, we tested the age and sex of the participants, the number of operated levels, the location of the lesion (upper cervical chordomas, corresponding to all lesions including at least a segment at the level of C2 or above, and lower cervical chordomas corresponding to those below the level of C2 without involving C2). These covariates were centered by their mean values within trials, so as to avoid potential ecological biases resulting from mixing within- and across-study information. The remaining variables were not tested due to large quantities missing data (precluding us from resorting to methods of imputation of missing data). A sensitivity analysis was performed comparing intralesional GTR (including lesions described as “*En bloc* with positive margins”) versus STR, as it is still uncertain whether removing all visible lesional tissue (even with positive margins) is associated with better outcomes than removing only a part of the lesion. A sensitivity analysis comparing lesions described as *en bloc*-GTR (including other descriptions of gross total resection with negative margins) versus STR was not performed, on account of the low number of participants undergoing *en bloc*-GTR. The comparison between *en bloc*-GTR and intralesional-GTR was not reported due to the low estimates of the precision and very high heterogeneity.

Statistical Analysis

All statistical analyses were completed using R software (v 4.0). The correlation between the pre-operative tumor volume and the extent of resection was determined through Pearson correlation coefficient.

Results

Case Series

We found 190 patients with surgical resection of CHO treated at our institutions, and then screened for patients with primary cervical CHO. After exclusion of patients with incomplete data, 25 patients were found. We excluded 3 patients with only biopsy and no surgical resection of their lesion resulting in 22 patients included in our analyses (Table 1). There were two patients with *en bloc*-GTR, six with intralesional-GTR, and fourteen patients with STR (**Fig. 1**). There was a median PFS of 45 months for patients with GTR (*en bloc*+ IL GTR) and a PFS of 15.8 months for those with STR of their tumor. The median PFS for patients that had high dose (> 70Gy) radiation was 49 months, while those patients who received < 70Gy had a PFS of 31 months. There were only three patients who had preoperative radiation, with all of these patients having STR of their tumors. One of these patients had local recurrence 13 months after surgery, and the other two remain recurrence free 9 and 29 months after surgery. Patients with upper cervical CHO had a median PFS of 16 months, while those in the subaxial spine had a median PFS of 35 months. There were 12 recurrences for the cohort combined, with 4 being in the patients with GTR and 8 being in the STR group. The median OS for patients with GTR (*en bloc*+ IL GTR) was 104.8 months while the OS for those with STR was 24.1 months. There were two patients with *en bloc* resection, and one of these patients had her surgery 12 months prior to this analysis and remains disease free. There was a moderate correlation between preoperative tumor volume and extent of resection achieved, with lower tumor volumes being more likely to have a more extensive resection (Fig. 2). There were three complications reported in our cohort, with two being in those with *en bloc* or IL-GTR of their tumor (dehiscence of posterior pharyngeal wall flap and hemidiaphragm paresis), with the other complication being in a patient with STR of their tumor (brachial plexopathy).

Table 1
 Characteristics and outcomes of patients with cervical chordoma at our institution.

Age, sex	Location	Surgical intervention	Surgical Complication	Adjuvant Radiotherapy	Radiotherapy Modality	Progression Free Survival (months)	Overall Survival (months)	Follow-Up (months)
55, F	C2-4	En bloc	Yes	NR	NR	12‡	12.2	12.2
36, M	C5-7	En bloc	NR	Yes	IMRT	45	155.6	155.6
66, F	C1-2	IL GTR	NR	Yes*	Proton	49.0	92.9	92.9
51, M	C4-5	IL GTR	No	Yes	Proton	35.0	116.7	116.7
51, F	C6	IL GTR	No	Yes*	Proton	33.9‡	33.9	33.9
58, M	C3	IL GTR	NR	Yes	SRS	31	142	142
49, M	C2	IL GTR	NR	Yes	Proton	4.6‡	4.6	4.6
28, F	C2	IL GTR	Yes	Yes	Proton	177‡	177	177
54, F	C1-4	STR	No	Yes*	Proton	7	9.2	9.2
53, F	C3	STR	NT	Yes	Proton	12	40	40
75, M	C2	STR	No	Yes	Proton	7‡	7.4	7.4
61, M	C2	STR	No	Yes*	Proton	16	111.5	111.5
57, F	C2	STR	No	Yes	Proton**	13	24.6	24.6
61, M	C3-5	STR	Yes	Yes	Proton**	29‡	29	29
64, F	C2-3	STR	No	Yes	Proton**	9‡	9	9
68, M	C2	STR	No	NR	NR	15.8	15.8	15.8
74, F	C4	STR	No	Yes	Proton	7.5‡	7.5	7.5
44, F	C1-2	STR	No	Yes	Proton	4	11.2†	11.2†
19, M	C5	STR	No	Yes*	Proton	17	74.8	74.8
68, F	C2-3	STR	No	Yes*	Proton	33‡	33	33

NR: Not reported; STR = Subtotal Resection; IL GTR = Intra-lesional Gross total

resection; †: Death; ‡; Progression-free at the time of analysis; *: > 70Gy; **: preoperative radiotherapy

Age, sex	Location	Surgical intervention	Surgical Complication	Adjuvant Radiotherapy	Radiotherapy Modality	Progression Free Survival (months)	Overall Survival (months)	Follow-Up (months)
68, F	C2-3	STR	NR	Yes*	Proton	11	123.4	123.4
54, M	C2-4	STR	No	Yes*	Proton	14.2‡	14.2	14.2
NR: Not reported; STR = Subtotal Resection; IL GTR = Intra-lesional Gross total resection; †: Death; ‡; Progression-free at the time of analysis; * : > 70Gy; ** : preoperative radiotherapy								

Meta-analyses

The search strategy resulted in 1524 articles, with 934 remaining after de-duplication. We then excluded 864 articles on the title and abstract. 70 articles underwent full-text review. Our search resulted in 12 articles including 139 patients with cervical CHO (Fig. 3). [17][18, 25, 26][27][28][19][29][30][31][32][33] Including our series resulted in 13 case series and 161 total patients with cervical CHO. There were 118 patients with GTR of their tumor, with 29 of these being an *en bloc* spondylectomy with negative margins. There were 89 patients with intralesional-GTR of their tumor, which includes 4 patients with attempted *en bloc* resection that had violated margins. There were 43 patients with STR of their tumor. The mean follow up for included studies ranged from 27 months to 67 months, with 8 of the 13 studies having greater than 50 months of mean follow-up for the included patients. The characteristics for each study are included in Table 2.

Table 2
Summary of Included Studies Including Patients with Resection of Cervical Chordoma

Author, Year	Patients	Mean age	M/F	Extent of Resection			Mean Local PFS (months)	Mean OS (months)	Mean Follow-up (months)
				En Bloc	IL GTR	STR			
Bergh, 2000	5	57.4	3/2	1	4	0	44.6	55.8	63.6
Barrenchea, 2007	7	34.1	4/3	0	6	1	57.4	58.7	67.1
Zileli, 2007	8	53.4	5/3	0	7	1	NR	46.8	46.8
Potluri, 2011	3	46.7	2/1	0	0	3	29.3	45.2	45.2
Wang, 2012	14	54.3	8/6	0	5	9	41.1	58.6	58.6
Wang, 2013	8	50.4	5/3	0	6	2	15.4	27.0	27.0
Hua, 2014	17	48.7	9/8	0	17	0	28.8	41.8	46.8
Molina, 2014	16	54.8	NR	12	4*	0	NR	58.1	58.1
Lockney, 2017	5	62.2	2/3	0	0	5	29.1	50.1	50.1
Wang, 2017	4	48.5	3/1	4	0	0	39.8	39.8	39.8
Hyun, 2018	12	38.0	10/2	0	5	7	39.4	54.5	54.5
Zhong, 2018	40	47.2	25/15	10	30	0	NR	57.4	57.4
Akinduro, 2020	22	55.2	10/12	2	5	15	30.0	54.8	56.6

Progression-Free Survival

A total of nine studies provided data on PFS, including 109 participants, with 49 events of local progression (Table 3). GTR was associated with a significant decrease in the risk of local progression (pooled HR = 0.22; 95% CI = 0.08–0.59; $p = 0.003$). The median HR was 2.72, representing high heterogeneity. Age, location, gender and the number of levels were not found to be moderators of heterogeneity. There was a trend towards significance for tumor location (pooled HR = 2.56, 95%CI = 0.95–6.88; $p = 0.063$), with tumors involving the atlantoaxial spine (C1/C2) having a worsened prognosis. This trend indicates that if there were more numbers, this variable would likely reach significance.

Table 3
Results of meta-analytical models comparing GTR vs STR on progression-free survival and including covariates and intervention-covariate interactions to identify potential moderators of heterogeneity

Variable	HR	95% CI	<i>p</i> -value	Median HR
GTR vs. STR	0.22	0.08–0.59	0.003	2.72
Age	1.02	1.00-1.05	0.073	2.72
Interaction: Age*Resection type	0.98	0.94–1.01	0.210	
Gender ^a	1.17	0.53–2.60	0.696	1.76
Interaction: Gender*Resection type	1.55	0.46–5.19	0.472	
Number of levels	0.89	0.60–1.30	0.542	2.98
Interaction: Number of levels*Resection type	1.16	0.57–2.35	0.678	
Lesion location	2.56	0.95–6.88	0.063	3.45
Interaction: Lesion location*Resection type	0.21	0.04–1.17	0.075	
"En bloc"-GTR vs. STR	0.06	0.01–0.77	0.030	3.49
Age	1.01	0.99–1.04	0.376	1.67
Interaction: Age*Resection type	0.86	0.67–1.09	0.219	
Intralesional GTR vs. STR	0.35	0.16–0.76	0.009	1.77
Age	1.02	1.00-1.05	0.094	1.74
Interaction: Age*Resection type	0.98	0.94–1.02	0.332	
Gender ^a	1.17	0.53–2.59	0.693	1.66
Interaction: Gender*Resection type	1.59	0.48–5.32	0.447	
Number of levels	0.89	0.61–1.32	0.575	1.87
Interaction: Number of levels*Resection type	1.13	0.53–2.40	0.758	
Location	2.52	0.94–6.76	0.065	2.06
Interaction: Lesion location*Resection type	0.32	0.06–1.63	0.171	
CI = Confidence interval; GTR = Gross total resection; HR = Hazard ratio; STR = Subtotal resection; ^a No data from two studies (Zhong et al, Zileli et al)				

A meta-regression analysis determined that *en bloc*-GTR was associated with a significant reduction in the risk of local progression (pooled hazard ratio = 0.06; 95%CI = 0.01–0.77; $p = 0.030$). The median HR was 3.49, representing high heterogeneity. Age, gender, location and the number of levels being operated were not found to be moderators of heterogeneity. Similar results were observed when comparing intralesional-GTR to STR – with significant reduction in the risk of local progression (pooled HR = 0.35; 95%CI = 0.16–0.76; $p = 0.009$), with only moderate heterogeneity (median HR = 1.77) and with no moderator variables identified.

Overall Survival

A total of twelve studies provided data on overall survival, encompassing a total of 143 participants, with 41 events of death (Table 4). GTR was associated with a significant decrease in the risk of death (pooled HR = 0.31; 95% CI = 0.12–0.83; $p = 0.020$). The median HR was 1.04, representing moderate heterogeneity. Age and gender were not found to be moderators of heterogeneity. By contrast, the number of levels was identified as a variable that potentially explains heterogeneity. In fact, despite the lack of association between the number of levels and overall survival (pooled HR = 0.83; 95%CI = 0.57-1.21; $p = 0.322$), we found significant association for the interaction between the number of levels and the type of resection achieved (pooled HR = 2.16; 95%CI = 1.10–4.26; $p = 0.026$).

Table 4

Results of meta-analytical models comparing GTR vs STR on overall survival and including covariates and intervention-covariate interactions to identify potential moderators of heterogeneity

Variable	HR	95% CI	<i>p</i> -value	Median HR
GTR vs. STR	0.31	0.12–0.83	0.020	1.04
Age	1.00	0.97–1.03	0.873	1.04
Interaction: Age*Resection type	0.98	0.94–1.02	0.379	
Gender ^a	1.51	0.45–5.08	0.510	1.50
Interaction: Gender*Resection type	0.51	0.11–2.22	0.368	
Number of levels	0.83	0.57–1.21	0.322	1.04
Interaction: Number of levels*Resection type	2.16	1.10–4.26	0.026	
“En bloc”-GTR vs. STR	0.14	0.01–1.27	0.134	2.65
Age	1.00	0.97–1.03	0.999	6.62
Interaction: Age*Resection type	1.13	0.96–1.33	0.145	
Number of levels	0.86	0.61–1.22	0.407	2.39
Interaction: Number of levels*Resection type	1.01	0.30–3.38	0.986	
Intralesional GTR vs. STR	0.25	0.08–0.79	0.019	1.50
Age	1.00	0.97–1.03	0.870	1.49
Interaction: Age*Resection type	0.98	0.94–1.02	0.258	
Gender ^a	1.52	0.45–5.14	0.498	1.42
Interaction: Gender*Resection type	0.67	0.15–2.96	0.596	
Number of levels	0.83	0.56–1.21	0.332	1.31
Interaction: Number of levels*Resection type	2.54	1.12–5.78	0.026	
CI = Confidence interval; GTR = Gross total resection; HR = Hazard ratio; STR = Subtotal resection; ^a No data from one study (Hua et al)				

En bloc-GTR was not associated with a significant decrease in the risk of death (pooled HR = 0.14; 95% CI = 0.01–1.27; $p = 0.134$). The median HR was 2.65, representing high heterogeneity. Age, gender, and number of levels were not found to be moderators of heterogeneity. We were unable to evaluate the lesion location as a variable moderator of heterogeneity due to lack of precision of the estimates. Intralesional-GTR was associated with a significant decrease in the risk of death when compared with STR (pooled hazard ratio = 0.25; 95%CI = 0.08–0.79; $p = 0.019$) The median HR was 1.50 indicating moderate heterogeneity. Age and gender were not found to be moderators of heterogeneity. The number of levels being operated was the

only variable potentially identified as a moderator of heterogeneity, as we found a significant association for the interaction between the number of levels and the type of resection achieved (pooled HR = 2.54; 95%CI = 1.12–5.78; p = **0.026**).

Intention to Treat Analyses

It is unclear whether intending to complete an *en bloc* resection has an effect on patient outcomes, even if the resection results in a violated margin. To account for this, we performed an intent-to-treat analysis and included patients who underwent *en bloc* resection with violated margins into the *en bloc* group. There was a nearly identical improvement in PFS for in this analysis of *en bloc* versus STR (pooled HR: 0.06; 95%CI: 0.01–0.77 **p = 0.031**) when compared to the analysis above (pooled hazard ratio = 0.06; 95%CI = 0.01–0.77; **p = 0.030**). The primary difference between the intent to treat analysis and the original analysis is that there was a nearly significant improvement in OS for the *en bloc* cohort when compared to the STR cohort (pooled HR: 0.15; 95%CI:0.02–1.22; p = 0.054). The results for the intention-to-treat analysis are displayed in **supplementary tables 1 & 2**.

Quality Assessment & Risk of Bias

The outcomes assessed for quality were OS and PFS for GTR vs. STR, *en bloc*-GTR vs. STR, and intralesional-GTR vs. STR. The certainty was graded as low for these analyses (Table 5). The GRADE assessment is included in Table 6, with a low certainty for the included analyses. Risk of bias assessment is included in **Fig. 4**.

Table 5
MOOSE Assessment for Quality of Evidence for All Included Studies

Study ID	Clear definition of Study Population?	Clear definition of outcomes and outcome assessment?	Independent assessment of outcome parameters?	Sufficient duration of follow-up?	No selective loss during follow-up?	Important confounders and prognostic factors identified?
Barrenchea, 2007	Y	Y	Y	Y	Y	Y
Zileli, 2007	Y	Y	Y	Y	N	Y
Potluri, 2011	Y	Y	Y	Y	Y	N
Wang, 2012	Y	Y	Y	Y	N	Y
Wang, 2013	Y	Y	Y	N	N	N
Hua, 2014	Y	N	N	Y	N	Y
Molina, 2014	N	N	Y	Y	N	Y
Lockney, 2017	Y	Y	Y	Y	Y	Y
Wang, 2017	Y	Y	Y	Y	N	N
Hyun, 2018	Y	Y	Y	Y	Y	N
Zhong, 2018	Y	Y	Y	Y	N	Y
Akinduro, 2020	Y	Y	Y	Y	Y	Y

Table 6

Grading of Recommendations, Assessment, Development and Evaluation Assessment for Reported Outcomes

Outcome	Summary statistic (HR, 95%CI)		Number of Cohorts (Studies)	Certainty Assessment					Certainty	
				Type of Evidence	Quality	Consistency	Directness	Effect Size		Overall Quality
OS	GTR	HR = 0.27; 95% CI = 0.09–0.79; p = 0.017	7	0	+1	0	0	+1	+2	Low
	vs. STR									
	En-bloc GTR	HR = 0.50; 95%CI = 0.19–1.27; p = 0.145								
PFS	GTR	HR = 0.19; 95%CI = 0.05–0.64; p = 0.008	8	0	+1	0	0	+1	+2	Low
	vs. STR									
	En-bloc GTR	HR = 0.22; 95%CI = 0.08–0.56; p = 0.002								
	IL-GTR	HR = 0.31; 95%CI = 0.13–0.78; p = 0.013								
	Vs. STR									

The overall quality score is determined based on the sum of the included domains. Type of evidence is based on design of the included studies (range, 0 to +1). The study quality reflects the blinding and allocation, follow-up and withdrawals, sparsity of data, and methodologic concerns (range, -1 to +1). Consistency is graded based on heterogeneity of included population and study end points with respect to one another (range, -1 to +1). Directness is graded based on generalizability of included results (0). Effect size is graded based on how consistent significant summary statistics are < 0.5 or > 2 if significant (range, 0 to +1). The overall quality of results for each outcome can be considered high (≥ 4 points), moderate (3 points), low (2 points), or very low (≤ 1 point). mRS, modified Rankin Score; sICH, symptomatic intracerebral hemorrhage; CI, confidence interval; HR, hazard ratio.

Discussion

Cervical CHOs are distinct from CHOs of other areas of the neuro-axis in that there is significant risk associated with close relation and often times juxtaposition of structures such as the vertebral arteries, *cervical* spinal cord, and esophagus. Surgical resection with *en bloc* spondylectomy is typically regarded as more challenging than resection of a tumor in another region such as the lumbar spine or sacrum, because damage to the aforementioned structures will lead to catastrophic complications and even death. GTR with either *en bloc* spondylectomy or intralesional-GTR of CHOs requires extensive planning and should typically be performed by spine surgeons at high volume tertiary academic centers with extensive experience managing these tumors. Literature has typically favored *en bloc* resection of CHOs in the sacrum, but there is limited data for or against this resection strategy in the cervical spine. [6]

Our study represents the first and only meta-analysis of patients with cervical CHO. This manuscript is also unique in that we performed an individual patient data meta-analysis which gives us the opportunity to assess PFS and OS for the all of the groups together to assess the effect of extent of resection on PFS and OS. We discovered that patients with GTR of their tumor did have an increased PFS and OS of their tumors compared to those with STR of their tumor. This forms the highest level of evidence to advocate for GTR of cervical CHOs and is consistent with previously published articles for sacral CHOs. Of note, the GTR group includes intralesional-GTR which involves piecemeal resection of the tumor, as well as *en bloc* spondylectomy with clear margins. Patients with positive margins were included in the intralesional-GTR group. Because these resection strategies are completely different, we performed a meta-regression analyses to determine if one particular type of GTR strategy should be favored over another. We also performed an intention-to-treat analysis including all patients with attempted *en bloc* resection in one group, regardless of the postoperative margins.

PFS was improved by GTR of the tumors in patients with cervical CHO. Unfortunately, our study was unable to perform an analysis to compare the intralesional-GTR and *en bloc* cases, as the number of events was insufficient for this comparison. However, it is important to note that there was a significant improvement in disease progression for patients *en bloc* spondylectomy (pooled HR = 0.06; 95%CI = 0.01–0.77; **p = 0.030**) and intralesional-GTR (pooled HR = 0.25; 95%CI = 0.08–0.79; **p = 0.019**) when compared to STR. Although we could not compare the intralesional-GTR and *en bloc* groups, the HR for *en bloc* was higher, which could at least indicate more benefit in risk of recurrence with *en bloc* resection of tumors. Although our case series was underpowered, using volumetric assessment of the pre-and postoperative tumors volumes, we were able to determine that there is a moderate correlation between the preoperative tumor size and the extent of resection, with smaller tumors being more likely to result in a more extensive resection. For OS, there was a significant improvement with intralesional-GTR, but not with *en bloc*-GTR. While this could be attributed to low numbers for this assessment, it is reasonable to conclude that *En bloc* spondylectomy is a high-risk technique that requires specialized training; thus, should only be performed by experienced spinal surgeons. It is possible that more extensive surgeries may result in greater morbidity and delayed radiation. Unfortunately, there was no way to determine that specific cause of death in the patients, which would provide more insight into this analysis. Our intent-to-treat analysis revealed that when all patients that had attempted *en bloc* resection (including those with violated margins) were compared to the STR cohort, there was a nearly significant improvement in OS (pooled HR: 0.15; 95%CI:0.02–1.22; p = 0.054). The surgical steps for performing an *en bloc* resection are much different than those for performing an intralesional resection of a tumor and subject a patient to a different set of complications and morbidity, but also may have more benefit that performing a planned intralesional resection. The improvement in OS when including all patients with attempted *en bloc* resection indicates that there may be a benefit in the procedure of *en bloc* resection, even if the surgery results in violated margins.

Radiation therapy with either proton or protons is considered the standard of care for patients with CHO of the skull base or spine. In this study, we sought the better understand the effect of radiation on patients with surgical resection of their CHO. Unfortunately, not all of the included studies commented on the use of radiation, and for the studies that did, there were very few patients who did not receive radiation, which is to be expected. Furthermore, these studies did not report on dosage, or timing of radiation. However, we were able to review the data from our series to determine the effect of high dose (> 70Gy) radiation. There was a higher mean PFS for patients that had high dose proton-based radiation (49 months), while patients who received < 70Gy radiation had a PFS of 31 months. Although this analysis was not significant due to low numbers, this poses the

question of whether the differences in PFS for the surgical groups are partially related to the dose of radiation given to the patients, but unfortunately, this data was not available in the larger study. However, 43% of the patients with GTR received high dose radiation, while 54% of patients with STR received high dose radiation, which indicates that patients who had residual tumor were slightly more likely to have received high dose radiation which possibly played a role in the outcomes.

Although there was more than two-fold increase in PFS for patients with primary cervical tumors of the subaxial spine when compared to those with tumors involving the atlas or axis, there was no significant difference in this analysis, but would likely have been significant if there were more numbers. When we look at all of the patients in all studies, there was a trend toward significance for the effect of tumor location (upper versus lower cervical) on PFS ($p = 0.063$). In addition to this, there was a trend toward significance for the effect that tumor location had on the type of resection achieved, with subaxial tumors being more likely to receive an extensive GTR ($p = 0.075$). In our cohort, we also assessed the effect of targeted therapy on PFS, but there was no significant difference between the groups. This is likely due to the fact that most patients undergoing targeted therapy for CHO had progressive and advanced disease at the time of initiation of the drug.

Limitations & Strengths

Cervical chordomas are rare tumors, and thus the case series was limited by numbers, which is why a meta-analysis was needed to be able to draw conclusions on this topic. This manuscript is subject to the inherent limitations of meta-analyses papers, as the quality of this manuscript primarily relies on the quality of the included studies. This manuscript was unable to quantitatively assess the use of high dose radiation in the large cohort due to lack of data from some of the included manuscripts. We were unable to separate patients with recurrent CHO from those with primary CHO, which may lead to slight skewing of the data, but this remains the highest level of evidence for patients with cervical CHO. Also, ideally our study would stratify STR patients into categories such as < 50% resection and 50–99% resection, to determine if there is benefit from the amount of tumor resection, even if a GTR cannot be achieved, but the study design did not allow for this in-depth analysis. Also, we were unable to confirm the extent of resection for the included studies. Our quality assessment revealed that quality of most of the assessments were rated as low certainty. This is not surprising due to the low numbers available for this specific pathology and should be considered when interpreting the results. CHOs are slow growing tumors, and follow-up of 5–10 years would be ideal for studies involving patients with CHO. This study was limited by variable follow-up of the included studies, but 8 of the included studies had a mean follow-up of at least 50 months. Future studies should consider assessing the percentage of resection to help guide clinicians when a GTR cannot be safely achieved. We were able to perform an individual participant data meta-analysis, which provides an advantage over normal meta-analyses studies with time-to-event outcomes for this large cohort. An additional strength of this study is the geographic location of the included institutions in the case series, with representation from the Southwest, Southeast, and Midwest.

Conclusions

Despite inherent confounders and the limitations of this study, this is the largest assessment of extent of resection in patients with cervical CHO. Our study indicates that GTR with either with piecemeal resection or *en bloc* spondylectomy may improve PFS more than STR of CHOs in the cervical spine. A meta-regression analysis of *en bloc* resection and intralesional-GTR compared to STR found that while they were both were associated with an improved PFS over STR, *en bloc* resection was associated with a lower HR, which indicates that there may be more benefit with this resection model, when feasible. Although *en bloc* resection appears to be the gold standard to prevent recurrence in cervical CHOs, surgeons should assess each patient's tumor carefully, as larger tumors are more difficult to completely remove.

Declarations

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Ethics approval: Not applicable

Author contributions: OOA: writing manuscript, search for systematic review, statistical analysis, reviewed final, DG: writing manuscript, tables, figures, RD: tables, figures, search for systematic review, TV: figures, edited manuscript, BS: statistical analysis, MB: critically revised manuscript, MJC: critically revised manuscript, ZLG: critically revised manuscript, MAK: critically revised manuscript, KA: critically revised manuscript, AQ: critically revised manuscript, study supervision

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Figures

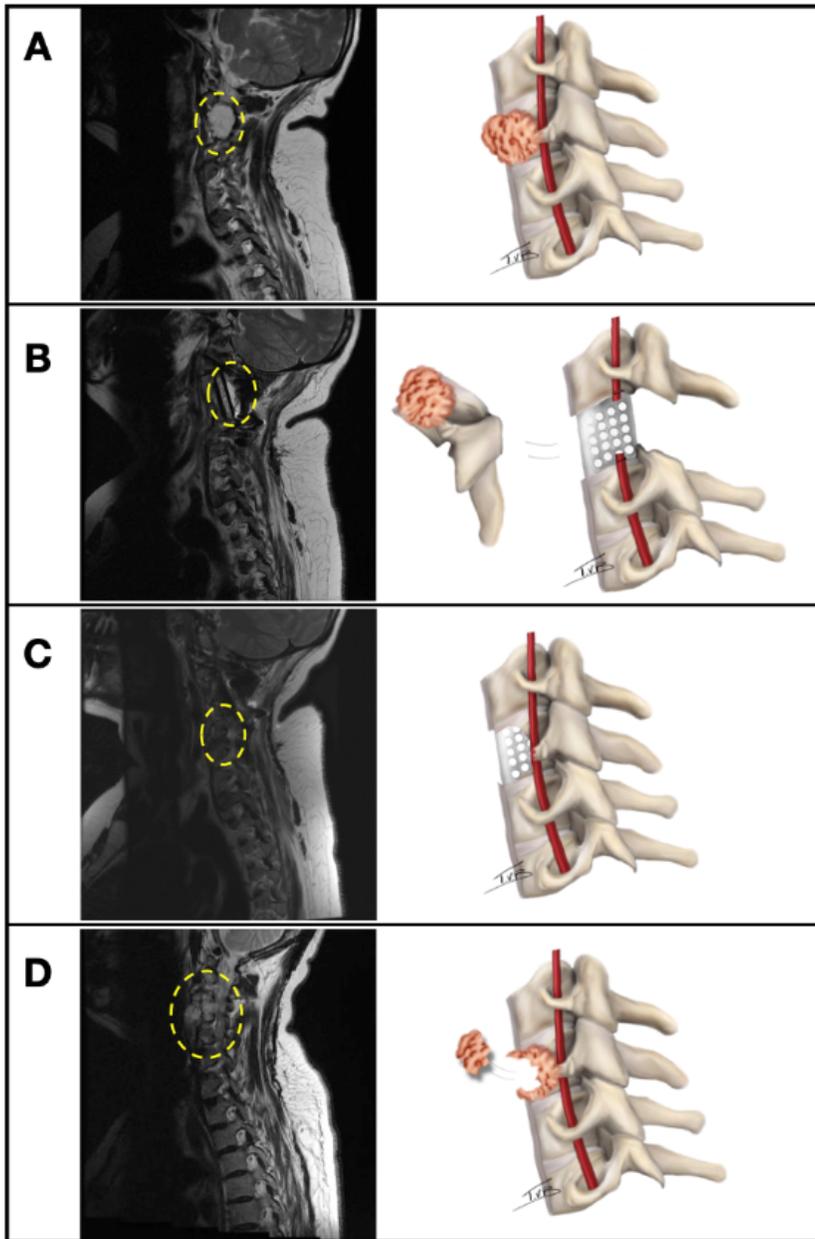


Figure 1

Combined magnetic resonance imaging and artist illustration of different surgical strategies for cervical chordoma. Panel A depicts preoperative imaging for a patient with upper cervical chordoma. Panels B-D depict cervical chordomas after en bloc

gross total resection with ligation of the vertebral artery (B), intralesional gross-total resection (C), and sub-total resection (D).

Extent of Resection Correlated to Pre-operative Volume

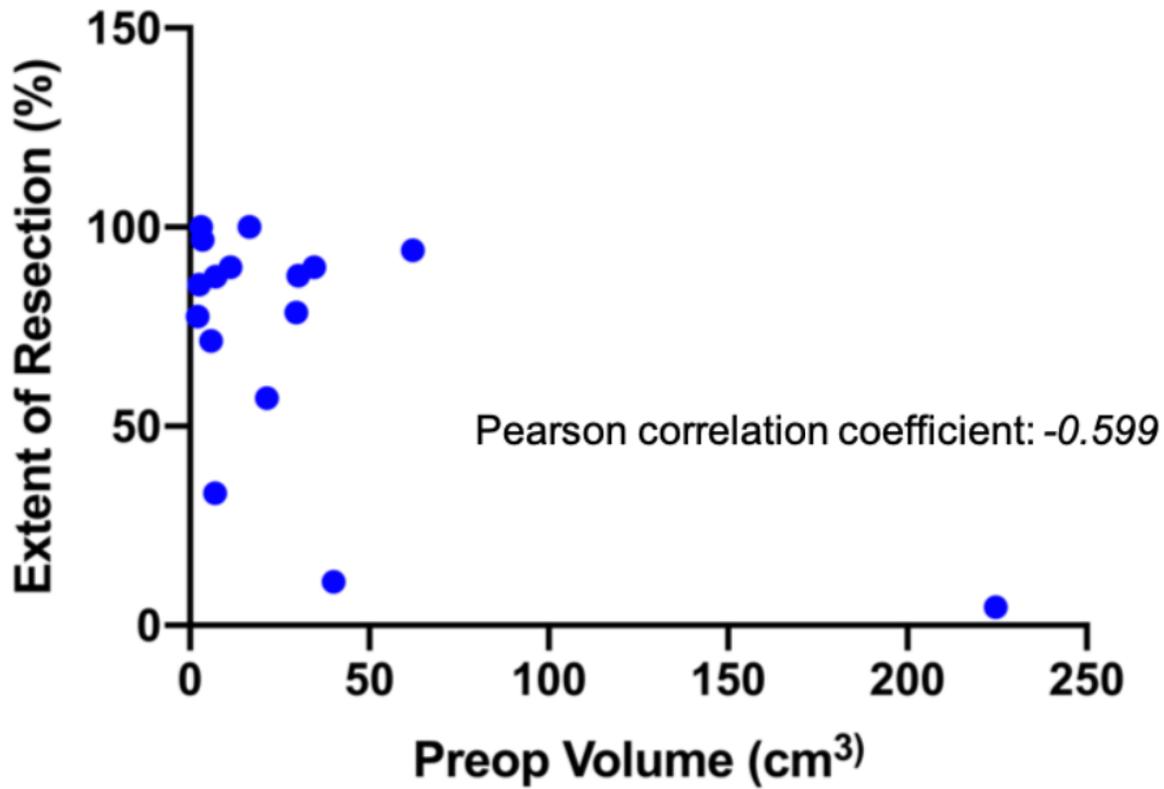
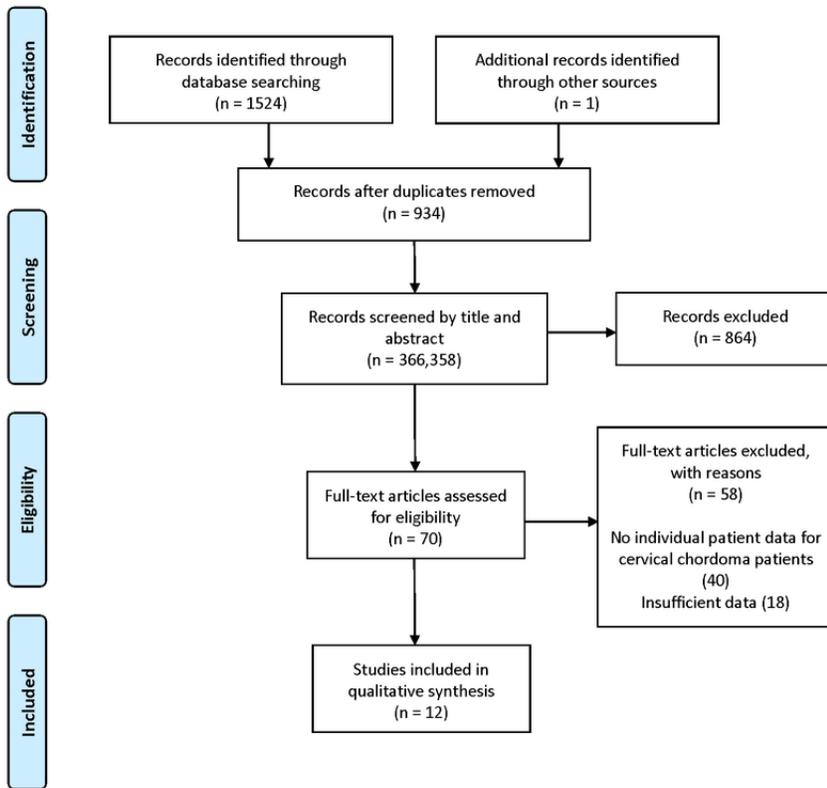


Figure 2

Graph plotting the preoperative tumor volume with the postoperative extent of resection. There is a moderate correlation between preoperative tumor volume and the extent of resection achieved, with smaller tumors having more extensive resection (Pearsons correlation coefficient: -0.599).



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 3

PRISMA Flow Diagram of the Search Strategy for this Study.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Barrenchea, 2007	+	+	+	+	+	?	+	-	-	-	+	-	+	-
Bergh, 2000	+	+	+	-	-	?	+	+	+	+	+	-	?	-
Hua, 2014	+	+	?	-	-	?	?	-	-	?	-	-	?	-
Hyun, 2018	+	+	+	-	-	?	+	+	+	-	+	-	+	-
Lockney, 2017	+	+	+	+	-	?	+	+	+	?	+	-	+	-
Molina, 2014	+	+	+	+	-	?	+	+	+	-	+	-	+	-
Potluri, 2011	+	+	+	+	-	?	?	+	+	?	+	-	+	-
Wang, 2012	+	+	+	-	-	?	+	+	+	-	+	-	+	-
Wang, 2013	+	+	+	-	-	?	?	-	-	-	-	-	+	-
Wang, 2017	+	+	+	-	-	?	+	-	-	?	-	-	+	-
Zhong, 2018	+	+	+	+	-	?	+	+	+	-	+	-	+	-
Zieli, 2007	+	+	+	-	-	?	+	-	-	-	-	-	+	-

: Yes
 : No
 : Not available

1. Research question clearly stated; 2. Study population clearly specified and defined; 3. Participation of eligible persons of at least 50%; 4. Population selection criteria clearly defined and uniformly applied; 5. Sample size justification or power analysis; 6. Exposure of interest measured before outcome; 7. Timeframe sufficient for outcome evaluation; 8. Different levels of exposure evaluated; 9. Independent variables clearly defined; 10. Exposure assessed more than once; 11. Dependent variables clearly defined; 12. Outcome assessors blinded to exposure status; 13. Loss to follow-up after baseline 20% or less; 14. Key confounders measured and adjusted statistically.

Figure 4

Risk bias assessment evaluated through the National Health’s Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplement.ChordomaResults17Dec20202.docx](#)
- [Supplement.MethodologyWriteup11.14.2020.docx](#)