Neurosurgical Review
https://doi.org/10.1007/s10143-020-01318-y

REVIEW

Microsurgical versus endoscopic trans-sphenoidal approaches for clivus chordoma: a pooled and meta-analysis

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Received: 25 March 2020 / Revised: 3 May 2020 / Accepted: 11 May 2020
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Abstract

Chordoma is a rare slow-growing neoplastic bone lesion. However, they show an invasive local growth and high recurrence rate, leading to an overall survival rate of 65% at 5 years and 35% at 10 years. We conducted a pooled and meta-analysis comparing recurrence rate, post-operative-complications, and survival in patients undergoing either microsurgical (MA) or endoscopic approaches (EA). Search of literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify surgical series of clivus chordomas published between January 1990 and March 2018 on Pubmed, Scopus, and Cochrane. Two different statistical analyses have been performed: a pooled analysis and a single-arm meta-analysis of overall recurrence rate and subgroup meta-analysis of complications in the subgroups open surgery and endoscopic surgery. After full-text screening, a total of 58 articles were included in the pooled analysis and 27 studies were included for the study-level meta-analysis. *Pooled analysis*—the extent of resection was the only association that remained significant (subtotal: HR = 2.18, $p = 0.004$; partial: HR = 4.40, $p < 0.001$). Recurrence was more prevalent among the surgical patients (45.5%) compared to endoscopic ones (23.7%). *Meta-analysis*—results of the cumulative meta-analysis showed an overall rate of recurrence of 25.6%. MA recurrence rate was 31.8% (99% CI 14-52.8), EA recurrence rate was 19.4% (5.4-39.2). CSF leak rate for the endoscopic group was 10.3% (99%CI 5-17.3) and 9.5% (99%CI 1.2-24.6) for the open surgery group. The partial removal versus total removal has an influence on recurrence rate ($p < 0.001$). MA recurrence rate was 31.8%; EA recurrence rate was 19.4%. The extent of resection is confirmed as a statistically significant factor affecting the risk for recurrence both with the pooled analysis and with the meta-analysis. Meta-analysis demonstrated that older patients tend to recur more than young patients, especially in surgical group.

Keywords Chordoma · Microsurgery · Endoscopic endonasal approach · EEA · Clival chordoma · Recurrence

Introduction

Chordoma is a rare slow-growing neoplastic bone lesion (overall incidence of 0.84/million) developing from residues of the embryonic notochord along the neuraxis [1]. Interestingly, there are also differences in epidemiology according to race and gender, since African American patients and women are more predisposed to be affected [2]. These tumors have commonly extracranial presence, such as in the spine (being the sacral spine region the most common location), followed by clival and paraclival sites [3]. Chordomas appear to be low-grade neoplasm at histopathological examination; they can however display invasive local growth and high recurrence rate, with possibility of dissemination toward extracranial sites [4], leading to an overall survival rate of 65% at 5 years and 35% at 10 years [5]. Limited evidence is available highlighting the ideal therapeutic management of skull base chordomas that therefore remains debated. The gold standard treatment consists of maximally surgical resection followed by adjuvant treatment which can be radiotherapy or radiosurgery [6]. In the most recent year, in case of clival chordomas, endoscopic endonasal approach (EEA) has been replacing the several available surgical approaches, because of the advantages presented by the approach in terms of tumor

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Published online: 29 May 2020

removal and visualization. However, the diffuse infiltrative growth, the involvement of surrounding neurovascular structures, and the deep anatomic location, makes the gross total resection a difficult goal to achieve [1, 7]. Given the many approaches available and the high recurrence of this pathology, we conducted a systematic review of the literature with the aim to investigate differences in terms of recurrence rates and complications between patients undergoing either microsurgical or endoscopic approaches, starting from the introduction of the endoscopic technique (1990-2017). Given the low incidence disease (one per million population) and consequently the low number of published cases, we choose a double statistical approach: the pooled approach allows us to obtain more stable estimates and the meta-analysis support statistical validity.

Methods

Search strategy

Search of literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify surgical series of clivus chordomas published between January 1990 and March 2018 on Pubmed, Scopus, and Cochrane. The following search strategies were used: "clival chordoma" or "clival chordomas" or "skull base chordoma" or "skull base chordomas" or "clivus chordoma" or "clivus chordomas". All articles were screened for title and abstract relevance by two authors, independently (DC and MPT). Discrepancies in study selection were resolved by discussion and consultation with the senior author. Only articles describing surgical series with primary chordomas arising from to the clivus were included in the analysis.

The inclusion criteria were the presence of information concerning the extent of resection (EOR), the recurrences during the follow-up period, and the postoperative complications. Articles in which chordoma data could not be discerned from other skull base lesions, including chondrosarcoma or chondroid chordoma, were excluded. Other exclusion criteria were pediatric population (< 18 years) studies, documents in language different from English, and publications with incomplete surgical and clinical outcomes description. Only articles in which data could be gathered at the individual level were collected in order to be able to perform a pooled analysis.

Data analysis: pooled analysis versus meta-analysis

Study characteristics were extracted from the full text of selected studies. The information searched included authors, publication year, country of origin, sample size, study design, and duration of study. Patient characteristics were extracted including sex, age, surgical approach, extent of resection, recurrence, post-operative complications, and adjuvant radiation therapy used. Surgical approaches were dichotomized as endoscopic (EA) and microscopic approaches (MA). EA included all endonasal approach (transpterygoid, transphenoidal, transseptal, etc.). MA included a fronto-temporal craniotomy with or without zygomatic osteotomy, a retrosigmoid or a posterior subtemporal—presigmoid transpetrous approach, a preauricular subtemporal approach, or an extreme lateral transcondylar approach.

In order to evaluate differences in MA compared to EA in terms of recurrence and postoperative complications, we performed a pooled analysis at the individual level. We also performed a cumulative sub-group meta-analysis on the data reported among the included studies; we considered the recurrence rate, the rate of ocular nerves complications, and the CSF leak rate. We also performed meta-regression analysis to explore the influence of the proportion of partially resected tumors on recurrence rates. For the meta-analysis, the same inclusion and exclusion criteria of the pooled analysis were used, the only difference being the exclusion of case reports given that these are not useful in a meta-analysis and would add just unnecessary statistical noise.

Statistical methods

Two different statistical analyses have been performed.

In the first part, for the pooled analysis, differences between groups were explored with chi-square test or *t* student test, were appropriated. Association with recurrence was determined with proportional hazard regression, and results were expressed as hazard ratio (HR) with a 95% confidence interval (CI). All variables with a p value < 0.2 at univariable analysis were considered for multivariable analysis. Multivariable results were corrected by year of publication. Data analysis was performed using Stata13 (StataCorp, Texas, USA). A p value < 0.05 was considered significant.

In the second part, a single-arm meta-analysis of overall recurrence rate and subgroup meta-analysis of complications in the subgroups open surgery and endoscopic surgery were performed. Analyses were done using "R" (R 2.10.1; "meta" package). Arcsine transformation of the data was performed for the analysis on overall detection rates. This has been shown to provide more reliable results than other transformations when rare events are examined [8]. As reported in a previous paper [9], given the observational nature of the included studies, we decided to adopt a statistical conservative approach; for this reason, a 99% confidence interval (CI) was chosen for calculations. Restricted maximum likelihood was the method used for the random effects meta-analysis on the overall recurrence rate. Moreover, care was taken to apply a minimal correction factor of 0.1 for "0" events. This was made in order to reduce the distortion of data for excessive

correction. A meta-regression analysis was conducted in order to assess the possible relationship of a specific study level covariate (mean age of studied patients) with the overall recurrence rate. I^2 statistic was used to assess heterogeneity. According to the Cochrane criteria, values from 0 to 40% may signify low heterogeneity, 30 to 60% may represent moderate heterogeneity, and 60 to 100% represent substantial heterogeneity [10].

Results

Articles screening

This process of document screening can be appreciated in Fig. 1 (PRISMA). The systematic search resulted in 437 articles on Pubmed; search on Scopus was complementary and no significant result has been found on Cochrane. After title and abstract screening, 351 articles were excluded, resulting in 86 articles for full-text evaluation. After full-text screening, a total of 58 articles were included in the pooled analysis, after exclusion of the case reports and the studies in which insufficient data were reported, 27 studies were included for the study-level meta-analysis. From the analysis of every single case reported in the literature, a total of 272 patients (M 51.5%) had undergone surgery for clivus chordomas (Fig. 1). The mean age was 47.4 years (range 18-80 years). When EA and MA were compared, there was not a significant difference for sex (50.4% vs 52.5%, $p = 0.808$). On the other hand, there was a difference by gender in the age of diagnosis (male 51 ± 16 vs female 45 ± 16, $p = 0.002$).

Pooled-analysis: MA versus EA at individual level

We evaluated the effect of several factors on the probability of chordoma recurrence. At univariate analysis, we observed an association with age (HR = 1.02, $p = 0.022$) and a statistical significance with the extent of resection (subtotal: HR = 2.34, $p = 0.001$; partial: HR = 4.31, $p < 0.001$) and a weak association with male gender (HR = 1.53, $p = 0.074$). However, after performing multivariate analysis, the extent of resection was the only association that remained significant (subtotal: HR = 2.18, $p = 0.004$; partial: HR = 4.40, $p < 0.001$) (Table 1). The association of recurrence with age for each therapeutic modality has been further investigated by stratifying patients into 3 groups according to their age: < 40 years, > 60 years, and between 40 and 60 years. Comparing microsurgical and endoscopic approaches, in patients younger than 40 years, an equal recurrence rate between MA and EA was noticed ($p = 0.785$). Interestingly, the recurrence rate becomes significantly higher for the surgical group when considering elderly patients. A visualization of this change can be appreciated in the histogram in Fig. 2. However, these significant findings are not present anymore when looking at the respective HR for each age group (Table 2).

Meta-analysis

Results of the cumulative meta-analysis showed an overall rate of recurrence of 25.6% (99% CI 13.8-39.7). I^2 statistics showed a high heterogeneity (83.1%). When the recurrence rate was analyzed by subgroup not statistically significant difference is highlighted and the results were as follows: open surgery recurrence rate was 31.8% (99% CI 14-52.8), endoscopic recurrence rate was 19.4% (5.4-39.2) (Fig. 3a).

The overall rate of occurrence of ocular nerve complications was 4.8% (99% CI 1.4-10) for the endoscopic group, I^2 statistics showed low heterogeneity (0%). The overall rate of occurrence was 17.2% in the open surgery group (99% CI 3.8-37.5) (Fig. 3b). Therefore, no statistically significant difference is appreciable. I^2 statistics showed high heterogeneity (78%). The cumulative rate of ocular nerve complications, i.e., when the two subgroups were analyzed together, was 9.5% (99% CI 4.0-17.0). Regarding CSF leak complication, the overall rate of occurrence was 10.1% (99% CI 5.1-16.6). I^2 statistics showed low heterogeneity (30.1%). CSF leak rate for the open surgery group was 9.5% (99%CI 1.2-24.6), for the endoscopic group was 10.3 (99%CI 5-17.3) (Fig. 3c). Also, for this complication, there is not a difference in outcomes statistically significant in between the two subgroups. Results of the meta-regression, after setting the proportion of partial resection in the single study as the co-variate, suggest that an increase in proportion of partially resected tumor (as opposed to totally resected) has an influence on recurrence rate ($p < 0.001$). Therefore, the extent of resection is confirmed as a statistically significant factor affecting the risk for recurrence. This analysis is shown in Fig. 4.

Discussion

Chordomas are relatively rare neoplasms with an overall incidence of approximately one per million population [1]. They seem to arise from notochordal elements. Chordomas show a slow rate of growth, but they are characterized by an aggressive and local malignancy, so, frequent local recurrence presents a survival rates of 65% and 35% at 5 and 10 year, respectively [3] Typically, chordomas are located at level of clivus and sacrum skeleton. The management of the skull base chordomas is still debated. Conventional microsurgical approaches and endoscopic trans-sphenoidal approach represent the main indications.

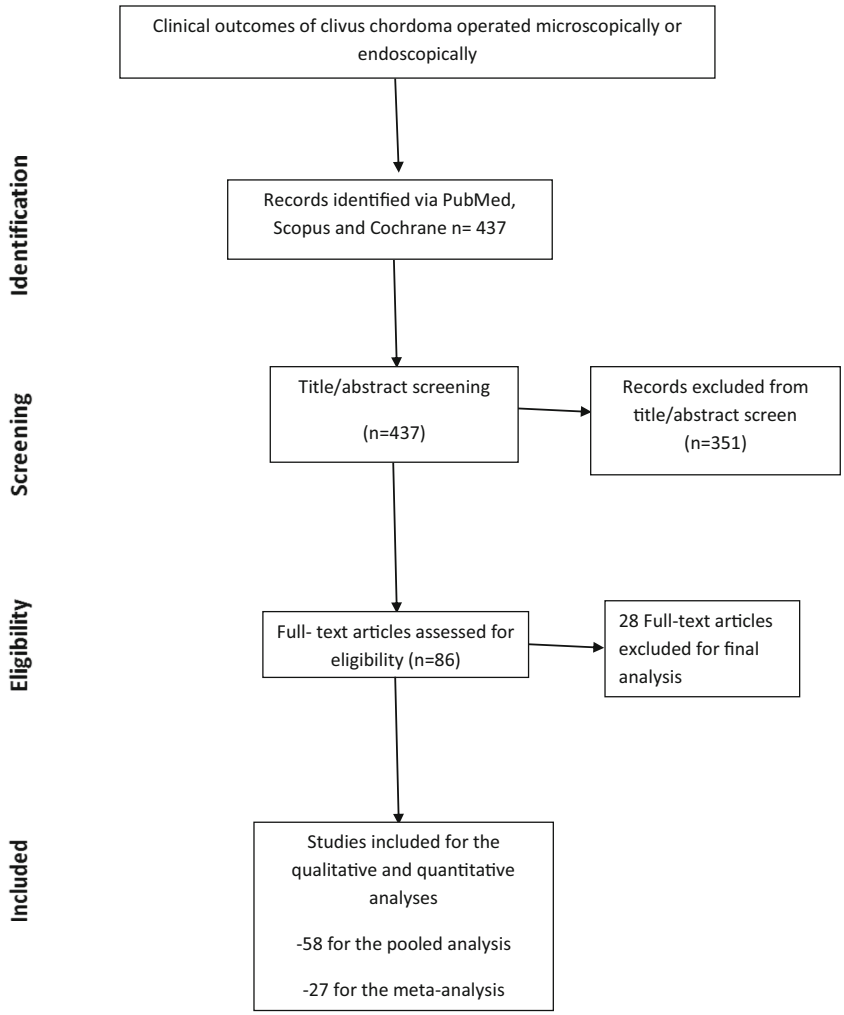


Fig. 1 Study selection process and articles included in final analysis

Surgical approaches: indications and technique

The clivus is the ventral part of the occipital bone, located at the center of the skull base separating the nasopharynx from the posterior cranial fossa. Multiple open surgical approaches have been described, including anterior, lateral, and posterior skull base approaches. Sekhar et al. [11] subdivided the clivus into 3 anatomic regions to aid in recognizing areas of potential tumor invasion and therefore in choosing the most appropriate approach for clival meningiomas: a fronto-temporal craniotomy with or without zygomatic osteotomy for upper clival lesions, a retrosigmoid or a posterior subtemporal—presigmoid transpetrous approach for middle clival tumors in a centro-lateral location, a pre-auricular subtemporal approach for lower clival lesions located medial to the lower cranial nerves, or an extreme lateral transcondylar approach for more lateral lower clival pathologies. Other "anterior" routes to the clivus have been reported, including transfacial, transmaxillary, transoral, transmandibular, and infratemporal approaches with associated morbidity in terms of cosmesis and function. Nowadays, EEAs are a valid option. Using the endoscope, it is possible to reach any part of the clivus from the dorsum sellae (with pituitary transposition) to its lower tip and even the craniocervical junction (CCJ). Lateral limits of the approach are venous structures, CNs, and arteries. However, it is now possible for experienced teams to reach

Table 1 Summary of the results obtained with univariate and multivariate regressions, according to each investigated factor. HR, hazard ratio; 95% CI, 95% confidence interval; *p*, *p* value; M, male; MA, microscopic approach

	Univariate regression		Multivariate regression	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender (M)	1.53 (0.96-2.44)	0.074	-	
Age	1.02 (1.00-1.03)	0.022	-	
Extent of resection				
Total	1		1	
Subtotal	2.34 (1.39-3.93)	0.001	2.18 (1.28-3.69)	0.004
Partial	4.31 (2.09-8.89)	< 0.001	4.40 (2.04-9.49)	< 0.001

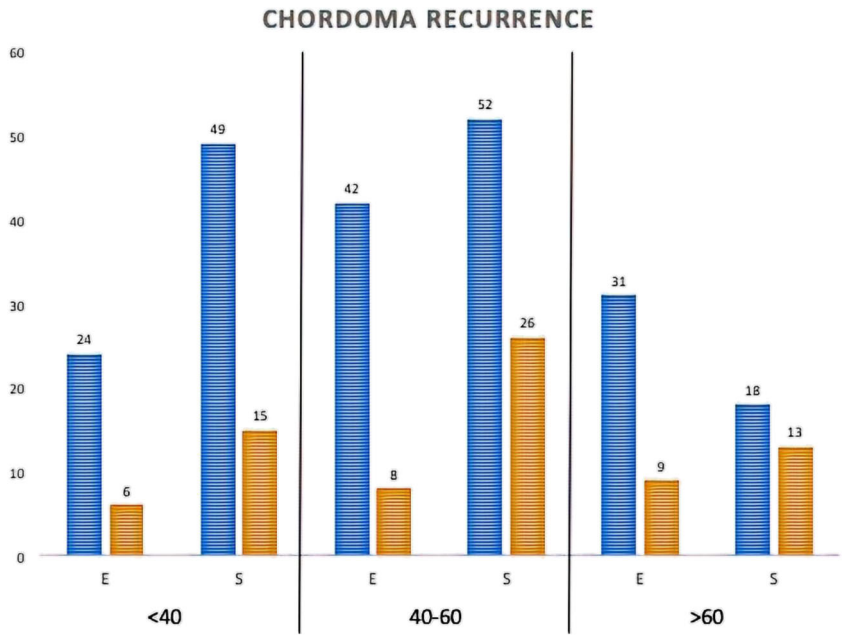


Fig. 2 Histogram showing the proportion of recurrent cases (orange columns) out of the total patients (blue columns) for each age group (below 40, in between 40-60 and over 60 years old) and subdivided according to the therapeutic approach. In the older group, the recurrence rate is clearly higher among the surgical cases. E, patients undergoing endoscopy; S, patients undergoing surgery

the lateral skull base and to control and work around these vessels and CNs with an acceptable risk [12, 13]. As described by Zoli et al. [14], for tumors located in the upper clivus, a standard endoscopic midline trans-sphenoidal approach with displacement or resection of the middle concha, followed by a posterior septostomy and a wide anterior sphenoidotomy is generally used. In case of lateral extension, EEA can be combined during the same or in a separate stage with transcranial approaches such as Dolenc transcavernous approach, subtemporal approach, anterior and/or posterior transpetrosal approaches, and CCJ anterolateral or posterolateral approaches (far and extreme lateral). In addition to the surgical resection, a craniocervical fixation may be needed [15].

Statistical considerations

Our pooled analysis examines 272 patients undergoing clival chordomas removal from 1990 to 2018 using MA or EA in order to determine statistical significance in terms of recurrence.

Table 2 HR of having a recurrence when comparing microsurgical vs endoscopic approach for each age group. HR, hazard ratio; 95% CI, 95% confidence interval; *p*, *p* value

	HR (95% CI)	*p*
< 40	0.61 (0.23-1.63)	0.325
40-60	1.67 (0.75-3.75)	0.211
> 60	1.44 (0.58-3.59)	*0.436*

Statistical analysis was conducted on the total sample and then corrected for survival. Our statistical analysis presents data similar to those reported in the literature [16–18].

A trend suggesting a link between recurrence rate and age of patients is present, where older patients tend to recur more. On the total sample, comparing the open surgical group and the endoscopic group, we can observe a superior frequency of recurrence in the open surgical group. Considering out pooled analysis recurrent cases are 23 out of 97 for the endoscopic approach (23.7%) compared to 54 out of 119 for microsurgery (45.5%).

When we analyze the same results corrected for long term survival in patients < 40 years old, we notice a recurrence rate equal between open surgical and the endoscopic group, whereas the recurrence rate which is significantly higher in the open surgical group for patients over 40 years.

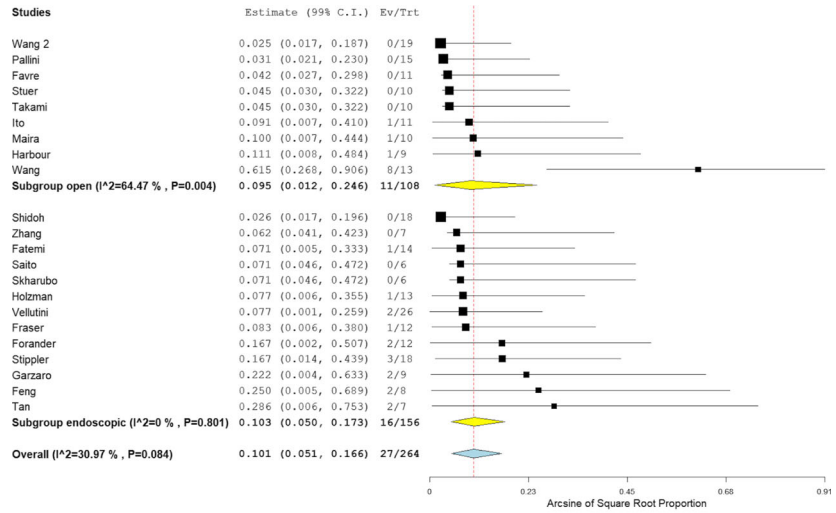
Gross total remove reduces recurrence rates in clivus chordomas [19].

As trusted, we confirm a linear relationship between amount of tumor removal and recurrence. This result is maintained in the correct analysis for survival and in two groups.

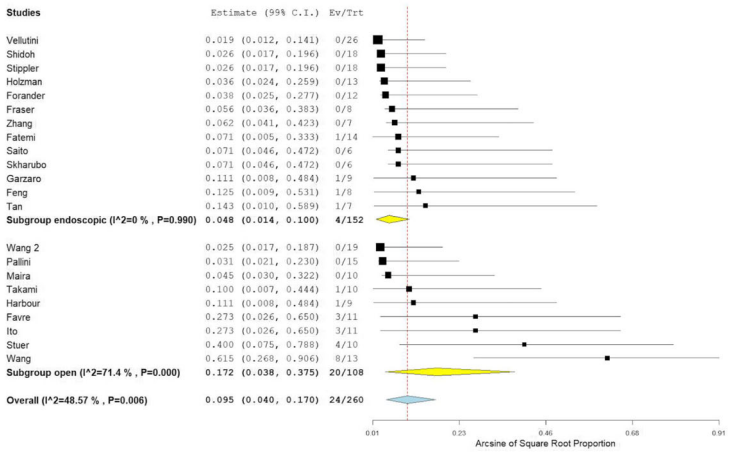
There are no notable differences in postoperative complications between open surgical and endoscopic groups.

Analyzing the data of pooled analysis, we highlighted that in elderly patients the recurrence rate compared to the young ones is greater in both groups. This evidence could be justified by the fact that elderly patients become, often, symptomatic when the tumors reach a high volume as compared to younger patients where the diagnosis is made often earlier. Also, despite the choice of approach in elderly patients, due to comorbidities, there is a slight tendency for debulking rather than total removal. From our analysis, it is clear that in patients

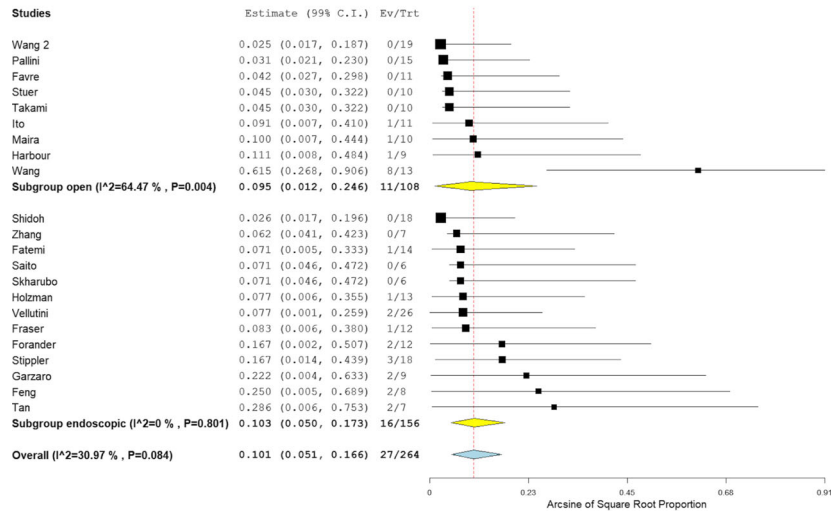
a Overall Recurrence MA compared to EA



b Ocular Nerve Complications MA compared to EA



c CSF Leakage MA compared to EA



◀ **Fig. 3** Results of the cumulative meta-analysis evaluating the difference in outcomes (recurrence risk (**a**), ocular nerve complications 3(**b**), CSF leakage 3(**c**)) between studies with patients undergoing open microsurgery (MA) and endoscopic patients. **a** Overall recurrence MA compared to EA. **b** Ocular nerve complications MA compared to EA. **c** CSF Leakage MA compared to EA. Results of the cumulative meta-analysis evaluating the difference in outcomes (recurrence risk (**a**), ocular nerve complications 3(**b**), CSF leakage 3(**c**)) between studies with patients undergoing open microsurgery (MA) and endoscopic patients

under the age of 40 the choice of approach can fall both on the endoscopic and open surgical approach, in terms of probability of recurrence, while in elderly patients it is preferable to choose the endoscopic approach, according to neurosurgeon experience.

In a surgical analysis, the gross total resection is a main predictor of recurrence and it can be comparable in different surgical approaches [20].

The cumulative results that emerge from our meta-analysis outline that the risk of recurrence is independent of the type of open surgical technique is 25.6% (99% CI 13.8-39.7), although subgroup analysis outcomes suggest that open surgery recurrence rate may be higher when open surgery is adopted compared to endoscopic techniques, 31.8% (99% CI 14-52.8) vs 19.4% (99% CI 5.4-39.2), respectively. In relation to the incidence of post-operative cranial nerve deficits, there is a great disparity in the data reported in the literature. In a recent large surgical endoscopic analysis of 127 patients, Shkarubo et al. define oculomotor disorders as the main complication in the postoperative period with a rate of 13.4% [21]. Zoli et al. reported a transient nerve palsy rate of 6.2% in a recent series of endoscopic cases [14]. Sekhar et al. [22] achieved a rate 21% of cranial nerve deficit.

This disparity could be linked to a bias in the analysis and collecting data, relation to timing and type of surgical approach, entity of rection, timing of deficit onset.

In our series, the overall rate of ocular nerve complications was 4.8% (99% CI 1.4-10) for the EA group, and 17.2% (99% CI 3.8-39.5) for the MA group. Comparisons between these two subgroups cannot be made for this particular complication, given that in the open surgery group a posterior approach is used, and this obviously cannot lead to an injury to the ocular nerves. At the same time, it was possible to outline that when open surgery with the anterior approach is the chosen surgical method, the risk of ocular nerve damage is still consistent. Unexpectedly, regarding CSF leak complication, results were similar among the analyzed subgroups, with a CSF leak rate for the open surgery group of 9.5% (99% CI 1.2-24.6) and for the endoscopic group of 10.3 (99% CI 5-17.3). This finding is probably related to the most refined reconstruction techniques of the skull base in trans-sphenoidal approach. At the same way, Conger et al. [23], recently, showed an overall CSF leak rate between 3 and 15.9% for mixed pathology series for the endonasal approach.

Labidi et al. [4] presented a rate of CSF leak from 9.5 to 22.5 % for different surgical approaches. Results of the meta-regression, after setting the proportion of partial resection in the single study as the covariate, suggest that an increase in proportion of partially resected tumor (as opposed to totally resected) has an influence on recurrence rate ($p < 0.001$).

Study limitations

Several limitations of this meta-analysis warrant consideration. One is the possible bias of the included studies, although we took several steps to mitigate this possibility. Our formal analyses also did not support publication bias. Although the strict inclusion criteria should reduce this possibility, variation in the studies themselves limits the generalizability of our results. Variable study quality could also have resulted in heterogeneity, and it is possible that the presence of other confounding factors could have led to the observed association between clival chordomas and rate of recurrence. Only English-language studies were reviewed, which could have led to the exclusion of some relevant studies. We adopted a likely statistically robust approach for the meta-analysis. We adopted a 99% CI, which allowed to have a wider and, for this reason, more conservative interval. Also, a reliable transformation of the data was performed, which better accounts for rare events.

The results are consistent among the single patient pooled analysis and the meta-analysis, this may lead to the conclusion that it is likely that our results are reliable. On the other hand,

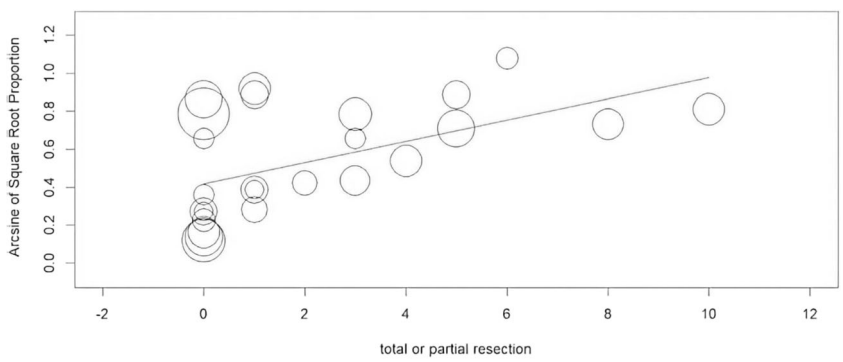


Fig. 4 Meta-regression showing that the more partial the resection is, the greater is the increase in the recurrence risk

no prospective randomized comparisons are available on this topic, which increases the risk of potential selection and reporting bias.

Undoubtedly, definitive conclusions are far to be reached and further research is needed on this topic.

Conclusions

Clivus chordomas are rare neoplasms. They are characterized by a high local recurrence rate. Open surgery and endoscopic approach represent valid treatment strategy related to radiological and anatomical tumor features and neurosurgeon expertise. We achieved a double statistical analysis that demonstrated that older patients tend to recur more than young patients, especially in the surgical group. Moreover, our analysis confirms, as reported in pertinent literature, that an increase in proportion of partially resected tumor (as opposed to totally resected) has a significant influence on the recurrence rate. The double statistical approaches allowed us to obtain a comprehensive analysis of an uncommon but highly-impact disease in neurosurgical practice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (include name of committee + reference number) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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