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Proton therapy for craniopharyngioma in adults: A protocol for systematic review and meta analysis

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Title page

Title

Proton therapy for craniopharyngioma in adults: A protocol for systematic review and meta analysis

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Abbreviations

PT= Proton therapy, GTR= gross total resection, STR= subtotal resection, RT= radiotherapy, PRISMA-P= The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, RCTs= randomized controlled trials.

Proton therapy for craniopharyngioma in adults: A protocol for systematic review and meta analysis

ABSTRACT

Introduction Craniopharyngioma is a benign tumor located in the Sellar region and parasellar region with localized invasiveness and adjacent important nerves and vessels. The total resection rate is low and the postoperative recurrence rate is high. Postoperative adjuvant radiotherapy can effectively reduce the recurrence rate, but traditional radiotherapy has many complications. In recent years, proton therapy (PT) has been more and more used in patients with craniopharyngioma, and achieved better efficacy and lower incidence of complications. However, there is no consensus. We conducted a systematic review and meta analysis on the basis of existing randomized controlled trials (RCTs) to evaluate the safety and efficacy of PT for craniopharyngioma in adults.

Methods and analysis We will search 7 databases (PubMed, EMBASE, Web of Science, Cochrane Library, PsycINFO, Amed, Scopus), clinical research registration websites and grey literature. Study selection, data extraction, bias risk and quality assessment. Review Manager software 5.2 and STATA software 16.0 are used for statistical analysis.

Ethics and dissemination Our study is based on the existing RCTs and does not require ethical approval. The results of the study will be published in a peer-reviewed journal or at a related conference.

PROSPERO registration number CRD42020200909.

Strengths and limitations of this study

► This is the first meta analysis of the safety and efficacy of PT for craniopharyngioma in adults.

► The results of this meta analysis will provide an important reference for clinical practice and future PT for craniopharyngioma in adults.

► Our study only included RCTs, which may limit the number of studies we can search.

► Different studies have different radiation doses for PT, which may be biased towards the final results.

INTEODUCTION

Craniopharyngioma is a benign tumor located in the Sellar region and parasellar region. Its limited invasiveness and its proximity to the hypothalamus, pituitary, optic nerve and carotid artery make it the most challenging tumor in neurosurgery. The incidence of craniopharyngioma is 1.3 parts per million, which can occur in all age groups, showing a bimodal age distribution (5-14 years old and 65-74 years old).[1] Craniopharyngioma accounts for a large proportion in adults, but its importance is not as high as in children. At present, the best treatment of craniopharyngioma is still controversial. Gross total resection (GTR) has long been the preferred method for reducing recurrence rates, but with a low total resection rate and the risk of optic nerve and endocrine damage.[2-6] It is reported that the recurrence rate of subtotal resection (STR) is as high as 50%-91%.[7,8] Therefore, postoperative radiotherapy for craniopharyngioma is necessary. In recent years, more and more evidence shows that postoperative adjuvant radiotherapy (RT) for STR can achieve the same tumor control rate as GTR.[9-12] A recent SEER analysis included 1218 patients with craniopharyngioma， and there is no significant difference in survival between RT, GTR and STR+ RT.[13] However,

traditional photonic radiotherapy has serious complications, such as cognitive impairment, optic nerve damage and a risk of developing a second cancer.[14-16]

With the development of radiotherapy technology, PT has been applied more and more in the treatment of craniopharyngioma, with better results and fewer complications.[17-21] The physical properties of proton beam and Bragg peak phenomenon minimize the damage to normal tissue and increase the damage to tumor. Many studies have compared different radiotherapy methods for craniopharyngioma, but the results are not consistent.[22-25] Therefore, we conducted a systematic review and meta analysis to evaluate the safety and efficacy of PT for craniopharyngiomas in adult.

Objective

Our study will combine existing RCTs to determine whether PT is safe and effective in treating craniopharyngioma in adults.

METHODS AND ANALYSIS

This study will be written strictly according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[26]

Inclusion and exclusion criteria

The target population of this study is adults aged 18 or above at the time of diagnosis. These results will also be considered if the study includes a mix of adults and minors. The diagnosis is confirmed by pathology. No serious postoperative complications, such as severe pulmonary infection, stroke and so on, may affect the survival time. The participants are followed up for at least 5 years for imaging examination.There is no restriction on gender,or race.

We will rule out studies that do not clearly distinguish the histological classification of craniopharyngioma. We will also exclude the inclusion of studies of people who have received postoperative chemotherapy and previous radiotherapy, as this may affect our conclusions. In addition, we will rule out studies with incomplete data and lack of access to the full text. Non-RCTs studies will also be excluded.

Intervention

Our intervention is Proton therapy as postoperative radiotherapy for craniopharyngioma in adults.

Comparator

Our comparator is conventional photon radiation or postoperative radiation not accepted.

Outcome

Primary outcome

Our primary outcome is tumor recurrence at at least 5 years of follow-up, and Treatment-related toxicity.

Evaluation indicators include：

(1) Tumor recurrence rate

(2) Treatment-related toxicity

Secondary outcome

Our secondary outcome is an assessment of survival.

Evaluation indicators include：

(1)Overall survival (OS)

(2)Progression-free survival (PFS)

(3)Five-year survival rate

Study design

The RCTs of Proton therapy for craniopharyngioma in adult will be included.

Information sources

From the beginning to September 28, 2020, We will search seven databases including (PubMed, EMBASE, Web of Science, Cochrane library, PsycINFO, AMED, Scopus).we will also search the clinical research registration website (WHO ICTRP and ISRCTN Register). In addition, grey literature (the Health Management Information Database, OpenSIGLE Database and the National Technical Information Service) will also be in our search scope.

Search strategy

Two researchers (KZ and JY) formulates the search strategy, and our search strategy will focus on the keywords of this study (Proton therapy, craniopharyngioma, and randomized controlled trial). Table 1 shows the search strategy for Pubmed, and other database search strategies will be adjusted slightly. Our search strategy will not be restricted by race, language, etc.

Study records

Data management

A researcher (SL) will import all search studies into the software to initially eliminate duplication. Another researcher (WJ) will remove the repetition twice according to the title and abstract.

Selection process

The selection process will be divided into two stages. In the first stage, two researchers (WJ and HW) will independently read titles and abstracts in the software. According to our inclusion and exclusion criteria, all studies will be divided into three categories: "YES", "NO" and "uncertainty", and the study of "NO" will be excluded. In the second stage, two researchers (SL and KZ) read the full text of "YES" and "uncertainty" and excluded unsuitable studies. If there is any dispute during this period, the four researchers (WJ, HW, SL, KZ) will discuss it together and make a decision. Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols flow diagram of the study selection process.

Data collection process

The two researchers (KZ and JY) will independently collect the data included in the study. Data collection will be divided into four parts. In the first part, the characteristics of the study include study author, publication date, journal name and country. In the second part, the characteristics of participants include gender, age and type of operation. The third part, intervention and control information, collect detailed intervention and control information as much as possible. The fourth part, outcome and follow-up information. The third researcher (HW) will be responsible for examining the information collected. If necessary, contact the author of the research newsletter for more information.

Risk of bias

The two researchers (PL and TZ) will independently use the Cochrane risk of bias tool outlined by The Cochrane Handbook for Systematic Reviews of Interventions to evaluate the offset risk. It includes randomness, double blindness, hidden distribution, blindness in result evaluation, integrity of result data, selective result report and other deviations.

We will classify the risk as "low risk", "high risk" and "uncertain risk". If there is any dispute, the third researcher (AA) will participate in the discussion and settlement.

Statistical analysis

We will use Review Manager software 5.2 and STATA software 16.0 to analyze the collected data. Summarize the specific characteristics and research results through the table. We will estimate the results with descriptive statistics and 95% confidence intervals. Heterogeneity is judged by calculating I^2 statistics. When $I^2 \leq 50\%$ indicates low heterogeneity, use fixed effect model, when $I^2 > 50\%$ indicates significant heterogeneity, use random effect model. If $I^2 \leq 50\%$, meta analysis is carried out on the basis of ensuring that the same result index is fully qualified. If $I^2 > 50\%$, we will conduct a subgroup analysis to determine its possible source and conduct a descriptive analysis.

Assessment of reporting biases

When the number of RCTs included exceeds 10, we will use funnel plots to assess reporting bias. Otherwise, we will use Egger test to assess reporting bias.

Subgroup analysis

We will conduct a subgroup analysis according to different diagnostic ages and different pathological types of craniopharyngioma to observe the possible heterogeneity in the study.

Patient and public involvement

No patient is involved in either the design or planning phase of this study.

Ethics and dissemination.

Our study does not involve individual patients, so there is no need for ethical approval. The results of this study will be published in peer-reviewed journals or related conferences to evaluate the efficacy and safety of proton therapy for craniopharyngiomas in adults.

DISCUSSION

This systematic review and meta analysis will answer a research question about the safety and efficacy of PT for craniopharyngiomas in adults.

The inclusion and exclusion criteria of our study will be explained here. First of all, participants must be pathologically confirmed craniopharyngioma. Patients who have not undergone surgery will be excluded. Because different histological types of craniopharyngiomas have different sensitivity to PT, it is not appropriate to include unknown histological types of craniopharyngiomas. It should be pointed out that this study only compares different radiotherapy methods or no postoperative radiotherapy. Patients with severe postoperative complications will be excluded because they may have an impact on the survival of our observed indicators. The absence of imaging follow-up for at least 5 years will also be excluded, which may also have an impact on our observed indicators of progression-free survival. Postoperative chemotherapy or previous radiotherapy will be excluded, which may also have an impact on the final outcome.

Considering that our study only included RCTs, the search database is expanded to include clinical research registration websites and grey literature.

As a new method of radiotherapy, PT can reduce the recurrence rate of craniopharyngioma and reduce the complications of radiotherapy. The purpose of this study is to provide evidence for clinical practice and the idea of future PT for craniopharyngioma.

Contributors PL conception of the study. PL and AA participated in the design study, while KZ and JY developed the search strategy. PL, AA participated in the first draft of the original manuscript. KZ, SL, JY and HW were involved in research screening and data collection. TZ is the reviewer of the study. All authors edited, modified, and approved the final version of this protocol.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

Conflict of interest The authors declare no conflicts of interest.

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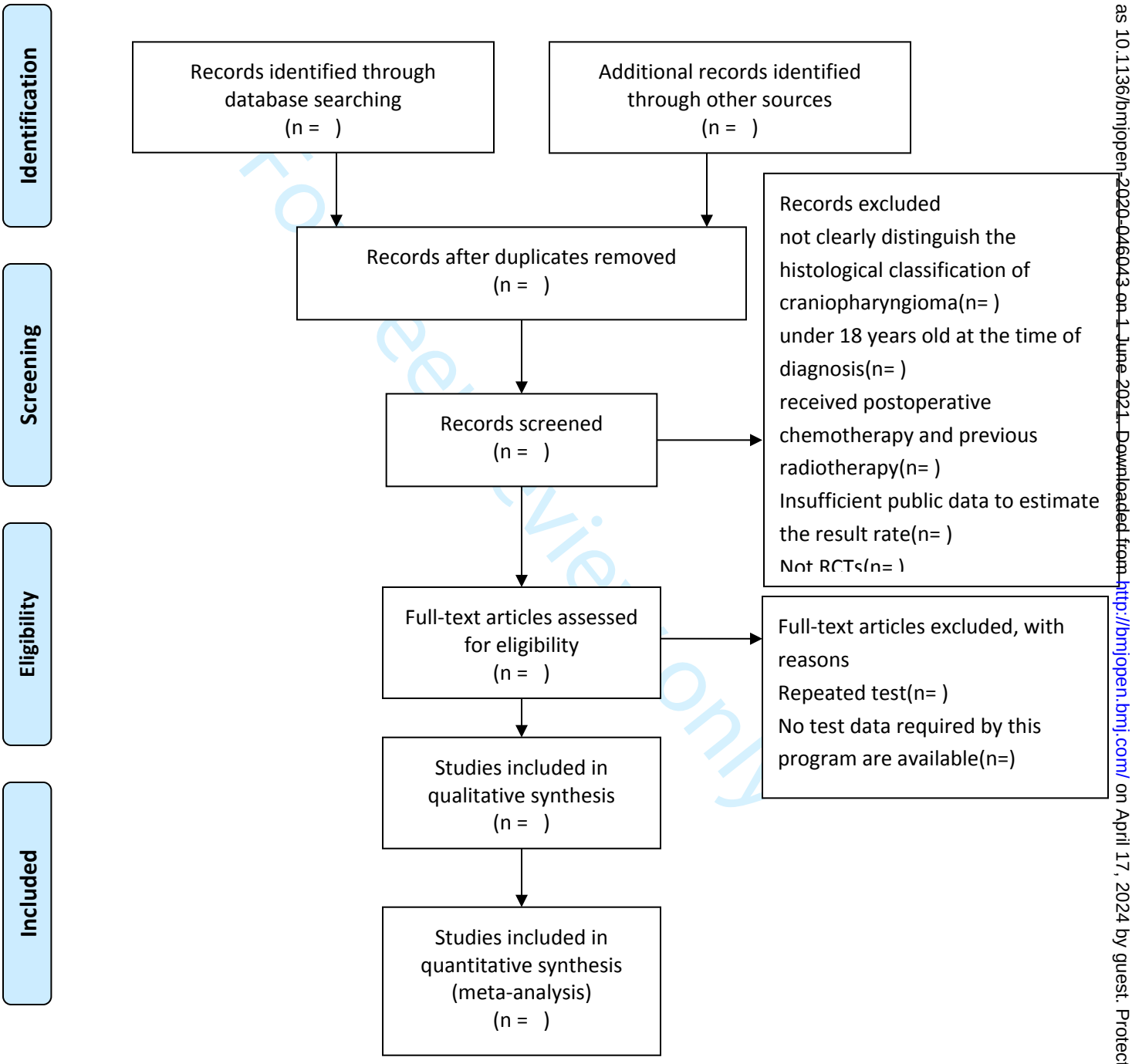
Table 1. Search strategy for PubMed database.

Number	Search items
1	craniopharyngioma/
2	(craniopharyngioma* or craniopharyngeoma* or pharyngioma* or pharyngeoma* or "cranio pharyngioma*" or "cranio pharyngeoma*").ti,ab,cl,oa,kw.
3	((Rathke* or "craniopharyngeal duct*" or "Dysodontogenic epithelial*" or "hypophyseal duct*" or "third ventricle*") adj3 (adenoma* or microadenoma* or neoplasm* or lesion*)).ti,ab,cl,oa,kw.
4	or/1-3
5	(proton* or proton beam* or particle radiation* or charged-particle* or photon* or radiotherapy* or radiation* or PBT or PT or RT).ti,ab,cl,oa,kw.
6	4 and 5
7	(randomized controlled trial* or randomized* or randomly* or RCT).ti,ab,cl,oa,kw.
8	6 and 7
9	remove duplicates from 8

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols flow diagram of the study selection process.

PRISMA 2009 Flow Diagram

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols flow diagram of the study selection process.



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

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Number	Search items
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4	or/1-3
5	(proton* or proton beam* or particle radiation* or charged-particle* or photon* or radiotherapy* or radiation* or PBT or PT or RT).ti,ab,cl,oa,kw.
6	4 and 5
7	(randomized controlled trial* or randomized* or randomly* or RCT).ti,ab,cl,oa,kw.
8	6 and 7
9	remove duplicates from 8

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	/
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7-8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	/
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Title page

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Abbreviations

PT= Proton therapy, GTR= gross total resection, STR= subtotal resection, RT= radiotherapy, PRISMA-P= The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, RCTs= randomized controlled trials.

Proton therapy for craniopharyngioma in adults: A protocol for systematic review and meta analysis

ABSTRACT

Introduction

Craniopharyngioma is the most challenging brain tumor with high recurrence rates, which can be effectively reduced by adjuvant radiotherapy. In recent years, proton therapy(PT) with its physical properties of proton beam and Bragg peak phenomenon has been more and more used in patients with craniopharyngioma, and achieved good results. The purpose of this study was to evaluate the efficacy of proton therapy for craniopharyngioma in adults.

Methods and analysis

We will search 6 databases (MEDLINE, EMBASE, Web of Science, Cochrane Library, Amed, Scopus), clinical research registration websites, grey literature, and search for studies on PT for craniopharyngioma in adult between 1 January 1954 and 28 September 2020, and will performe study selection, data extraction, bias risk and quality evaluation, as well as the use of Review Manager software 5.2 (RevMan 5.2) for data analysis.

Ethics and dissemination

Our study is based on the existing RCTs and does not require ethical approval. The results of the study will be published in a peer-reviewed journal or at a related conference.

PROSPERO registration number CRD42020200909.

Strengths and limitations of this study

► This is the first meta-analysis of the safety and efficacy of PT for craniopharyngiomas in adults.

► The results of this meta-analysis will provide an important reference for the treatment of craniopharyngioma in adults.

► Only randomized controlled trials (RCTs) will be included in this study.

► When sufficient data are available, we will perform subgroup analysis according to different craniopharyngioma subtypes, locations and tumor sizes.

► Craniopharyngioma is a rare disease, which may face the problem of insufficient sample size.

INTEODUCTION

Craniopharyngioma is a benign tumor located in the Sellar region and parasellar region. Its limited invasiveness and its proximity to the hypothalamus, pituitary, optic nerve and carotid artery make it the most challenging tumor in neurosurgery. The incidence of craniopharyngioma is 1.3 parts per million, which can occur in all age groups, showing a bimodal age distribution (5-14 years old and 50-74 years old).[1] Craniopharyngioma accounts for a high proportion in adults but are less important than children. The operation of craniopharyngioma is difficult, and the rate of disability and mortality after gross total resection (GTR) are very high, but the recurrence rate of subtotal resection (STR) was 50% - 91%.[2-4] In recent years, more and more evidence shows that postoperative adjuvant radiotherapy (RT) for STR can achieve the same tumor control rate as GTR.[5-8] A recent SEER analysis including 1218 patients with craniopharyngiomas also demonstrated no significant difference in survival between RT, GTR and STR+ RT.[9] Since Craniopharyngioma are located deep in the skull base, it is difficult to achieve enough radiation doseonly by

conventional X ray beam radiation therapy, and they are prone to serious radiation-related toxicity, such as endocrine disorders, cognitive disorders, optic nerve injury and development of the second type of cancer.[10-12]

With the development of radiotherapy technology, proton therapy has been increasingly used in the treatment of craniopharyngioma.[13-17] The physical properties of proton beam and Bragg peak phenomenon can reduce the damage to normal tissues and enlarge the damage to tumors, which has achieved good results.[18-21] In view of the lack of comprehensive evaluation on the efficacy and safety of proton therapy for adult craniopharyngiomas, this study will comprehensively evaluate the tumor recurrence rate, Median overall survival, Progression-free survival (PFS) and treatment-related toxicity of proton therapy for craniopharyngiomas in adult through systematic review and meta-analysis, so as to provide clinical basis for PT.

Objective

Our study will combine existing RCTs to determine whether PT is safe and effective in the treatment of adults with craniopharyngiomas.

METHODS AND ANALYSIS

This study will be written strictly according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[22]

Inclusion and exclusion criteria

Types of study

Studies to be included should meet the following criteria:

(1) parallel-group RCTs; (2) Objective to evaluate the efficacy and safety of proton therapy for craniopharyngioma in adults; (3) The study with mixed population will be included in our study if the subgroup analysis of adults and children is carried out, otherwise it will be excluded; (4) Studies of patients who have received postoperative chemotherapy and previous radiotherapy will also be excluded, as this may affect our

conclusions; (5) In addition, we will exclude studies that do not describe our outcome indicators such as the tumor recurrence rate, Median overall survival, Progression-free survival (PFS) and treatment-related toxicity; (6) Study without ethnic and language restrictions; (7) Repetitive studies will be excluded.

Types of participants

The target population of this study is adults aged 18 or above at the time of diagnosis, who were pathologically confirmed to be free from serious postoperative complications, such as severe pulmonary infection, stroke and other complications that could affect survival time.

Intervention

Our intervention is Proton therapy as a treatment for craniopharyngioma in adults.

Comparator

Our comparator is conventional X-ray beam radiotherapy as a treatment for craniopharyngioma in adults.

Outcome

Primary outcome

Our primary outcome, tumor recurrence and survival, will be used to assess the safety and efficacy of proton therapy for craniopharyngiomas in adults.

Evaluation indicators include：

(1) Tumor recurrence rate

(2) Median overall survival

(3) Progression-free survival (PFS)

Secondary outcome

Our secondary outcome is an assessment of Treatment-related toxicity (endocrine disorders, cognitive impairment, optic nerve injury and development of the second cancer).

Study design

The parallel-group RCTs of proton therapy for craniopharyngioma in adult will be included.

Information sources

From January 1, 1954 to September 28, 2020, We will search 7 databases (MEDLINE, EMBASE, Web of Science, Cochrane library, PsycINFO, AMED, Scopus) and the clinical research registration websites (WHO ICTRP and ISRCTN Register). In addition, grey literature (the Health Management Information Database, OpenSIGLE Database and the National Technical Information Service) will be included in the search.

Search strategy

Two researchers (KZ and JY) formulates the search strategy, and our search strategy will focus on the keywords of this study (Proton therapy, craniopharyngioma, and randomized controlled trial). Table 1 shows the search strategy for MEDLINE, and other database search strategies will be adjusted slightly. Our search strategy will not be restricted by race, language.

Study records

Data management

A researcher (SL) will first import all search studies into the software to initially eliminate duplication, and then another researcher (WJ) will delete them twice based on the title and summary.

Selection process

The selection process will be divided into two stages. In the first stage, two researchers (WJ and HW) will independently read titles and abstracts in the software and classify all studies into three categories of "YES", "NO" and "Uncertainty" based on our inclusion and exclusion criteria, excluding no studies. In the second stage, two researchers (SL and KZ) will read the full text of "YES" and "Uncertainty" and exclude inappropriate studies. If there is any

controversy during this period, the decision will be discussed and made by four researchers (WJ, HW, SL, KZ) together.

Data collection process

The two researchers (KZ and JY) will independently collect the data included in the study. Data collection will be divided into four parts. In the first part, the characteristics of the study include study author, publication date, journal name and country. In the second part, the characteristics of participants include gender, age and type of operation. The third part, intervention and control information, the more detailed the better. The fourth part, outcome and follow-up information. The third researcher (HW) will be responsible for examining the information collected and, if necessary, contact the author of the Study Newsletter for further information.

Risk of bias

The two researchers (PL and TZ) will use the Cochrane Collaboration RoB tool for randomised trials (RoB V.2) to evaluate the quality of included RCTs, which is divided into five domains of bias (bias from the randomization process, bias due to deviations from intensified inter events, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result). In each domain, a series of questions (signalling questions) need to be answered to obtain information on characteristics relevant to the study and a risk of bias calculated for each domain to ultimately obtain the full text of the risk of bias judgement (low risk of bias, some concerns, high risk of bias). If there is any dispute, the third researcher (AA) will participate in the discussion and settlement.

Measures of treatment effect

We will use RevMan 5.2 for data synthesis and analysis. Dichotomous data will be analyzed using a risk ratio with 95% CIs. For continuous outcomes data, the mean difference with 95% CIs will be used for analysis.

Assessment of heterogeneity

We will use the Mantel-Haenszel χ^2 test and I square (I^2) statistic of homogeneity by RevMan 5.2. According to the Cochrane Handbook, I^2 value can be used to evaluate heterogeneity. 0%-40%: might not be important ; 30%–60%: may represent moderate heterogeneity; 50%–90%:may represent substantial heterogeneity; 75%-100%: considerable heterogeneity.[23] When P<0.10 and I2>50%, there is obvious heterogeneity. I^2>50% and P<0.10 showed significant statistical heterogeneity.

Data synthesis

RevMan 5.3 will be used for data synthesis. Three or more studies with no or low heterogeneity ($I^2 < 50\%$) will be combined for Meta-analysis, and the results will be pooled using a fixed-effects model. If significant heterogeneity exists, $I^2 \geq 50\%$, the results will be combined with a random-effects model, and if the Meta-analysis is not feasible due to clinical and methodological heterogeneity, the results will be summarized qualitatively.

Assessment of reporting biases

When the number of included studies reaches 10 or more, we will create a funnel plot of the outcome and evaluate whether there is a reporting bias based on its symmetry.

Subgroup analysis

We will conduct the following subgroup analysis to assess potential heterogeneity.

1.The classification of craniopharyngioma (eg, adamantinomatous croniopharyngioma, ACP and papillary croniopharyngioma, PCP).[24-25]

2. The location of craniopharyngioma. (eg, QST classification system).[26]

3. The tumor size of craniopharyngioma (eg, greater than 4cm and less than 4cm).[27]

Sensitivity analysis

We will conduct a sensitivity analysis to assess the reliability of the meta-analysis by excluding studies with high risk of bias or missing reported data.

Patient and public involvement

No patient is involved in either the design or planning phase of this study.

Ethics and dissemination.

Our study does not involve individual patients, so there is no need for ethical approval. The results of this study will be published in peer-reviewed journals or related conferences to evaluate the efficacy and safety of proton therapy for craniopharyngiomas in adults.

DISCUSSION

PT is an advanced radiotherapy method with less toxicity and better therapeutic effect than traditional X-ray radiotherapy.[28] At present, PT has become an international focus and emphasis on tumor radiotherapy technology. The medical application of proton beam was first proposed by Wilson in 1946.[29] In 1954, Tobias and others carried out the first PT in the world at Lawrence Berkeley National Laboratory at the University of California,and since then, Sweden, the former Soviet Union and other countries have successively carried out clinical studies on PT. According to Particle Therapy Co-Operative Group PTCOG, nearly 100 medical institutions around the world are currently using proton and heavy ion radiotherapy technology to implement tumor treatment, and there are more than 100 proton radiotherapy centers under construction, and nearly 200000 patients have received proton radiotherapy worldwide.[30]

The main techniques of PT for tumor treatment are active scanning and passive scattering. The Bragg peak of proton is obtained by modulator and collimator. At present, the common treatment methods of proton used in clinical tumor radiotherapy in the world are as follows: ① proton point scan irradiation, to achieve precise control of tumor, but the operation process is more complex; ② proton stereotactic radiotherapy, the main treatments of which are target area high-dose irradiation and fractional irradiation, with a limited clinical application; ③ intensity-modulated proton therapy(IMPT), realizes dose intensity modulation and optimizes dose distribution, especially the application of pen beam scanning in impt, which avoids or reduces the radiation dose to surrounding normal tissues. In the treatment of

head and neck tumors, PT can increase the radiation dose of the target area and reduce the toxicity of organs.[31-33]

The new version of the 2018 National Comprehensive Cancer Network guidelines takes PT as one of the standard treatments for head and neck cancer.[34] A European center study of 18 patients with craniopharyngiomas who received proton therapy found that one patient progressed 8.7 months after PT and then underwent surgery. Of the remaining patients at 18.4 months, 5 patients had complete remission, 4 patients had partial remission, 7 patients had stable disease, and there was no serious treatment-related toxicity during the treatment.[17] Weber et al. Included 16 patients with craniopharyngioma, and finally analyzed 15 patients, showing a 3 year overall survival rate of 75%. While PT has similar efficacy to conventional X-ray radiotherapy, it is more protective to the temporal lobe and hippocampal formation.[35]

At present, there is a lack of comprehensive review on the efficacy and safety of proton therapy for adults with craniopharyngioma, therefore, our study will comprehensively evaluate the recurrence rate, survival, and treatment-related toxicity of proton therapy for adults with craniopharyngioma through a systematic review and meta-analysis to provide a clinical basis for PT.

Contributors PL conceived the original idea for this systematic review. PL and SL drafted the manuscript. AA, KZ, JY, HW, JW and TZ revised the manuscript. All authors have read and approved the final manuscript.

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Competing interests None declared.

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Conflict of interest The authors declare no conflicts of interest.

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Table 1. Search strategy for MEDLINE

Number	Search items
1.	Craniopharyngioma/
2.	(craniopharyngioma* or craniopharyngeoma* or pharyngioma* or pharyngeoma* or "craniopharyngioma*" or "craniopharyngeoma*").ti,ab,cl,oa,kw.
3.	((Rathke* or "craniopharyngeal duct*" or "Dysodontogenic epithelial" or "hypophyseal duct*" or "third ventricle") adj3 (tumo?r* or adenoma* or microadenoma* or neoplasm* or lesion*)).ti,ab,cl,oa,kw.
4.	or/1-3
5.	(proton* or proton beam* or new radiation* or PT or PBT).ti,ab,cl,oa,kw.
6.	4 and 5
7.	limit 6 to adult
8.	remove duplicates from 7

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	/
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	/
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4-5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging
Keywords:	NEUROSURGERY, Adult oncology < ONCOLOGY, Radiation oncology < RADIOTHERAPY, Neuroradiology < NEUROLOGY

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Title page

Title

Proton therapy for craniopharyngioma in adults: A protocol for systematic review and meta analysis

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Abbreviations

PT= proton therapy, GTR= gross total resection, STR= subtotal resection, RT= radiotherapy, PRISMA-P= The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, RCTs= randomized controlled trials.

Proton therapy for craniopharyngioma in adults: A protocol for systematic review and meta analysis

ABSTRACT

Introduction

Craniopharyngioma is the most challenging to treat brain tumor with high recurrence rates, which can be effectively reduced by adjuvant radiotherapy. In recent years, proton therapy (PT), with its physical properties of heavy ion beam, i.e. Prague peak phenomenon, has been more frequently used in patients with craniopharyngioma. Compared with Conventional X-ray beam radiotherap, PT can reduce the damage to normal tissues and enlarge the damage to tumors. Some studies have shown that PT has advantages in the treatment of craniopharyngioma in adults. However, the optimal management of craniopharyngioma remains controversial. The purpose of this study was to evaluate the efficacy and safety of PT for craniopharyngioma in adults.

Methods and analysis

We will search 6 databases (MEDLINE, EMBASE, Web of Science, Cochrane Library, Amed, Scopus), clinical research registration websites and grey literature, aiming to identify randomized controlled trials (RCTs) on PT for craniopharyngioma in adults between 1 January 1954 and 28 September 2021. In the RCTs, PT will be used as the intervention group, and conventional X-ray beam radiotherapy will be used as the comparator group. Tumor recurrence and survival will be the primary outcome, and treatment-related toxicity will be the secondary outcome. The studies' selection, data extraction, bias risk and quality evaluation will be operated by 2-4 researchers independently. We will use Review Manager 5.2 (Revman

5.2) for data analysis. If there is significant heterogeneity, we will identify the source of heterogeneity by subgroup analysis.

Ethics and dissemination

Our study is based on ~~the~~ existing RCTs and does not require ethical approval. The results of the study will be published in a peer-reviewed journal or at a related conference.

PROSPERO registration number CRD42020200909.

Strengths and limitations of this study

►First meta-analysis of which we are aware of the safety and efficacy of PT for craniopharyngiomas in adults.

► The results of this meta-analysis will provide an important reference for the treatment of craniopharyngioma in adults.

► Only RCTs will be included in this study.

► We will perform subgroup analysis according to different craniopharyngioma subtypes, locations and tumor sizes.

► Craniopharyngioma is a rare disease, which may face the problem of insufficient sample size.

INTEODUCTION

Craniopharyngioma is a benign tumor located in the sellar and parasellar regions of the brain. Its limited invasiveness and its proximity to the hypothalamus, pituitary, optic nerve and carotid artery make it the most challenging tumor in neurosurgery. The incidence of craniopharyngioma is 1.3 parts per million, which can occur in all age groups, showing a bimodal age distribution (5-14 years old and 50-74 years old).[1] However, the attention of

craniopharyngioma in adults is far less than that in children. Surgical treatment of craniopharyngioma is difficult, and the rate of disability and mortality after gross total resection (GTR) are very high, but the recurrence rate of subtotal resection (STR) was 50%-91%.[2-4] In recent years, more and more evidence shows that postoperative adjuvant radiotherapy (RT) for STR can achieve the same tumor control rate as GTR.[5-8] A recent SEER analysis including 1218 patients with craniopharyngiomas also demonstrated no significant difference in survival between RT, GTR and STR+ RT.[9] Conventional X-ray beam radiotherapy is difficult to achieve enough doses, and is prone to serious radiation-related toxicity, such as endocrine disorders, cognitive disorders, optic nerve injury and development of the second type of cancer.[10-12]

With the development of radiotherapy technology, PT has been increasingly used in the treatment of craniopharyngioma.[13-17] The physical properties of proton beam and Bragg peak phenomenon can reduce the damage to normal tissues and enlarge the damage to tumors, which has achieved good results.[18-21] But the optimal management of craniopharyngioma remains controversial. In view of the lack of comprehensive evaluation on the efficacy and safety of PT for craniopharyngiomas in adults, this study will comprehensively evaluate the tumor recurrence rate, median overall survival, progression-free survival (PFS) and treatment-related toxicity of PT for craniopharyngiomas in adults through systematic review and meta-analysis, so as to provide clinical basis for PT.

Objective

Our study will combine evidence/data from existing RCTs to determine whether PT is safe and effective in the treatment of adults with craniopharyngiomas.

METHODS AND ANALYSIS

This study will be written strictly according to the Preferred Reporting Items for Systematic Review and meta-analysis Protocols (PRISMA-P) guidelines.[22]

Inclusion and exclusion criteria

Types of study

Studies to be included should meet the following criteria:

(1) parallel-group RCTs; (2) Objective to evaluate the efficacy and safety of PT for craniopharyngioma in adults; (3) Studies with mixed population (ie including both adults and children) will be included in our study if the subgroup analysis of adults and children is carried out, otherwise it will be excluded; (4) Studies of patients who have received postoperative chemotherapy and previous radiotherapy will also be excluded, as this may affect our conclusions; (5) In addition, we will exclude studies that do not describe our outcome indicators such as the tumor recurrence rate, median overall survival, PFS and treatment-related toxicity; (6) There will be no restriction on language or publication status; (7) Repeated studies will retain the latest one.

Types of participants

The target population of this study is adults aged 18 or above at the time of diagnosis, who were pathologically confirmed to be free from serious postoperative complications, such as severe pulmonary infection, stroke and other complications that could affect survival time. The same cohort of patients were reported in more than one study, and we will keep the latest one. There will be no restriction of race, nationality, and source of participants.

Intervention

Our intervention is proton therapy as a treatment for craniopharyngioma in adults.

Comparator

Our comparator is conventional X-ray beam radiotherapy as a treatment for craniopharyngioma in adults.

Outcome

Primary outcome

Our primary outcome, tumor recurrence and survival, will be used to assess the safety and efficacy of PT for craniopharyngiomas in adults.

Evaluation indicators include：

(1) Tumor recurrence rate

(2) Median overall survival

(3) Progression-free survival

Secondary outcome

Our secondary outcome is an assessment of treatment-related toxicity (endocrine disorders, cognitive impairment, optic nerve injury and development of the second cancer).

Study design

Parallel-group RCTs of PT for craniopharyngioma in adults will be included.

Information sources

We will search 6 databases (MEDLINE, EMBASE, Web of Science, Cochrane Library, Amed, Scopus), clinical research registration websites (WHO ICTRP and ISRCTN Register) and grey literature (the Health Management Information Database, OpenSIGLE Database and the National Technical Information Service), aiming to identify randomized controlled trials (RCTs) on PT for craniopharyngioma in adults between 1 January 1954 and 28 September 2021.

Search strategy

Two researchers (KZ and JY) formulated the search strategy, and the search strategy was based on the keywords of this study (proton therapy, craniopharyngioma, and randomized controlled trial). Table 1 shows the search strategy for MEDLINE, and other database search strategies were adjusted slightly. Our search strategy will not be restricted by ethnicity of the target population or language of publication.

Table 1. Search strategy for MEDLINE

Number	Search items
1.	Craniopharyngioma/
2.	(Craniopharyngioma* or craniopharyngeoma* or pharyngioma* or pharyngeoma* or "craniopharyngioma*" or "craniopharyngeoma*").ti,ab,cl,oa,kw.
3.	((Rathke* or "craniopharyngeal duct*" or "dysodontogenic epithelial" or "hypophyseal duct*" or "third ventricle") adj3 (tumo?r* or adenoma* or microadenoma* or neoplasm* or lesion*)).ti,ab,cl,oa,kw.
4.	Or/1-3
5.	(Proton* or proton beam* or new radiation* or PT or PBT).ti,ab,cl,oa,kw.
6.	4 and 5
7.	Limit 6 to adult
8.	Remove duplicates from 7

Study records

Data management and Selection process

We will import all the retrieved studies into Endnote software (version X9). The selection process will be divided into two stages. In the first stage, two researchers (JW and HW) will independently read titles and abstracts in the software and classify all studies into three categories of "Yes", "No" and "Uncertainty" based on our inclusion and exclusion criteria, excluding "No". In the second stage, two researchers (SL and KZ) will independently read the full text of "Yes" and "Uncertainty" and exclude inappropriate studies. The reasons for exclusion will be recorded in detail. If there is any controversy during this period, the decision will be discussed and made by four researchers (JW, HW, SL, KZ) together.

Data collection process

Two researchers (KZ and JY) will independently collect the data included in the study. Data collection will be divided into four parts. In the first part, the characteristics of the study include study author, publication date, journal name and country. In the second part, the characteristics of participants include gender, age and type of operation. The third part, intervention and control information, the more detailed the better. The fourth part, outcome and follow-up information. The third researcher (HW) will be responsible for examining the information collected and, if necessary, contact the author of the study newsletter for further information.

Risk of bias

Two researchers (PL and TZ) will use the Cochrane tool for assessing risk of bias in randomised trials 2 (RoB 2) to evaluate the quality of included RCTs, which is divided into five domains of bias (bias from the randomization process, bias due to deviations from intensified inter events, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result).[23] In each domain, a series of questions (signalling questions) need to be answered to obtain information on characteristics relevant to the study and a risk of bias calculated for each domain to ultimately obtain the full text of the risk of bias judgement (low risk of bias, some concerns, high risk of bias). If there is any dispute, the third researcher (AA) will participate in the discussion and settlement.

Measures of treatment effect

We will use RevMan 5.2 for data synthesis and analysis. Dichotomous data will be analyzed using a risk ratio with 95% CIs. For continuous outcomes data, the mean difference with 95% CIs will be used for analysis.

Assessment of heterogeneity

We will use the Mantel-Haenszel χ^2 test and I square (I^2) statistic of homogeneity by RevMan 5.2. According to the Cochrane Handbook, I^2 value can be used to evaluate heterogeneity. 0%-40%: might not be important ; 30%–60%: may represent moderate heterogeneity; 50%–90%:may represent substantial heterogeneity; 75%-100%: considerable heterogeneity.[24] When

P<0.10 and I^2>50%, there is obvious heterogeneity. I^2>50% and P<0.10 showed significant statistical heterogeneity.

Data synthesis

We will combine three or more studies for meta-analysis using random-effect model. Heterogeneity will be judged by I^2. If meta-analysis is not feasible due to clinical and methodological heterogeneity, the results will be summarized qualitatively.

Assessment of reporting biases

When the number of included studies reaches 10 or more, we will create a funnel plot of the outcome and evaluate whether there is a reporting bias based on its symmetry.

Subgroup analysis

We will conduct the following subgroup analysis to assess potential heterogeneity.

1.The classification of craniopharyngioma (eg, adamantinomatous croniopharyngioma, ACP and papillary croniopharyngioma, PCP).[25-26]

2. The location of craniopharyngioma. (eg, QST classification system).[27]

3. The tumor size of craniopharyngioma (eg, greater than 4cm and less than 4cm).[28]

Sensitivity analysis

We will conduct a sensitivity analysis to assess the reliability of the meta-analysis by excluding studies with high risk of bias or missing reported data.

Patient and public involvement

No patient is involved in either the design or planning phase of this study.

Ethics and dissemination.

Our study does not involve individual patients, so there is no need for ethical approval. The results of this study will be published in peer-reviewed journals or related conferences to evaluate the efficacy and safety of PT for craniopharyngiomas in adults.

DISCUSSION

PT is an advanced radiotherapy method with less toxicity and better therapeutic effect than traditional X-ray radiotherapy.[29] At present, PT has become an international focus and emphasis on tumor radiotherapy technology. The medical application of proton beam was first proposed by Wilson in 1946.[30] In 1954, Tobias and others carried out the first PT in the world at Lawrence Berkeley National Laboratory at the University of California,and since then, Sweden, the former Soviet Union and other countries have successively carried out clinical studies on PT. According to Particle Therapy Co-Operative Group PTCOG, nearly 100 medical institutions around the world are currently using proton and heavy ion radiotherapy technology to implement tumor treatment, and there are more than 100 proton radiotherapy centers under construction, and nearly 200000 patients have received proton radiotherapy worldwide.[31]

The main techniques of PT for tumor treatment are active scanning and passive scattering. The Bragg peak of proton is obtained by modulator and collimator. At present, the common treatment methods of proton used in clinical tumor radiotherapy in the world are as follows: ① proton point scan irradiation, to achieve precise control of tumor, but the operation process is more complex; ② proton stereotactic radiotherapy, the main treatments of which are target area high-dose irradiation and fractional irradiation, with a limited clinical application; ③ intensity-modulated proton therapy(IMPT), realizes dose intensity modulation and optimizes dose distribution, especially the application of pen beam scanning in impt, which avoids or reduces the radiation dose to surrounding normal tissues. In the treatment of head and neck tumors, PT can increase the radiation dose of the target area and reduce the toxicity of organs.[32-34]

The new version of the 2018 National Comprehensive Cancer Network guidelines takes PT as one of the standard treatments for head and neck cancer.[35] A European center study of 18

patients with craniopharyngiomas who received PT found that one patient progressed 8.7 months after PT and then underwent surgery. Of the remaining patients at 18.4 months, 5 patients had complete remission, 4 patients had partial remission, 7 patients had stable disease, and there was no serious treatment-related toxicity during the treatment.[17] Weber et al. Included 16 patients with craniopharyngioma, and finally analyzed 15 patients, showing a 3 year overall survival rate of 75%. While PT has similar efficacy to conventional X-ray radiotherapy, it is more protective to the temporal lobe and hippocampal formation.[36]

At present, there is a lack of comprehensive review on the efficacy and safety of PT for adults with craniopharyngioma, therefore, our study will comprehensively evaluate the recurrence rate, survival, and treatment-related toxicity of PT for adults with craniopharyngioma through a systematic review and meta-analysis to provide a clinical basis for PT.

Contributors PL conceived the original idea for this systematic review. PL and JW drafted the manuscript. AA, KZ, JY, HW, SL and TZ revised the manuscript. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Conflict of interest The authors declare no conflicts of interest.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	/
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	/
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4-5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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