BMJ Open

Incidence of hypopituitarism in adults undergoing radiotherapy for neck and head cancer: protocol for a systematic review and meta-analysis

Shamir Barros-Sevillano,[1,2] Miguel Cabanillas-Lazo,[3] Franshesca L Sedano-Chiroque,[2] Camila Escajadillo-Vergara,[4] David Espinoza-Martinez ,[1,2] Isabel Pinedo-Torres[5]

To cite: Barros-Sevillano S, Cabanillas-Lazo M, Sedano-Chiroque FL, *et al*. Incidence of hypopituitarism in adults undergoing radiotherapy for neck and head cancer: protocol for a systematic review and meta-analysis. *BMJ Open* 2024;**14**:e078595. doi:10.1136/bmjopen-2023-078595

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-078595).

Received 06 August 2023
Accepted 21 March 2024

For numbered affiliations see end of article.

Correspondence to
Shamir Barros-Sevillano;
Shamir.bs17@gmail.com

ABSTRACT

Introduction When children with head and neck cancer receive radiation therapy as part of their treatment, a considerable frequency of hypopituitarism has been recognised. However, in adults, it has been little studied and it is possible that patients may be inadvertently affected. The objective is to estimate the incidence of anterior pituitary dysfunction in adults undergoing radiotherapy for head and neck cancer.

Methods and analysis A total of five databases will be used to perform the document search: PubMed, Scopus, Web of Science (Core Collection), Ovid-MEDLINE and Embase. Cohort studies will be included without restriction by language or date. The main outcome will be the incidence of adenohypophyseal dysfunction for each axis: prolactin, growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, luteinising hormone and follicle-stimulating hormone. Incidence meta-analysis will be performed using the Freeman-Tukey double arcsine method. In addition, a random-effects model will be used along with a 95% CI. Subgroup analyses will be performed according to tumour location, radiation dose and endocrine assessment time. Meta-regression will be applied according to patient's age and time elapsed until diagnosis.

Ethics and disclosure Since this will be a systematic review of published data, no ethics committee approval is required. The results will be presented at conferences and finally published in a peer-reviewed journal.

PROSPERO registration number CRD42021235163.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prior exploration, this is the first systematic review to evaluate the overall incidence of hypopituitarism after head and neck radiation in adult patients.
⇒ There are no concise guidelines for endocrine monitoring in adult patients. The results of the systematic review could help to determine the magnitude of the problem and encourage greater awareness for timely diagnosis and treatment.
⇒ In the quantitative synthesis, the certainty of incidence of the included studies will be evaluated. The Grading of Recommendation, Assessment, Development and Evaluation tool will be used.
⇒ There may be significant variations between studies due to sample size, follow-up time, age and dose. However, to try to control for this heterogeneity, subgroup analysis, sensitivity analysis and logistic regression will be used.

INTRODUCTION

In recent decades, cancer survival rates have steadily increased due to advances in early diagnosis and treatment.[1] However, multiple endocrine functions may be affected after cranial radiation therapy (CRT).[2 3] Hypothalamic–pituitary dysfunction is one of the most frequent endocrine late effects after CTR.[4–7] The risk will clearly depend on the total radiation dose applied and the irradiation field,[3] with the somatotrophic axis being the most frequently affected, giving symptoms related to growth hormone (GH) deficiency. Likewise, the gonadotrophic axis usually presents symptomatology due to luteinising hormone (LH) and follicle-stimulating hormone (FSH) deficiency.[8] There are radiotherapeutic technologies that offer new alternatives to improve the prognosis of these patients,[2–5] radiosurgery, linear accelerator mounted on a robotic arm and proton beam therapy are possible techniques to reduce radiation to unwanted areas,[3] however, many of them are not within the reach of the vast majority of countries.

It is important to see the epidemiological issue in this topic. Incidence and prevalence studies show a framework of reality in order to see the burden of disease to plan the management of comorbidity services, determine priorities regarding public health initiatives, assess temporal changes and disease trends.[8] For pituitary dysfunction due to RTC, little is known about the burden across groups in

many countries, according to dose, time of assessment and other important parameters. However, the reported prevalence and incidence changes significantly between each study and is significantly increasing over the years.[2–7] Therefore, a synthesis may be useful in these cases to provide a more integrated view of the incidence of this specific issue.

Pituitary insufficiency following CRT in children is a better known complication. Until recently, recommendations for screening for pituitary dysfunction after the event were incorporated.[9 10] It has been reported to affect up to 50% of childhood cancer survivors.[11] There is an established high incidence of pituitary insufficiency after exposure to intracranial irradiation for brain or nasopharyngeal tumours, including total body irradiation for haematological malignancies.[12–16] Consequently, there are strict and specific recommendations for children for long-term follow-up up to 10 years after exposure to radiotherapy.[3]

Up to date, as reported by one study, the prevalence of any form of hypopituitarism after CRT is 66% in adults. However, depending on the study, it can vary from almost no cases presented to 100% of affected patients.[6] Despite this, there are currently no endocrine surveillance guidelines for adult patients, but there are guidelines for the paediatric population.[10] Therefore, it is likely that an increasing number of adult patients will also be affected by endocrine complications of cranial irradiation, given the limited guidelines for this population.[11]

Endocrine dysfunction can lead to a reduction in the quality of life, in addition to a possible radiation-induced neurocognitive degeneration,[17] therefore, even adult patients with a limited life expectancy could benefit from a respective follow-up. The improvement of the guidelines in a global analysis on the information obtained from each of the studies for the improvement of each of the aspects of the disease, as well as the sociopolitical aspects that should take relevance in this subject.

Therefore, the main objective of this systematic review will be to estimate the incidence of anterior pituitary dysfunction in patients adults undergoing radiotherapy for head and neck cancer.

METHODS AND ANALYSIS

Protocol and registration

This will be a systematic review that will be prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocol 2015 guidelines (online supplemental material 1).[18] The recommendations for the development of systematic reviews of incidence and prevalence from the Joanna Briggs Institute will also be followed.[19] The protocol was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO)[20] under registration number CRD42021235163. This study is scheduled to be conducted in January 2024 and concluded in June of the same year.

Eligibility criteria

Studies that meet the following criteria will be included: (1) Cohort studies (retrospective, prospective or mixed). For studies with the same cohort of patients, only the article with the longest duration of follow-up will be included. (2) Adult patients (≥18 years) at the time of radiotherapy. In cases of mixed population studies, the population will be separated if possible. (3) Patients diagnosed with any type of head and/or neck cancer. (4) Survivors of their external radiotherapy treatment. In case of combination of treatments, only if radiotherapy was described as the main treatment will be included. (5) Studies that evaluated the incidence of anterior pituitary dysfunction defined as partial or complete loss of production of one or more anterior pituitary hormones.

On the other hand, the following studies will be excluded: (1) Patients surviving radiotherapy secondary to pituitary tumours. (2) Unclear diagnostic criteria in which the methods are not detailed. (3) All secondary literature sources, including clinical guidelines, reviews, editorials, dissertations, theses and protocol studies.

Information source

Bibliographic searches will be performed in five international databases: PubMed, Scopus, Web of Science (Core Collection), Ovid-MEDLINE and Embase. As recommended by the Cochrane guidelines,[21] we will also manually search the reference lists of studies and similar review articles to identify other potential studies. Additional information sources, such as Google Scholar and OpenGrey, will complement the search for sources of the critical literature.

Search strategy

The search strategy for each database is detailed in online supplemental material 2. If necessary, the results will be updated if more than 1 year has elapsed since the last search. Initially, the existence of controlled descriptors such as MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors) terms, Emtree and their synonyms (keywords) will be extracted in each database. The second stage will involve of conducting additional searches combining terms related to hypopituitarism using truncation and spelling variations, using wildcards. Search terms will be combined using the Boolean operators ‘AND’ and ‘OR’. They will not be restricted by language or date of publication.

Data management and selection process

One of the authors (SB-S) will be responsible for storing, organising and managing all references and ensuring a systematic and exhaustive search using EndNote online bibliographic software. He will also be responsible for identifying and eliminating duplicate studies in the results.

Two authors (SB-S and MC-L) will independently review the articles by title and abstract according to the inclusion and exclusion criteria using the rayyan platform

(rayyan-qcri.org) to select potentially relevant studies. Subsequently, the same authors will evaluate the full-text articles to finally analyse whether they entered the study. Discrepancies will be referred to a third author (IP-T) to reach a consensus. A comprehensive record of articles that will not be included in the full-text study review will be provided in online supplemental material. The study selection process and results will be recorded in the PRISMA flow chart.

Data extraction and management

Two authors (SB-S and MC-L) will extract data independently using previously prepared Microsoft Excel 2022 spreadsheets. Again, discrepancies will be consulted with another author (IP-T) who will also review the articles and data extractions to avoid duplication of information.

Data extracted from each study will be author/year of publication, country of study, study design, randomisation, total number of participants, age, sex, tumour location, type of radiotherapy, overall radiation dose, radiation dose to pituitary region, time of radiotherapy, time from last radiotherapy to endocrine evaluation, diagnostic tests for endocrine evaluation and number of patients with pituitary dysfunction by GH, FSH/LH, adrenocorticotropic hormone, thyroid-stimulating hormone and prolactin axis (main outcome).

Assessment of risk of bias in included studies

Two independent investigators (SB-S and CPS) will evaluate the methodological well-being of each cohort study using the Newcastle-Otawa Scale (NOS). One point will be awarded for each item, except for comparability, where up to two points will be awarded. In awarding the NOS, a maximum score of 9 points, a score ≥7 points will be considered a low risk of bias and a score ≤6 a high risk of bias.[22] In case of disagreement, a resolution will be reached by consensus.

Statistical analysis

Prevalence and incidence data are often presented as proportions. To perform a meta-analysis combining these proportions, it is necessary to transform the data. Freeman-Tukey transformation will be chosen, also known as the arcsine square root transformation, because of its ability to effectively stabilise the variance and solve the problem of confidence limits that extend beyond the interval 0–1.[23]

A random-effects model based on the method described by DerSimonian and Laird together with a 95% CI according to the exact method will be used to report the cumulative incidence of anterior hypopituitarism secondary to CRT. This model will be chosen because it allows the variation between studies by assuming that the incidence estimates of individual studies follow a normal distribution.[24] The results will be presented graphically in a forest diagram.

Furthermore, we will execute univariate random-effects meta-regression analysis to assess study-level moderators. Heterogeneity among studies will be statistically assessed with the χ^2,[25] where a $p<0.05$ will indicate significant heterogeneity among studies. To quantify heterogeneity, the Higgins I^2 statistic[26] will be used, where an $I^2<30$ %, I^2 30%–60% and $I^2 > 60$% will define low, moderate and high heterogeneity, respectively. The calculation of the I^2 statistic will be performed only within a subgroup formed by four or more studies, following the recommendation of previous research,[27 28] because small-scale meta-analyses tend to underestimate the level of heterogeneity. For meta-analyses comprising fewer than four studies, heterogeneity will be assessed by a visual assessment examining the overlap of CI. In addition, to assess the trend of the pooled incidence estimate over time, a cumulative random-effects meta-analysis based on the year of publication will be applied.

A subgroup analysis will be performed to assess sources of heterogeneity among primary studies according to tumour location (nasopharyngeal vs intracerebral), radiation dose (20–40, 41–60 and >60 Gy), time from last radiotherapy to endocrine evaluation (0–5, 6–10 and >10 years) and diagnostic tests for endocrine evaluation (serum, urine and others). This subgroup analysis may involve additional regression analyses to explore relationships between these factors and the observed heterogeneity.

Sensitivity analysis will be used to assess the robustness of the final estimates by examining the influence of any individual study, calculating the cumulative incidence according to the risk of bias of the studies (low-moderate and high risk of bias), the type of study (retrospective vs prospective) and the type of sampling of the studies (randomised vs non-randomised).

Publication bias will be assessed visually using Deek's funnel graph. In addition, Egger's regression test and the trim-and-fill method will be used to calculate the final linear estimator. All analyses will be performed with Stata V.15.1 (StataCorp).

If the material to be analysed is not appropriate for a meta-analysis, the most valuable information from each study will be described qualitatively. Also, if possible, comparison tables will be made to group and better understand the differences or similarities regarding the main and secondary outcome.

Evaluation of certainty of the evidence

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE)[29] tool will be used. This critical appraisal will be based on considerations such as study design, inconsistency, indirectness, imprecision and publication bias, as outlined in the GRADE manual.[30] The assessment will be adapted to frequency estimates. Certainty will be determined as very low, low, moderate or high. Results will be reported in the form of a summary results table, performed in the GRADE online tool (http://gradepro.org).

Ethics and diffusion

Ethical approval will be not required for this study as data will be obtained from already published literature. Once

the systematic review is completed, the preliminary findings will be disseminated at congresses and subsequently the final results in a peer-reviewed medical journal.

Patient and public involvement

There will be no involvement of patients or the public in the current study.

DISCUSSION

The treatment of head and neck cancer represents a clinical challenge due to adverse effects. Radiotherapy directed to this area can have a negative impact on the function of the pituitary gland, leading to the development of hypopituitarism.[4] However, to date, there is a lack of accurate data on the incidence of this specific complication in adult patients undergoing radiotherapy to this anatomical region.

Understanding the incidence of hypopituitarism in this setting would allow us to identify the frequency of patients at risk of developing this condition and, therefore, to optimise medical care and therapeutic management.[11] Because hypopituitarism can have significant consequences for quality of life and long-term health,[8] it is fundamental to develop appropriate prevention and follow-up strategies for this population.

On the other hand, defining the incidence of hypopituitarism in adult patients would provide a solid basis for future research. These studies could focus on developing early preventive and therapeutic interventions specific to hypopituitarism, as well as identifying modifiable risk factors that could be addressed to reduce the incidence of this complication.

Consequently, this research is crucial to fill the current knowledge gap. It will provide vital information for determining the current burden, prioritising medical care, planning future research and implementing effective precautionary measures.

This study has some probable limitations. First, the available data could be subject to reporting bias due to differences in diagnostic criteria, clinical practices or lack of standardisation. However, specific and well-defined selection criteria will help reduce bias and improve representativeness. Second, radiotherapy treatment may vary in terms of dose, fractionation and timing, as well as patients' own characteristics. These variabilities could influence the incidence of hypopituitarism. Nevertheless, patients will be grouped into subgroups with similar characteristics and stratified or subgroup analyses will be performed.

Author affiliations
[1]Facultad de Ciencias de la Salud, Escuela de Medicina, Universidad César Vallejo, Trujillo, Peru
[2]Sociedad Científica de Estudiantes de Medicina de la Universidad César Vallejo, Trujillo, Peru
[3]Sociedad Científica de San Fernando, Universidad Nacional Mayor de San Marcos, Lima, Peru
[4]Facultad de Ciencias de la Salud, Escuela Profesional de Medicina, Universidad Privada de Tacna, Tacna, Peru
[5]Universidad Científica del Sur, Lima, Peru

Contributors SB-S, MC-L, FLS-C, CE-V, DE-M and IP-T contributed to the conception, design, data collection, data interpretation and manuscript drafting. All authors approved the final version of the manuscript and reached a consensus on all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
David Espinoza-Martinez http://orcid.org/0000-0002-1166-2531

REFERENCES

1 Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: a population-based study. *Lancet* 2015;385:1206–18.
2 Darzy KH, Shalet SM. Hypopituitarism following radiotherapy. *Pituitary* 2009;12:40–50.
3 Pekic S, Miljic D, Popovic V, *et al*. Endotext. South Dartmouth (MA): MDText.com, Inc, 2000. Available: http://www.ncbi.nlm.nih.gov/books/NBK532082/
4 Sathyapalan T, Dixit S. Radiotherapy-induced hypopituitarism: a review. *Expert Rev Anticancer Ther* 2012;12:669–83.
5 Ipekci SH, Cakir M, Kiyici A, *et al*. Radiotherapy-induced hypopituitarism in nasopharyngeal carcinoma: the tip of an iceberg. *Exp Clin Endocrinol Diabetes* 2015;123:411–8.
6 Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, *et al*. Pituitary dysfunction in adult patients after cranial radiotherapy systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:2330–40.
7 Appelman-Dijkstra NM, Malgo F, Neelis KJ, *et al*. Pituitary dysfunction in adult patients after cranial irradiation for head and nasopharyngeal tumours. *Radiother Oncol* 2014;113:102–7.
8 Sociedad Argentina de Endocrinología. Secuelas Endocrinológicas del Tratamiento de Las Enfermedades Oncológicas en La Infancia Y Adolescencia. *Rev Argent Endocrinol Metab* 2009;24–38. Available: https://pesquisa.bvsalud.org/portal/resource/pt/lil-641948
9 Chemaitilly W, Cohen LE. Diagnosis of endocrine disease: endocrine late-effects of childhood cancer and its treatments. *Eur J Endocrinol* 2017;176:R183–203.
10 Sklar CA, Antal Z, Chemaitilly W, *et al*. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2018;103:2761–84.
11 Gebauer J, Higham C, Langer T, *et al*. Long-term endocrine and metabolic consequences of cancer treatment: a systematic review. *Endocr Rev* 2019;40:711–67.
12 Shalet SM, Beardwell CG, Jones PH, *et al*. Growth hormone deficiency after treatment of acute leukaemia in children. *Arch Dis Child* 1976;51:489–93.

13 Oeffinger KC, Mertens AC, Sklar CA, *et al*. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355:1572–82.
14 Alvarez JA, Scully RE, Miller TL, *et al*. Long-term effects of treatments for childhood cancers. *Curr Opin Pediatr* 2007;19:23–31.
15 Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, *et al*. Assessment of the hypothalamo-pituitary-adrenal axis in patients treated with radiotherapy and chemotherapy for childhood brain tumor. *J Clin Endocrinol Metab* 2003;88:3149–54.
16 Constine LS, Woolf PD, Cann D, *et al*. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med* 1993;328:87–94.
17 Gondi V, Pugh SL, Tome WA, *et al*. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014;32:3810–6.
18 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement | EQUATOR network. 2015. Available: https://www.equator-network.org/reporting-guidelines/prisma-protocols/
19 Munn Z, Moola S, Lisy K, *et al*. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015;13:147–53.
20 Schiavo JH. PROSPERO: an international register of systematic review protocols. *Med Ref Serv Q* 2019;38:171–80.
21 James T. Cochrane handbook for systematic reviews of interventions [Internet], 2. Wiley, 2019:728.Available: https://training.cochrane.org/handbook/archive/v5.1/
22 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
23 Barendregt JJ, Doi SA, Lee YY, *et al*. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67:974–8.
24 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
25 Deeks JJ, Higgins JP, Altman DG, *et al*. Analysing data and undertaking meta-analyses. En: cochrane handbook for systematic reviews of interventions. John Wiley & Sons, Ltd, 2019. Available: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.ch10
26 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
27 Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014;72:39.
28 von Hippel PT. The heterogeneity statistic I2 can be biased in small meta-analyses. *BMC Med Res Methodol* 2015;15:35.
29 Balshem H, Helfand M, Schünemann HJ, *et al*. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.
30 Schünemann H, Brożek J, Guyatt G, eds. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, 2013. Available: https://gdt.gradepro.org/app/handbook/handbook.html