

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

SUPPLEMENTARY MATERIAL

Supplementary Material 1. Checklist of PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols).

Section and topic	Item No	Checklist item	Part of the protocol reporting
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Described in the title (page 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	Described in the study design (page 4)
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Described on the first page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	-
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	Described in the "funding statement" section (page 13)
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of the sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Described in the Introduction (page 3)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Described at the end of the Introduction (page 4)
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.	Described in the eligibility criteria section (page 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	Described in the information source section (page 5)
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	Described in the search strategy (page 5)
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Described in the data management and selection process section (page 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)	Described in the data management and selection process section. (page 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	Described in the section on data extraction and management (page 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	Described in the data extraction section (page 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	Described in the section on data extraction and management (page 6)
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	Described in the risk of bias assessment section (page 6)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Described in the statistical analysis section (page 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)	Described in the statistical analysis section (page 7)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Described in the statistical analysis section (page 7)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Described in the section on statistical analysis (page 7)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Described in the section on assessment of risk of bias in included studies. (page 6)

Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	Described in the section on assessing the certainty of the evidence (page 7)
-----------------------------------	---	--

Supplementary Material 2. Search strategy for each database.

Database	Search strategy	Results
PubMed	<p>#1 (((cancer[TI] OR neoplas*[TI] OR malignant[TI] OR malignancy[TI] OR carcinoma*[TI] OR tumor*[TI] OR tumour*[TI]) AND (Esophageal[TI] OR Facial[TI] OR eyelid[TI] OR mouth[TI] OR gingival[TI] OR palatal[TI] OR "Salivary Gland"[TI] OR Tongue[TI] OR otorhinolaryngologic[TI] OR Ear[TI] OR Laryngeal[TI] OR Nose[TI] OR pharyngeal[TI] OR parathyroid[TI] OR thyroid[TI] OR Tracheal[TI] OR brain[TI])) OR ("Brain Neoplasms"[mesh] NOT "Pituitary Neoplasms"[mesh]) OR "Head and Neck Neoplasms"[Mh] OR "brain tumor*"[TIAB] OR "intracranial tumor*"[TIAB] OR "cranial tumor*"[TIAB] OR "cerebral tumor*"[TIAB] OR "Nasopharyngeal Neoplasms"[mesh] OR "Nasopharynx Neoplasms"[TIAB] OR "Esophageal Neoplasms"[Mh] OR "Esophageal Squamous Cell Carcinoma"[Mesh] OR "Facial Neoplasms"[Mh] OR "Eyelid Neoplasms"[Mh] OR "Mouth Neoplasms"[Mh] OR "Gingival Neoplasms"[Mh] OR "Leukoplakia Oral"[Mh] OR "Lip Neoplasms"[Mh] OR "Palatal Neoplasms"[Mh] OR "Salivary Gland Neoplasms"[Mh] OR "Tongue Neoplasms"[Mh] OR "Otorhinolaryngologic Neoplasms"[Mh] OR "Ear Neoplasms"[Mh] OR "Laryngeal Neoplasms"[Mh] OR "Nose Neoplasms"[Mh] OR "Pharyngeal Neoplasms"[Mh] OR "Parathyroid Neoplasms"[Mh] OR "Squamous Cell Carcinoma of Head and Neck"[Mh] OR "Thyroid Neoplasms"[Mh] OR "Thyroid Cancer Papillary"[Mh] OR "Thyroid Nodule"[Mh] OR "Tracheal Neoplasms"[Mh] OR "Esophageal Neoplasms"[TIAB] OR "Esophageal Squamous Cell Carcinoma"[Mesh] OR "Facial Neoplasms"[Title/Abstract] OR "Eyelid Neoplasms"[TIAB] OR "Mouth Neoplasms"[TIAB] OR "Gingival Neoplasms"[TIAB] OR "Leukoplakia Oral"[TIAB] OR "Lip Neoplasms"[TIAB] OR "Palatal Neoplasms"[TIAB] OR "Salivary Gland Neoplasms"[TIAB] OR "Tongue Neoplasms"[TIAB] OR "Otorhinolaryngologic Neoplasms"[TIAB] OR "Ear Neoplasms"[TIAB] OR "Laryngeal Neoplasms"[TIAB] OR "Nose Neoplasms"[TIAB] OR "Pharyngeal Neoplasms"[TIAB] OR "Parathyroid Neoplasms"[TIAB] OR "Squamous Cell Carcinoma of Head and Neck"[TIAB] OR "Thyroid Neoplasms"[TIAB] OR "Thyroid Cancer Papillary"[TIAB] OR "Thyroid Nodule"[TIAB] OR "Tracheal Neoplasms"[TIAB])</p> <p>#2 ("radiotherapy"[MeSH] OR radiotherapy*[Tiab] OR radiotherapy*[OT] OR Radiotherapies[Tiab] OR "Radiation Therap*"[Tiab] OR "Radiation Treatment*"[Tiab] OR "Targeted Radiotherap*"[Tiab] OR Brachytherapy[Mh] OR "Cranial Irradiation"[Mh] OR "Heavy Ion Radiotherapy"[Mh] OR "Proton Therapy"[Mh] OR "Lymphatic Irradiation"[Mh] OR "Radioimmunotherapy"[Mh] OR "Radiosurgery"[Mh] OR "Radiotherapy Dosage"[Mh] OR "Dose Fractionation Radiation"[Mh] OR "Radiotherapy Setup Errors"[Mh] OR "Radiotherapy Computer-Assisted"[Mh] OR "Radiotherapy Conformal"[Mh] OR "Radiotherapy High-Energy"[Mh] OR "Neutron Capture Therapy"[Mh] OR "Radioisotope Teletherapy"[Mh] OR "Radiotherapy Image-Guided"[Mh] OR "Re-Irradiation"[Mh] OR "X-Ray Therapy"[Mh] OR "Whole brain radiotherapy"[OT])</p> <p>#3 (Hypopituitarism[Mh] OR Hypopituitarism[TIAB] OR Hypopituitarism[OT] OR "radiation-induced hypopituitarism"[OT] OR "Pituitary insufficiency"[TIAB] OR "pituitary hormone deficiency"[OT] OR "pituitary gland"[Mh] OR "pituitary glands"[TIAB] OR "pituitary gland"[TIAB] OR "pituitary function"[TIAB] OR hypophysis[TIAB] OR Corticotrophs[TIAB] OR Gonadotrophs[TIAB] OR "Gonadotrophin deficiency"[TIAB] OR Lactotrophs[TIAB] OR Somatotrophs[TIAB] OR Thyrotrophs[TIAB] OR "Pituitary Function Tests"[mesh] OR "pituitary axis"[TIAB] OR "endocrine late effects"[OT] OR "hypothalamic-pituitary dysfunction"[OT] OR "growth hormone deficiency"[OT] OR "GH deficiency"[TIAB] OR "hypophyseal insufficiency"[TIAB] OR "hypophysis deficiency"[TIAB] OR "hypophysis failure"[TIAB] OR "hypophysis hypofunction"[TIAB] OR "hypophysis insufficiency"[TIAB] OR "hypopituitarism"[TIAB] OR Panhypopituitarism[TIAB] OR "pituitary failur"[TIAB] OR "pituitary gland failure"[TIAB] OR "pituitary hypofunction" OR "secondary hypopituitarism"[TIAB] OR "Growth Hormone"[Mh] OR "Human Growth Hormone"[Mh] OR "Growth Hormone-Secreting Pituitary Adenoma"[Mh] OR "Pituitary Growth Hormone"[TIAB] OR "Somatotropin"[TIAB] OR "Growth Hormone Pituitary"[TIAB] OR "Recombinant Growth Hormone"[TIAB] OR</p>	<p>485 130</p> <p>342 296</p> <p>198 004</p>

	<p>“Recombinant Somatotropin”[TIAB] OR “Adrenocorticotrophic Hormone”[Mh] OR thyrotropin [TIAB] OR “thyroid stimulating hormone”[TIAB])</p> <p>*#1 AND #2 AND #3</p>	742
Scopus	<p>#1 TITLE((cancer OR neoplas* OR malignant OR malignancy OR carcinoma* OR tumor* OR tumour*) AND (Esophageal OR Facial OR eyelid OR mouth OR gingival OR palatal OR “Salivary Gland” OR Tongue OR otorhinolaryngologic OR Ear OR Laryngeal OR Nose OR pharyngeal OR parathyroid OR thyroid OR Tracheal OR brain OR intracerebral OR intracranial OR nasopharyngeal)) OR TITLE-ABS-KEY(("Brain Neoplasms" OR "Head and Neck Neoplasms" OR "brain tumor*" OR "intracranial tumor*" OR "intracerebral tumor*" OR "cranial tumor*" OR "cerebral tumor*") AND NOT ("Pituitary Neoplasms")) OR TITLE-ABS-KEY("Nasopharyngeal Neoplasms" OR "Nasopharynx Neoplasms" OR "Esophageal Neoplasms" OR "Esophageal Squamous Cell Carcinoma" OR "Facial Neoplasms" OR "Eyelid Neoplasms" OR "Mouth Neoplasms" OR "Gingival Neoplasms" OR "Leukoplakia Oral" OR "Lip Neoplasms" OR "Palatal Neoplasms" OR "Salivary Gland Neoplasms" OR "Tongue Neoplasms" OR "Otorhinolaryngologic Neoplasms" OR "Ear Neoplasms" OR "Laryngeal Neoplasms" OR "Nose Neoplasms" OR "Pharyngeal Neoplasms" OR "Parathyroid Neoplasms" OR "Squamous Cell Carcinoma of Head and Neck" OR "Thyroid Neoplasms" OR "Thyroid Cancer Papillary" OR "Thyroid Nodule" OR "Tracheal Neoplasms")</p> <p>#2 TITLE-ABS-KEY(radiotherap* OR “Radiation Therap*” OR “Radiation Treatment*” OR “Targeted Radiotherap*” OR “Radiation w/3 Therap*” OR Brachytherapy OR “Cranial Irradiation” OR “Heavy Ion Radiotherapy” OR “Proton Therapy” OR “Radiotherapy Dosage” OR “Dose Fractionation Radiation” OR “Radiotherapy Setup Errors” OR “Radiotherapy Computer-Assisted” OR “Radiotherapy Conformal” OR “Radiotherapy High-Energy” OR “Neutron Capture Therapy” OR “Radioisotope Teletherapy” OR “Radiotherapy Image-Guided” OR “Re-Irradiation” OR “X-Ray Therapy” OR “Whole brain radiotherapy”)</p> <p>#3 TITLE-ABS-KEY(Hypopituitarism OR “hypophysis hypofunction” OR “pituitary gland failur” OR “hypophysis failure” OR “radiation-induced hypopituitarism” OR “Pituitary insufficiency” OR “pituitary hormone deficiency” OR "pituitary gland*" OR "pituitary function“ OR hypophysis OR Corticotrophs OR Gonadotrophs OR “Gonadotrophin deficiency” OR "Pituitary Function Tests" OR “pituitary axis” OR “endocrine late effects” OR “hypothalamic-pituitary dysfunction” OR “Pituitary Dysfunction” OR “growth hormone deficiency” OR “GH deficiency”)</p> <p>*#1 AND #2 AND #3</p>	471 383 484 377 175 756 1 098
WoS (Core Collection)	<p>#1 TI=((cancer OR neoplas* OR malignant OR malignancy OR carcinoma* OR tumor* OR tumour*) AND (Esophageal OR Facial OR eyelid OR mouth OR gingival OR palatal OR “Salivary Gland” OR Tongue OR otorhinolaryngologic OR Ear OR Laryngeal OR Nose OR pharyngeal OR parathyroid OR thyroid OR Tracheal OR brain OR intracerebral OR intracranial OR nasopharyngeal)) OR TS=(("Brain Neoplasms" OR "Head and Neck Neoplasms" OR "brain tumor*" OR "intracranial tumor*" OR "intracerebral tumor*" OR "cranial tumor*" OR "cerebral tumor*") NOT ("Pituitary Neoplasms")) OR TS=(("Nasopharyngeal Neoplasms" OR "Nasopharynx Neoplasms" OR "Esophageal Neoplasms" OR "Esophageal Squamous Cell Carcinoma" OR "Facial Neoplasms" OR "Eyelid Neoplasms" OR "Mouth Neoplasms" OR "Gingival Neoplasms" OR "Leukoplakia Oral" OR "Lip Neoplasms" OR "Palatal Neoplasms" OR "Salivary Gland Neoplasms" OR "Tongue Neoplasms" OR "Otorhinolaryngologic Neoplasms" OR "Ear Neoplasms" OR "Laryngeal Neoplasms" OR "Nose Neoplasms" OR "Pharyngeal Neoplasms" OR "Parathyroid Neoplasms" OR "Squamous Cell Carcinoma of Head and Neck" OR "Thyroid Neoplasms" OR "Thyroid Cancer Papillary" OR "Thyroid Nodule" OR "Tracheal Neoplasms")</p> <p>#2 TS=(radiotherap* OR “Radiation Therap*” OR “Radiation Treatment*” OR “Targeted Radiotherap*” OR “Radiation NEAR/3 Therapy” OR Brachytherapy OR “Cranial Irradiation” OR “Heavy Ion Radiotherapy” OR “Proton Therapy” OR “Radiotherapy Dosage” OR “Dose Fractionation Radiation” OR “Radiotherapy Setup Errors” OR “Radiotherapy Computer-Assisted” OR “Radiotherapy Conformal” OR “Radiotherapy High-Energy” OR “Neutron Capture Therapy” OR “Radioisotope Teletherapy” OR “Radiotherapy Image-Guided” OR “Re-Irradiation” OR “X-Ray Therapy” OR “Whole brain radiotherapy”)</p> <p>#3 TS=(Hypopituitarism OR “hypophysis hypofunction” OR “pituitary gland failur” OR “hypophysis failure” OR “radiation-induced hypopituitarism” OR “Pituitary insufficiency” OR “pituitary hormone deficiency” OR "pituitary gland*" OR "pituitary function“ OR hypophysis OR Corticotrophs OR Gonadotrophs OR “Gonadotrophin deficiency” OR "Pituitary Function Tests" OR “pituitary axis” OR “endocrine late effects” OR “hypothalamic-pituitary dysfunction” OR “Pituitary Dysfunction” OR “growth hormone deficiency” OR “GH deficiency”)</p>	198 957 341 037 36 966 356

	*#1 AND #2 AND #3	
Embase	#1 ('head and neck tumor'/exp OR 'ent tumor' OR 'ent tumour' OR 'orl tumor' OR 'orl tumour' OR 'ear nose throat tumor' OR 'ear nose throat tumour' OR 'head and neck neoplasms' OR 'head and neck tumor' OR 'head and neck tumour' OR 'head neck tumor' OR 'head neck tumour' OR 'otorhinolaryngeal tumor' OR 'otorhinolaryngeal tumour' OR 'otorhinolaryngologic neoplasms' OR 'otorhinolaryngologic tumor' OR 'otorhinolaryngologic tumour' OR 'otorhinolaryngological tumor' OR 'otorhinolaryngological tumour' OR 'tumor, head and neck' OR 'tumour, head and neck')	341 925
	#2 ('radiotherapy'/exp OR 'bioradiant therapy' OR 'bucky irradiation' OR 'bucky radiation' OR 'bucky radiotherapy' OR 'bucky ray' OR 'bucky ray radiation' OR 'bucky therapy' OR 'fractionated radiotherapy' OR 'hemibody irradiation' OR 'hypophysectomy, radiation' OR 'hypophysis irradiation' OR 'hypophysis radiation' OR 'irradiation therapy' OR 'irradiation treatment' OR 'irradiation, hypophysis' OR 'lymphatic irradiation' OR 'pituitary irradiation' OR 'radiation beam centration' OR 'radiation repair' OR 'radiation therapy' OR 'radiation treatment' OR 'radio therapy' OR 'radio treatment' OR 'radiohypophysectomy' OR 'radiology, therapeutic' OR 'radiotherapy' OR 'radiotherapy setup errors' OR 'radiotreatment' OR 'roentgen irradiation, therapeutic' OR 'roentgen therapy' OR 'roentgen treatment' OR 'rontgen therapy' OR 'therapeutic radiology' OR 'therapy, irradiation' OR 'therapy, radiation' OR 'therapy, roentgen' OR 'treatment, irradiation' OR 'treatment, radiation' OR 'treatment, roentgen' OR 'x radiotherapy' OR 'x ray therapy' OR 'x ray treatment' OR 'x-ray therapy')	799 318
	#3 ('hypopituitarism'/exp OR 'hypophyseal insufficiency' OR 'hypophysis deficiency' OR 'hypophysis failure' OR 'hypophysis hypofunction' OR 'hypophysis insufficiency' OR 'hypopituitarism' OR 'hypopituitarism' OR 'panhypopituitarism' OR 'pituitary failure' OR 'pituitary gland failure' OR 'pituitary hypofunction' OR 'pituitary insufficiency' OR 'relative hypopituitarism' OR 'secondary hypopituitarism' OR 'hypophysis' OR 'Corticotrophs' OR 'Gonadotrophs' OR 'Gonadotrophin deficiency' OR 'Pituitary Function Tests' OR 'pituitary axis' OR 'endocrine late effects' OR 'hypothalamic-pituitary dysfunction' OR 'Pituitary Dysfunction' OR 'growth hormone deficiency' OR 'GH deficiency')	167 021
	*#1 AND #2 AND #3	652
Ovid MEDLINE	#1: (exp "Head and Neck Neoplasms"/ or ("Head and Neck Neoplasms" or "head or neck cancer").mp.) not (exp Pituitary Neoplasms/ or Pituitary Neoplasms.mp.)	315 179
	#2: Radiotherapy.mp. or exp Radiotherapy/	338 423
	#3: Hypopituitarism.mp. or Hypopituitarism/ or (Secondary hypopituitarism or Iatrogenic hypopituitarism or Drug induced hypopituitarism or radiotherapy hypopituitarism or Panhypopituitarism or Postirradiation hypopituitarism or adenoypophyseal hyposecretion or hyposecretion, adenoypophyseal or insufficiency, pituitary or pituitary insufficiency).mp. or exp Pituitary Hormones/	283 362
	*#1 AND #2 AND #3	542