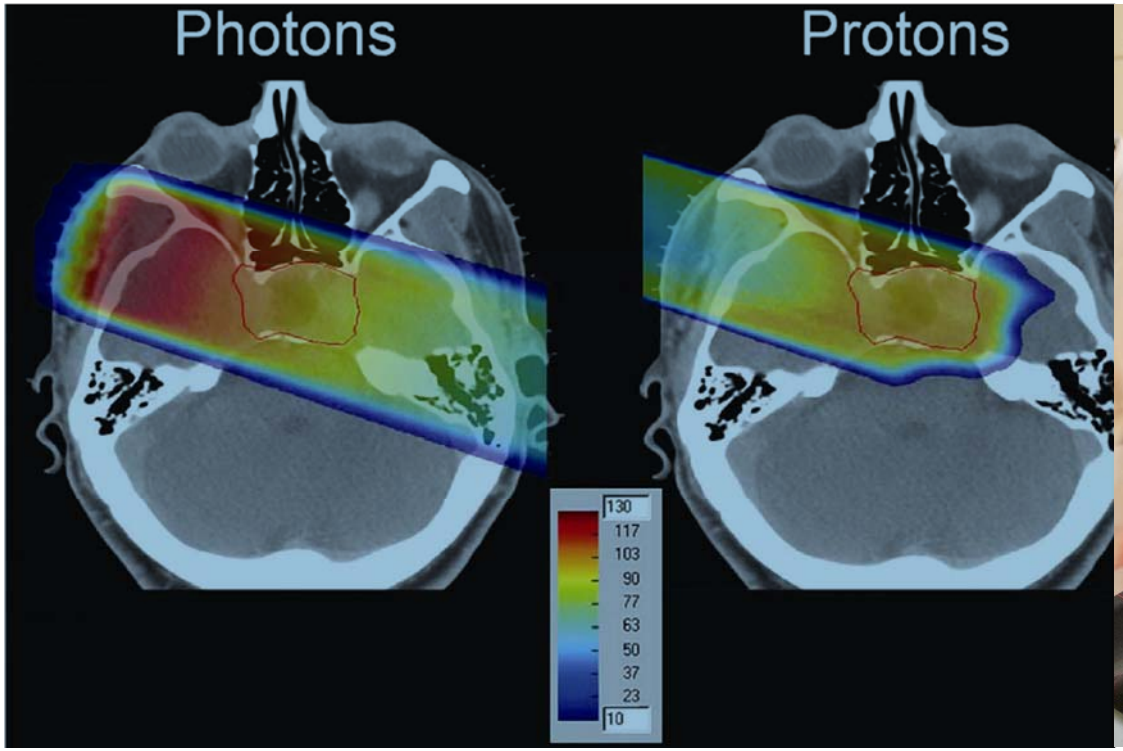
KCE REPORT 235S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

APPENDIX

HADRON THERAPY IN CHILDREN

AN UPDATE OF THE SCIENTIFIC EVIDENCE FOR 15 PAEDIATRIC CANCERS



KCE REPORT 235S
HEALTH TECHNOLOGY ASSESSMENT

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APPENDIX

HADRON THERAPY IN CHILDREN

AN UPDATE OF THE SCIENTIFIC EVIDENCE FOR 15 PAEDIATRIC CANCERS

ROOS LEROY, NADIA BENAHMED, FRANK HULSTAERT, FRANÇOISE MAMBOURG, NICOLAS FAIRON, LIESBET VAN EYCKEN, DIRK DE RUYSSCHER

COLOPHON

Title:	Hadron therapy in Children – an update of the scientific evidence for 15 paediatric cancers – Appendix
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This document is available on the website of the Belgian Health Care Knowledge Centre.

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1. SEARCH STRATEGIES

1.1. Electronic reference databases: Medline (through OVID), EMBASE and the Cochrane Library

Date	**2014-03-21 & update on 2014-09-11**		
Database	**Medline (OVID)**		
Search Strategy	**#**	**Query**	Results
	1	heavy ions/ae, tu	330
	2	elementary particles/ae, tu	48
	3	protons/ae, tu	1345
	4	alpha particles/ae, tu	350
	5	Radiotherapy, High-Energy/ae, ct, ec, sn, ut	1490
	6	exp Proton Therapy/	244
	7	hadrontherap*.tw.	79
	8	protontherap*.tw.	54
	9	carbontherap*.mp.	1
	10	carbon-ion? beam?.tw.	255
	11	proton? beam?.tw.	2018
	12	ion? gantry.tw.	6
	13	(hadron? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap*)).tw.	83
	14	(carbon-ion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap*)).tw.	379
	15	(carbonion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap*)).tw.	1
	16	(heavy-ion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap*)).tw.	216
	17	(proton? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap*)).tw.	3725
	18	(particle? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap*)).tw.	1668

19	(ion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap*)).tw.	1715
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	10060
21	heavy ions/ or elementary particles/ or protons/ or alpha particles/ or Radiotherapy, High-Energy/	38304
22	(therapy or therapies or therapeut* or treatment?).tw.	4004261
23	th.xs.	5409897
24	radiotherap*.tw.	113699
25	22 or 23 or 24	7146075
26	21 and 25	12645
27	20 or 26	18874
28	(proton? adj3 pump).tw.	11098
29	ion? channel?.mp.	63263
30	exp ion pumps/	135999
31	exp ion channels/	192989
32	exp Hydrogen-Ion Concentration/	262091
33	protonation.tw.	9201
34	28 or 29 or 30 or 31 or 32 or 33	593638
35	34 and (6 or 7 or 8 or 9)	0
36	27 not 34	16566
37	acid.tw.	1179968
38	(acid adj2 amin*).tw.	317684
39	(acid adj2 (ribo* or desoxyribo*)).tw.	15117
40	(acid adj2 (DNA or RNA)).tw.	7078
41	38 or 39 or 40	336703
42	37 not 41	843265

	43	42 not (1 or 2 or 4 or 6 or 7 or 8 or 9 or 10 or 13 or 14 or 15 or 16 or 18)	843133
	44	36 not 43	16277
	45	exp animals/ not humans.sh.	3903063
	46	44 not 45	15003
	47	limit 46 to yr="2007 -Current"	4042
	48	exp neoplasms/	2516827
	49	(tumor* or tumour* or neoplasm* or cancer* or sarcoma* or oncolog* or malignan* or chordoma* or chordomas or chondrosarcom* or rhabdomyosarcom* or retinoblastom* or glioma* or ependymoma* or craniopharyngeoma* or pineoblastoma* or esthesioneuroblastoma* or medulloblastoma* or osteosarcoma* or melanoma* or carcinoma* or meningioma*).ti,ab.	2258484
	50	48 or 49	3059606
	51	47 and 50	2363
	52	exp Intracranial Arteriovenous Malformations/	7048
	53	arteriovenous.ti,ab.	30776
	54	aneurysm?.ti,ab.	80528
	55	fistula?.ti,ab.	70226
	56	53 or 54 or 55	163720
	57	brain.ti,ab.	671425
	58	cerebral.ti,ab.	267107
	59	cranial.ti,ab.	53775
	60	intracranial.ti,ab.	75372
	61	57 or 58 or 59 or 60	926515
	62	56 and 61	27129
	63	52 or 62	30477
	64	47 and 63	15

	65	51 or 64	2375
	66	limit 65 to (comment or editorial or letter)	110
	67	65 not 66	**2265**

Date	**2014-03-21**		
Database	**Embase (Embase.com)**		
Search Strategy	#	**Query**	**Results**
	#1	'proton radiation'/exp	2,397
	#2	'carbon-ion beam':ab,ti	155
	#3	'carbon-ions beam':ab,ti	0
	#4	'carbon-ion beams':ab,ti	200
	#5	'carbon-ions beams':ab,ti	1
	#6	'proton beam':ab,ti	2,134
	#7	'protons beam':ab,ti	5
	#8	'protons beams':ab,ti	5
	#9	'proton beams':ab,ti	721
	#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	4,134
	#11	'heavy ion'/exp	902
	#12	'hadron'/exp	196
	#13	'carbon ions':ab,ti	640
	#14	'carbon ion':ab,ti	926
	#15	'hadron':ab,ti	272
	#16	'hadrons':ab,ti	106
	#17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	2,391
	#18	'proton':ab,ti OR 'protons':ab,ti	87,746
	#19	'proton'/de	26,588
	#20	#18 OR #19	97,606
	#21	proton* NEAR/3 pump	55,546
	#22	ion* NEAR/3 channel*	189,894

	#23	'proton pump'/exp	3,275
	#24	'proton pump inhibitor'/exp	50,287
	#25	'proton ionophore'/exp	22
	#26	'ion channel'/exp	167,924
	#27	'ion transport'/exp	189,703
	#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	357,502
	#29	acid:ab,ti	1,353,982
	#30	acid NEAR/2 amin*	1,606,983
	#31	acid NEAR/2 (ribo* OR desoxyribo*)	26,518
	#32	acid NEAR/2 (dna OR rna)	100,186
	#33	#29 NOT (#30 OR #31 OR #32)	847,696
	#34	#20 NOT (#28 OR #33)	59,014
	#35	#17 OR #34	60,746
	#36	'radiation'/exp	414,202
	#37	'irradiation'/exp	58,639
	#38	'beam':ab,ti	66,478
	#39	'irradiation':ab,ti	170,586
	#40	#36 OR #37 OR #38 OR #39	583,449
	#41	'cosmic radiation'/exp	3,305
	#42	'cosmonaut'/exp	2,243
	#43	'space'/exp	3,174
	#44	#41 OR #42 OR #43	8,212
	#45	#35 AND #40	9,704
	#46	#10 OR #45	10,171
	#47	#46 NOT #44	9,499
	#48	'therapy'/exp	6,210,657
	#49	therapy:ab,ti OR therapeut*:ab,ti OR therapies:ab,ti OR treatment:ab,ti OR treatments:ab,ti OR radiotherapy:ab,ti	5,208,365
	#50	#48 OR #49	8,843,360
	#51	#47 AND #50	5,787
	#52	'megavoltage radiotherapy'/exp	5,558

	#53	'radiotherapy'/de	84,317
	#54	'beam therapy'/de	3,907
	#55	'external beam radiotherapy'/de	11,728
	#56	'computer assisted radiotherapy'/de	7,637
	#57	'cancer radiotherapy'/de	115,909
	#58	'image guided radiotherapy'/de	1,459
	#59	#52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58	217,520
	#60	#35 AND #59	3,048
	#61	#51 OR #60	6,528
	#62	'proton therapy'/exp	2,303
	#63	'ion therapy'/exp	772
	#64	hadrontherap*	141
	#65	protontherap*	201
	#66	carbontherap*	1
	#67	'hadron therapy'	126
	#68	'hadrons therapy'	0
	#69	'hadron therapies'	0
	#70	'hadrons therapies'	0
	#71	'carbon ion therapy':ab,ti	169
	#72	'carbon ions therapy':ab,ti	2
	#73	'carbon ion therapies':ab,ti	3
	#74	'carbon ions therapies':ab,ti	0
	#75	#62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74	3,279
	#76	'proton therapy':ab,ti	1,558
	#77	'protons therapies':ab,ti	0
	#78	'proton therapies':ab,ti	5
	#79	'protons therapy':ab,ti	1
	#80	#76 OR #77 OR #78 OR #79	1,560
	#81	#80 NOT (#28 OR #33)	1,537
	#82	#75 OR #81	3,754

#83	hadron* NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)	182
#84	'carbon ion' NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)	554
#85	'carbon ions' NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)	83
#86	carbonion* NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)	5
#87	'heavy ion' NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)	320
#88	'heavy ions' NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)	64
#89	(particle* NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)):ab,ti	2,033
#90	#83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89	2,866
#91	(proton* NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)):ab,ti	5,336
#92	((ion OR ions) NEAR/3 (therapy OR therapeut* OR therapies OR treatment OR treatments OR radiotherapy)):ab,ti	2,183
#93	#91 OR #92	7,354
#94	#93 NOT (#28 OR #33)	4,677
#95	#90 OR #94	6,552
#96	#61 OR #82 OR #95	10,242
#97	'animal'/exp NOT 'human'/exp	4,282,997
#98	#96 NOT #97	9,160
#99	#98 AND (2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py)	5,336
#100	#99 AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'erratum'/it OR 'review'/it)	5,046
#101	#100 NOT #44	5,033
#102	#101 AND [medline]/lim	2,841
#103	#101 NOT #102	2,192
#104	'neoplasms'/exp	3,401,129

	#105	tumor*:ab,ti OR tumour*:ab,ti OR neoplasm*:ab,ti OR cancer*:ab,ti OR sarcoma*:ab,ti OR oncolog*:ab,ti OR malignan*:ab,ti OR chordoma*:ab,ti OR chordomas:ab,ti OR chondrosarcom*:ab,ti OR rhabdomyosarcom*:ab,ti OR retinoblastom*:ab,ti OR glioma*:ab,ti OR ependymoma*:ab,ti OR craniopharyngeoma*:ab,ti OR pineoblastoma*:ab,ti OR esthesioneuroblastoma*:ab,ti OR medulloblastoma*:ab,ti OR osteosarcoma*:ab,ti OR melanoma*:ab,ti OR carcinoma*:ab,ti OR meningioma*:ab,ti	2,821,762
	#106	'brain arteriovenous malformation'/exp	6,249
	#107	arteriovenous:ab,ti	36,864
	#108	aneurysm:ab,ti	76,114
	#109	fistula:ab,ti	67,536
	#110	#107 OR #108 OR #109	164,605
	#111	brain:ab,ti	815,658
	#112	intracranial:ab,ti	95,892
	#113	cerebral:ab,ti	331,694
	#114	cranial:ab,ti	66,214
	#115	#111 OR #112 OR #113 OR #114	1,129,350
	#116	#110 AND #115	27,409
	#117	#106 OR #116	30,062
	#118	#103 AND #117	10
	#119	#104 OR #105	3,876,571
	#120	#103 AND #119	1,628
	#121	#118 OR #120	1,633
	#122	**#101 AND (#115 OR #119)**	**3,480**

Date	2014-03-17		
Database	**Cochrane**		
Search Strategy	**#**	**Query**	**Results**
	#1	MeSH descriptor: [Heavy Ions] explode all trees and with qualifier(s): [Adverse effects - AE, Therapeutic use - TU]	8
	#2	MeSH descriptor: [Elementary Particles] explode all trees and with qualifier(s): [Adverse effects - AE, Therapeutic use - TU]	86
	#3	MeSH descriptor: [Protons] explode all trees and with qualifier(s): [Adverse effects - AE, Therapeutic use - TU]	22
	#4	MeSH descriptor: [Alpha Particles] explode all trees and with qualifier(s): [Adverse effects - AE, Therapeutic use - TU]	3
	#5	MeSH descriptor: [Radiotherapy, High-Energy] explode all trees and with qualifier(s): [Adverse effects - AE, Contraindications - CT, Economics - EC, Statistics & numerical data - SN, Utilization - UT]	90
	#6	MeSH descriptor: [Proton Therapy] explode all trees	4
	#7	hadrontherap*:ti,ab,kw	2
	#8	protontherap*:ti,ab,kw	1
	#9	carbontherap*:ti,ab,kw	0
	#10	"carbon-ion beam":ti,ab,kw or "carbon-ions beam":ti,ab,kw or "carbon-ion beams":ti,ab,kw or "carbon-ions beams":ti,ab,kw	1
	#11	"proton beam":ti,ab,kw or "protons beam":ti,ab,kw or "proton beams":ti,ab,kw or "protons beams":ti,ab,kw	47
	#12	"ion gantry":ti,ab,kw or "ions gantry":ti,ab,kw	0
	#13	((hadron or hadrons) near/3 (therapy or therapeut* or therapies or treatment or treatments)):ti,ab,kw	1
	#14	((carbon-ion or carbon-ions or carbonions or carbonion) near/3 (therapy or therapeut* or therapies or treatment or treatments)):ti,ab,kw	12
	#15	((heavy-ion or heavy-ions) near/3 (therapy or therapeut* or therapies or treatment or treatments)):ti,ab,kw	0
	#16	((proton or protons) near/3 (therapy or therapeut* or therapies or treatment or treatments)):ti,ab,kw	481
	#17	((particle or particles) near/3 (therapy or therapeut* or therapies or treatment or treatments)):ti,ab,kw	119
	#18	((ion or ions) near/3 (therapy or therapeut* or therapies or treatment or treatments)):ti,ab,kw	107

#19	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	878
#20	MeSH descriptor: [Heavy Ions] this term only	8
#21	MeSH descriptor: [Elementary Particles] this term only	10
#22	MeSH descriptor: [Protons] this term only	129
#23	MeSH descriptor: [Alpha Particles] this term only	4
#24	MeSH descriptor: [Radiotherapy, High-Energy] this term only	304
#25	#20 or #21 or #22 or #23 or #24	441
#26	(therapy or therapies or therapeut* or treatment or treatments):ti,ab,kw	416175
#27	MeSH descriptor: [Neoplasms] explode all trees	49382
#28	(cancer or cancers or tumor or tumors or tumour or tumours or malignanc*):ti,ab,kw	67939
#29	radiotherap*:ti,ab,kw	11257
#30	#26 or #27 or #28 or #29	449626
#31	#25 and #30	394
#32	#19 or #31	1134
#33	((proton or protons) near/3 (pump or pumps)):ti,ab,kw	1905
#34	("ion channel" or "ions channel" or "ions channels" or "ion channels"):ti,ab,kw	127
#35	MeSH descriptor: [Ion Pumps] explode all trees	978
#36	MeSH descriptor: [Ion Channels] explode all trees	953
#37	MeSH descriptor: [Hydrogen-Ion Concentration] explode all trees	2934
#38	protonation:ti,ab,kw	0
#39	#33 or #34 or #35 or #36 or #37 or #38	6487
#40	#39 and (#6 or #7 or #8 or #9)	0
#41	#32 not #39	670
#42	"magnetic resonance spectroscopy":ti,ab,kw	654
#43	MeSH descriptor: [Magnetic Resonance Spectroscopy] explode all trees	469
#44	#42 or #43	676

	#45	#44 and (#6 or #7 or #8 or #9)	0
	#46	#41 not #44	621
	#47	(acid or acidity):ti,ab,kw	55481
	#48	(acid near/2 amin*):ti,ab,kw	7058
	#49	(acid near/2 (ribo* or desoxyribo*)):ti,ab,kw	149
	#50	(acid near/2 (DNA or RNA)):ti,ab,kw	89
	#51	#48 or #49 or #50	7262
	#52	#47 not #51	48219
	#53	#52 not (#1 or #2 or #4 or #6 or #7 or #8 or #9 or #13 or #14 or #15 or #17)	48204
	#54	#46 not #53	610
	#55	MeSH descriptor: [Animals] explode all trees	6516
	#56	MeSH descriptor: [Humans] explode all trees	1125
	#57	#55 not #56	5391
	#58	#54 not #57	609
	#59	**#58 Publication Date from 2007 to 2014**	**146**

1.2. HTA agencies

1.2.1. Methods

Search terms: hadron (therapy), proton (beam therapy), carbon (ion therapy), particle beam

Exclusion criteria: published before 2007; indications covered other than those specified in the list of indications (see Report); non-English, non-French, non-Dutch, non-German publications

Search date: 14-18 March 2014

1.2.2. List of consulted HTA agencies and related websites

Table 1 – List of consulted HTA agencies and related websites

Organisation		Country	Search date	Results
INAHTA	International Network of Agencies for Health Technology Assessment	International	17/03/2014	0
AETMIS	Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada	18/03/2014	1
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain	18/03/2014	0
AETSA	Andalusian Agency for Health Technology Assessment	Spain	18/03/2014	0
AHRQ	Agency for Healthcare Research and Quality	US	17/03/2014	4
AHTA	Adelaide Health Technology Assessment	Australia	18/03/2014	0
AHTAPol	Agency for Health Technology Assessment in Poland	Poland	18/03/2014	0
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia	18/03/2014	0
AVALIA-T	Galician Agency for Health Technology Assessment	Spain	18/03/2014	0
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada	18/03/2014	2
CAHTA	Catalan Agency for Health Technology Assessment and Research	Spain	18/03/2014	0
CEDIT	Comité dÉvaluation et de Diffusion des Innovations Technologiques	France	18/03/2014	0
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico	18/03/2014	no access
CMT	Center for Medical Technology Assessment	Sweden	18/03/2014	0
CRD	Centre for Reviews and Dissemination	United Kingdom	14/03/2014	10
CVZ	College voor Zorgverzekeringen	The Netherlands	17/03/2014	3
DACEHTA	Danish Centre for Evaluation and Health Technology Assessment	Denmark	18/03/2014	no access to http://www.dacehta.dk
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany	18/03/2014	only access to HTA reports with code
DECIT-CGATS	Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil	18/03/2014	0
DSI	Danish Institute for Health Services Research	Denmark	18/03/2014	http://dsi.dk/english/ transferred to http://www.kora.dk/velkommen (all in danish)
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland	18/03/2014	0

GR	Gezondheidsraad	The Netherlands	18/03/2014	2
HAS	Haute Autorité de Santé	France	18/03/2014	2 (report + supplements)
HTA.HCA.WA	Health Technology Assessment Program, Washington State Health Care Authority	US	28/04/2014	1
HunHTA	Unit of Health Economics and Health Technology Assessment	Hungary	18/03/2014	0
IAHS	Institute of Applied Health Sciences	United Kingdom	18/03/2014	0
ICTAHC	Israel Center for Technology Assessment in Health Care	Israel	18/03/2014	0
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina	18/03/2014	0
IHE	Institute of Health Economics	Canada	18/03/2014	0
IMSS	Mexican Institute of Social Security	Mexico	18/03/2014	0
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany	18/03/2014	0
KCE	Belgian Federal Health Care Knowledge Centre	Belgium	18/03/2014	1
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria	14/03/2014	1
MAS	Medical Advisory Secretariat	Canada	18/03/2014	0
MSAC	Medical Services Advisory Committee	Australia	18/03/2014	0
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland	18/03/2014	0
NCCHTA	National Coordinating Centre for Health Technology Assessment	United Kingdom	18/03/2014	0
NHS QIS	Quality Improvement Scotland	United Kingdom	18/03/2014	0
NHSC	National Horizon Scanning Center	United Kingdom	18/03/2014	0
NOKC	Norwegian Knowledge Centre for Health Services	Norway	18/03/2014	0
NZHTA	New Zealand Health Technology Assessment	New Zealand	18/03/2014	0
OSTEBA	Basque Office for Health Technology Assessment	Spain	18/03/2014	0
SBU	Swedish Council on Technology Assessment in Health Care	Sweden	18/03/2014	0
UETS	Unidad de evaluacíon Technologias Santarias	Spain	18/03/2014	0
VATAP	VA Technology Assessment Program	US	17/03/2014	0
VSMTVA	Health Statistics and Medical Technologies State Agency	Latvia	18/03/2014	0
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands	18/03/2014	0
Related websites				
AGENAS	Agenzia nazionale per i servizi sanitari regionali	Italy	14/03/2014	1

ANZHSN	Australia and New Zealand Horizon Scanning Network	Australia & New Zealand	14/03/2014	2
BHTC	Belgian Hadron Therapy Centre	Belgium	14/03/2014	1
GIN	Guidelines International Network	International	17/03/2014	0
NCCN	National Comprehensive Cancer Network	US	18/03/2014	0
NICE	National Institute for Health and Care Excellence	UK	17/03/2014	0

1.2.3. Retrieved publications

1.2.3.1. INAHTA members' websites

AETMIS - Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé

- La protonthérapie. Note informative. Agence d'évaluation des technologies et des modes d'intervention en santé. 2010

AHRQ - Agency for Healthcare Research and Quality

- Radiotherapy Treatments for Head and Neck Cancer. Update. AHRQ. 2014
- Proton Beam Radiotherapy in the U.S. Medicare Population. AHRQ. 2012
- Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer. Clinician guide. AHRQ.2010
- Particle Beam Radiation Therapies for Cancer. Summary. AHRQ. 2009

CADTH - Canadian Agency for Drugs and Technologies in Health

- Proton Beam Therapy: Clinical and Cost-Effectiveness and Guidelines for Use. CADTH. 2008
- Carbon Ion Radiation Therapy. Environmental scan. CADTH. 2009

CRD – Centre for Reviews and Dissemination

- Wang Z, Nabhan M, Schild SE, Stafford SL, Petersen IA, Foote RL, Murad MH. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. International Journal of Radiation Oncology, Biology, Physics 2013; 86(1): 18-26
- Ramaekers BL, Pijls-Johannesma M, Joore MA, van den Ende P, Langendijk JA, Lambin P, Kessels AG, Grutters JP. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons. Cancer Treatment Reviews 2011; 37(3): 185-201
- Maucort-Boulch D, Baron MH, Pommier P, Weber DC, Mizoe JE, Rochat J, Boissel JP, Balosso J, Tsujii H, Amsallem E. Rationale for carbon ion therapy in high-grade glioma based on a review and a meta-analysis of neutron beam trials. Cancer Radiotherapie 2010; 14(1): 34-41
- Flynn K. Proton beam therapy for cancer. Boston: VA Technology Assessment Program (VATAP). 2010
- Ross Jenny, Al-Shahi Salman Rustam. Interventions for treating brain arteriovenous malformations in adults. Cochrane Database of Systematic Reviews: Reviews 2010; Issue 7
- Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. Neurosurgical Review 2009; 32(4): 403-416
- Bekkering GE, Rutjes AW, Vlassov VV, Aebersold DM, von Bremen K, Juni P, Kleijnen J. The effectiveness and safety of proton radiation therapy for indications of the eye: a systematic review. Strahlentherapie und Onkologie 2009; 185(4): 211-221
- Lodge M, Pijls-Johannesma M, Stirk L, Munro A J, De Ruysscher D, Jefferson T. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. Radiotherapy and Oncology 2007; 83(2): 110-122.
- Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S). Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures Stepney: Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S). Horizon Scanning Report. 2007
- Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S). Proton beam therapy for the treatment of uveal melanoma. Stepney: Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S). Horizon Scanning Report. 2007

CVZ - College voor Zorgverzekeringen

- Indicaties voor protonentherapie (deel 2): Model-based indicaties. CVZ. 2011
- Indicaties voor protonentherapie (deel 1): Intra-oculaire tumoren, chordomen/chondrosarcomen, pediatrische tumoren. CVZ. 2010
- Protonentherapie. Rapport. CVZ.2009

GR - Gezondheidsraad

- Proton radiotherapy. Horizon scanning report. 2009
- Protonenbehandeling. Signalement. 2009

HAS – Haute Authorité de Santé

- Hadrontherapie. Rapport preliminaire. HAS. 2010
- Hadrontherapie. Annexes au rapport preliminaire. HAS. 2010

HTA.HCA.WA - Health Technology Assessment Program, Washington State Health Care Authority

- Proton Beam Therapy. Final Evidence Report. 2014

KCE - Belgian Health Care Knowledge Centre

- Hadrontherapy. KCE report 67A. 2007

LBI - Ludwig Boltzmann Institut für Health Technology Assessment

- Hadronentherapie: Protonen und Kohlenstoff- Ionen. Eine Übersicht: Refundierungsstatus, Evidenz und Forschungsstand. Ludwig Boltzmann Institut. November 2013 // Wild C, Hintringer K, Narath M. Hadron therapy: Proton and carbon ion therapy - A review of clinical evidence of efficacy, ongoing research and reimbursement. HTA-Projektbericht 74. Ludwig Boltzmann Institut für Health Technology Assessment. 2013

1.2.3.2. Related websites

ANZHSN - Australia and New Zealand Horizon Scanning Network

- Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures. Horizon Scanning Report. ANZHSN. 2007
- Proton beam therapy for the treatment of uveal melanoma. Horizon Scanning Report. ANZHSN. 2007.

AGENAS - Agenzia nazionale per i servizi sanitari regionali

- Hadrontherapy for cancer treatment: Overview of the evidence on safety and effectiveness. AGENAS. 2011

BHTC – Belgian Hadron Therapy Centre

- Feasability study of a Hadron Therapy Centre in Belgium

  Refereed in BHTC study
- An evidence-based report on the clinical and cost-effectiveness of particle therapy. Prepared by the targeted particle therapy review group. Cochrane Cancer Institute. July 2011.

1.3. Clinical trials.gov

1.3.1. Methods

Search terms: proton beam therapy, carbon ion therapy, heavy particles

Note: no results obtained with “hadron therapy”

Exclusion criteria: indications other than those specified in Table 2

Search date: 16 April 2014

1.3.2. List of (ongoing) studies

Table 2 – List of ongoing studies

Indication	Study details
Chordoma	
Title:	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Chordoma of the Skull Base
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Chordoma|Tumor|Treatment
Interventions:	Radiation: Carbon ion|Radiation: Protons
URL:	http://ClinicalTrials.gov/show/NCT01182779
Population :	Adults
Start date :	July 2010
Estimated primary completion date:	August 2015
Title:	Ion Irradiation of Sacrococcygeal Chordoma
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Exposure to Artificially Accelerated Beams of Ionized Particles Generated by Synchrotrons
Interventions:	Radiation: protons|Radiation: carbon ions
URL:	http://ClinicalTrials.gov/show/NCT01811394
Population :	Adults
Start date :	January 2013
Estimated primary completion date:	January 2015
Title:	Proton Beam Therapy for Chordoma Patients
Recruitment:	Active, not recruiting
Study Results:	No Results Available
Conditions:	Chordoma
Interventions:	Radiation: Proton Beam Therapy|Radiation: Photon Beam Therapy

URL:	http://ClinicalTrials.gov/show/NCT00496119
Population :	Not mentioned
Start date :	September 2006
Estimated primary completion date:	September 2014
Chondrosarcoma	
Title:	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Low and Inter-mediate Grade Chondrosarcoma of the Skull Base
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Chondrosarcoma
Interventions:	Radiation: carbon ion therapy|Radiation: proton therapy
URL:	http://ClinicalTrials.gov/show/NCT01182753
Population :	Adults
Start date :	August 2010
Estimated primary completion date:	August 2022
Title:	Proton Beam Therapy for Chondrosarcoma
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Chondrosarcoma
Interventions:	Procedure: Proton Beam Therapy
URL:	http://ClinicalTrials.gov/show/NCT00496522
Population :	Not mentioned
Start date :	April 2006
Estimated primary completion date:	April 2015
Chordoma & Chondrosarcoma	
Title:	Proton Therapy for Chordomas and/or Chondrosarcomas
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Chordomas|Chondrosarcomas
Interventions:	
URL:	http://ClinicalTrials.gov/show/NCT00797602
Population :	Adults
Start date :	January 2007
Estimated primary completion date:	January 2022
Title:	Proton Radiation for Chordomas and Chondrosarcomas
Recruitment:	Recruiting

Study Results:	No Results Available
Conditions:	Chordomas|Chondrosarcomas
Interventions:	Radiation: Proton Therapy
URL:	http://ClinicalTrials.gov/show/NCT01449149
Population :	Adults
Start date :	
Estimated primary completion date:	
Title:	High Dose Intensity Modulated Proton Radiation Treatment +/- Surgical Resection of Sarcomas of the Spine, Sacrum and Base of Skull
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Chordoma of Spine|Chordoma of Sacrum|Chordoma of Base of Skull|Chondrosarcoma of the Spine|Chondrosarcoma of the Sacrum
Interventions:	Radiation: High Dose Intensity Modulated Proton Radiation
URL:	http://ClinicalTrials.gov/show/NCT01346124
Population :	Adults
Start date :	March 2010
Estimated primary completion date:	March 2014
Adult soft tissue sarcoma	
Title:	Hyperthermia and Proton Therapy in Unresectable Soft Tissue Sarcoma
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Soft Tissue Sarcoma
Interventions:	Radiation: Hyperthermia and Proton Beam
URL:	http://ClinicalTrials.gov/show/NCT01904565
Population :	Adults
Start date :	February 2014
Estimated primary completion date:	December 2018
Title:	Proton Beam Radiation Therapy in Treating Patients With Retroperitoneal Sarcoma
Recruitment:	Completed
Study Results:	No Results Available
Conditions:	Adult Soft Tissue Sarcoma
Interventions:	Radiation: Proton Beam Radiation Therapy
URL:	http://ClinicalTrials.gov/show/NCT01034566
Population :	Adults
Start date :	November 2009
Estimated primary completion date:	November 2014

Title:	A Phase II Trial of Preoperative Proton Therapy in Soft-tissue Sarcomas of the Extremities and Body Wall
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Soft Tissue Sarcoma
Interventions:	Radiation: proton radiation + Procedure: surgery (wide local excision; limb preservation surgery)
URL:	http://clinicaltrials.gov/ct2/show/NCT01819831
Population :	Adults
Start date :	March 2013
Estimated primary completion date:	March 2015 (final data collection date for primary outcome measure)
Title:	Proton Radiation for the Treatment of Pediatric Bone and Non-Rhabdomyosarcoma Soft Tissue Sarcomas
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Non-rhabdomyosarcoma Soft Tissue Sarcoma, Bone Sarcoma
Interventions:	Radiation: Proton Beam Radiation
URL:	http://clinicaltrials.gov/ct2/show/NCT00592293
Population :	up to 30 years
Start date :	September 2006
Estimated primary completion date:	June 2015
Title:	Proton Radiotherapy for Extremity Soft Tissue Sarcoma
Recruitment:	Completed
Study Results:	No Results Available
Conditions:	Soft Tissue Sarcoma of the Extremities
Interventions:	Radiation: Proton Therapy
URL:	http://clinicaltrials.gov/ct2/show/NCT01561495
Population :	Adults
Start date :	June 2010
Estimated primary completion date:	May 2014
Rhabdomyosarcoma	
Title:	Treatment of Localized Rhabdomyosarcoma With Chemotherapy, Radiotherapy, and Surgery
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Rhabdomyosarcoma
Interventions:	Drug: Vincristine|Drug: Dactinomycin|Drug: Cyclophosphamide|Procedure: Surgical Resection|Procedure: Radiation|Drug: Bevacizumab|Drug: Sorafenib|Drug: Myeloid Growth Factor|Procedure: Lymph Node Sampling
URL:	http://ClinicalTrials.gov/show/NCT01871766
Population :	Adults
Start date :	June 2013

Estimated primary completion date:	June 2021
Title:	Proton RT for the Treatment of Pediatric Rhabdomyosarcoma
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Rhabdomyosarcoma
Interventions:	Radiation: Proton Beam Radiation
URL:	http://ClinicalTrials.gov/show/NCT00592592
Population :	Adults
Start date :	October 2004
Estimated primary completion date:	June 2015
Ewing sarcoma	
Title:	Therapeutic Trial for Patients With Ewing Sarcoma Family of Tumor and Desmoplastic Small Round Cell Tumors
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Desmoplastic Small Round Cell Tumor|Ewing Sarcoma of Bone|Localized Ewing Sarcoma/Peripheral Primitive Neuroectodermal Tumor|Metastatic Ewing Sarcoma/Peripheral Primitive Neuroectodermal Tumor
Interventions:	Drug: vincristine|Drug: doxorubicin|Drug: cyclophosphamide|Drug: ifosfamide|Drug: etoposide|Drug: temozolomide|Drug: temsirolimus|Drug: bevacizumab|Drug: sorafenib|Procedure: surgery|Radiation: radiation
URL:	http://ClinicalTrials.gov/show/NCT01946529
Population :	Children up to 25 y.o.
Start date :	November 2013
Estimated primary completion date:	January 2019
Retinoblastoma	
Title:	Proton Beam Radiation Therapy for Intraocular and Periocular Retinoblastoma
Recruitment:	Terminated
Study Results:	No Results Available
Conditions:	Retinoblastoma
Interventions:	Radiation: Proton Beam Radiation Therapy|Procedure: Ophthalmic EUA
Study design:	Safety/efficacy study
URL:	http://ClinicalTrials.gov/show/NCT00432445
Population:	Not mentioned
Start date :	January 2007
Estimated primary completion date:	February 2014
Title:	Protocol for the Study and Treatment of Participants With Intraocular Retinoblastoma
Recruitment:	Recruiting
Study Results:	No Results Available

Conditions:	Retinoblastoma
Interventions:	Drug: vincristine|Drug: topotecan|Drug: filgrastim|Drug: PEG-filgrastim|Drug: carboplatin|Other: focal therapy|Drug: etoposide|Drug: cyclophosphamide|Drug: MESNA|Drug: doxorubicin|Procedure: enucleation|Radiation: external beam radiation
Study design:	Non-Randomized
URL:	http://ClinicalTrials.gov/show/NCT01783535
Population :	Children
Start date :	June 2013
Estimated primary completion date:	June 2020
Glioma	
Title:	Carbon Ion Radiotherapy for Recurrent Gliomas
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Glioma
Interventions:	Radiation: Carbon Ion Radiotherapy|Radiation: Fractionated Stereotactic Radiotherapy (FSRT)
URL:	http://ClinicalTrials.gov/show/NCT01166308
Population :	Adults
Start date :	August 2010
Estimated primary completion date:	July 2014
Title:	Stem Cell Radiotherapy and Temozolomide for Newly Diagnosed High-grade Glioma
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Glioblastoma|Malignant Glioma|Brain Tumors|Anaplastic Astrocytoma
Interventions:	Radiation: Stem Cell Radiotherapy (ScRT) and Temozolomide
URL:	http://ClinicalTrials.gov/show/NCT02039778
Population :	Adults
Start date :	December 2013
Estimated primary completion date:	December 2018
Title:	Late Effects of Proton Radiation Therapy in Patients With Low-Grade Glioma
Recruitment:	This study is ongoing, but not recruiting participants
Study Results:	No Results Available
Conditions:	Low Grade Gliomas
Interventions:	Radiation: Proton Radiation Therapy
URL:	http://clinicaltrials.gov/ct2/show/NCT00681473
Population :	Adults
Start date :	July 2007
Estimated primary completion date:	August 2015

Title:	Phase II Study of Proton Radiation Therapy for Low Grade and Favorable Grade 3 Gliomas
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Low Grade Glioma, WHO Grade 3 Glioma With IDH1 Mutation, WHO Grade 3 Glioma With 1p/19q Codeletion
Interventions:	Radiation: Proton radiation
URL:	http://clinicaltrials.gov/ct2/show/NCT01358058
Population :	Adults
Start date :	May 2011
Estimated primary completion date	May 2015
Esthesioneuroblastoma	
Title:	Multidisciplinary Approach for Poor Prognosis Sinonasal Tumors in Operable Patients
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Sinonasal Tumors
Interventions:	Drug: Cisplatin|Drug: Docetaxel|Drug: 5-fluorouracil|Drug: Etoposide|Drug: Adriamycin|Drug: Ifosfamide|Drug: Leucovorin|Radiation: Radiotherapy - Patients needing Elective Nodal Volume (ENI)|Radiation: Radiotherapy - Patients not needing ENI|Radiation: Radiotherapy - Patients needing curative neck irradiation
URL:	http://ClinicalTrials.gov/show/NCT02099175
Population :	Adults
Start date :	November 2013
Estimated primary completion date:	January 2016
Title:	Multidisciplinary Approach for Poor Prognosis Sinonasal Tumors in Operable Patients
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Unresectable Sinonasal Tumors
Interventions:	Drug: Cisplatin|Drug: Docetaxel|Drug: 5-fluorouracil|Drug: Etoposide|Drug: Adriamycin|Drug: Ifosfamide|Drug: Leucovorin|Radiation: Radiotherapy - Patients needing Elective Nodal Volume (ENI)|Radiation: Radiotherapy - Patients not needing ENI|Radiation: Radiotherapy - Patients needing curative neck irradiation
URL:	http://ClinicalTrials.gov/show/NCT02099188
Population :	Adults
Start date :	November 2013
Estimated primary completion date:	January 2016
Medulloblastoma	
Title:	Proton Beam Radiotherapy for Medulloblastoma and Pineoblastoma
Recruitment:	Recruiting
Study Results:	No Results Available

Conditions:	Brain Tumor|Medulloblastoma|Pineoblastoma
Interventions:	Radiation: proton beam radiation
URL:	http://ClinicalTrials.gov/show/NCT01063114
Population :	Children and young adults
Start date :	April 2010
Estimated primary completion date:	April 2018
Title:	Proton Beam Radiation Therapy in Treating Young Patients Who Have Undergone Biopsy or Surgery for Medulloblastoma or Pineoblastoma
Recruitment:	Active, not recruiting
Study Results:	No Results Available
Conditions:	Brain and Central Nervous System Tumors|Long-term Effects Secondary to Cancer Therapy in Children
Interventions:	Radiation: radiation therapy
URL:	http://ClinicalTrials.gov/show/NCT00105560
Population :	Children and young adults
Start date :	May 2002
Estimated primary completion date:	December 2014
Title:	A Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Medulloblastoma
Interventions:	Radiation: Craniospinal Irradiation with boost to the primary tumor site|Drug: Cyclophosphamide|Drug: Cisplatin|Drug: Vincristine|Drug: Vismodegib|Drug: Pemetrexed|Drug: Gemcitabine|Other: Aerobic Training|Other: Neurocognitive Remediation
URL:	http://ClinicalTrials.gov/show/NCT01878617
Population :	Children and young adults
Start date :	June 2013
Estimated primary completion date:	June 2023
Central Nervous System Germ Cell Tumor	
Title:	Proton Beam Radiation Therapy for Central Nervous System (CNS) Germ Cell Tumors
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Germ Cell Tumor|Central Nervous System Germ Cell Tumor
Interventions:	Radiation: Proton Beam radiation
URL:	http://ClinicalTrials.gov/show/NCT01049230
Population :	Children
Start date :	June 2010
Estimated primary completion date:	October 2015

Craniopharyngioma	
Title:	A Phase II Trial of Limited Surgery and Proton Therapy for Craniopharyngioma or Observation After Radical Resection
Recruitment:	August 2011
Study Results:	No Results Available
Conditions:	Craniopharyngioma
Interventions:	Procedure: Radical Surgery or Limited Surgery + Radiation: Proton Therapy
URL:	http://clinicaltrials.gov/ct2/show/NCT01419067
Population :	Adults
Start date :	August 2011
Estimated primary completion date:	August 2022 (final data collection date for primary outcome measure)
Osteosarcoma	
Title:	Therapy Trial to Determine the Safety and Efficacy of Heavy Ion Radiotherapy in Patients With Osteosarcoma
Recruitment:	Not yet recruiting
Study Results:	No Results Available
Conditions:	Osteosracoma
Interventions:	Radiation: heavy ion radiotherapy (C12)
URL:	http://ClinicalTrials.gov/show/NCT01005043
Population :	Patients older than 6 years
Start date :	December 2010
Estimated primary completion date:	January 2015
Title:	Proton Radiation for the Treatment of Pediatric Bone and Non-Rhabdomyosarcoma Soft Tissue Sarcomas
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Non-rhabdomyosarcoma Soft Tissue Sarcoma|Bone Sarcoma
Interventions:	Radiation: Proton Beam Radiation
URL:	http://ClinicalTrials.gov/show/NCT00592293
Population :	Up to 30 y.o.
Start date :	September 2006
Estimated primary completion date:	June 2015
More than 1 indication	
Title:	Registry for Proton Beam Radiation Therapy
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Carcinoma
Interventions:	

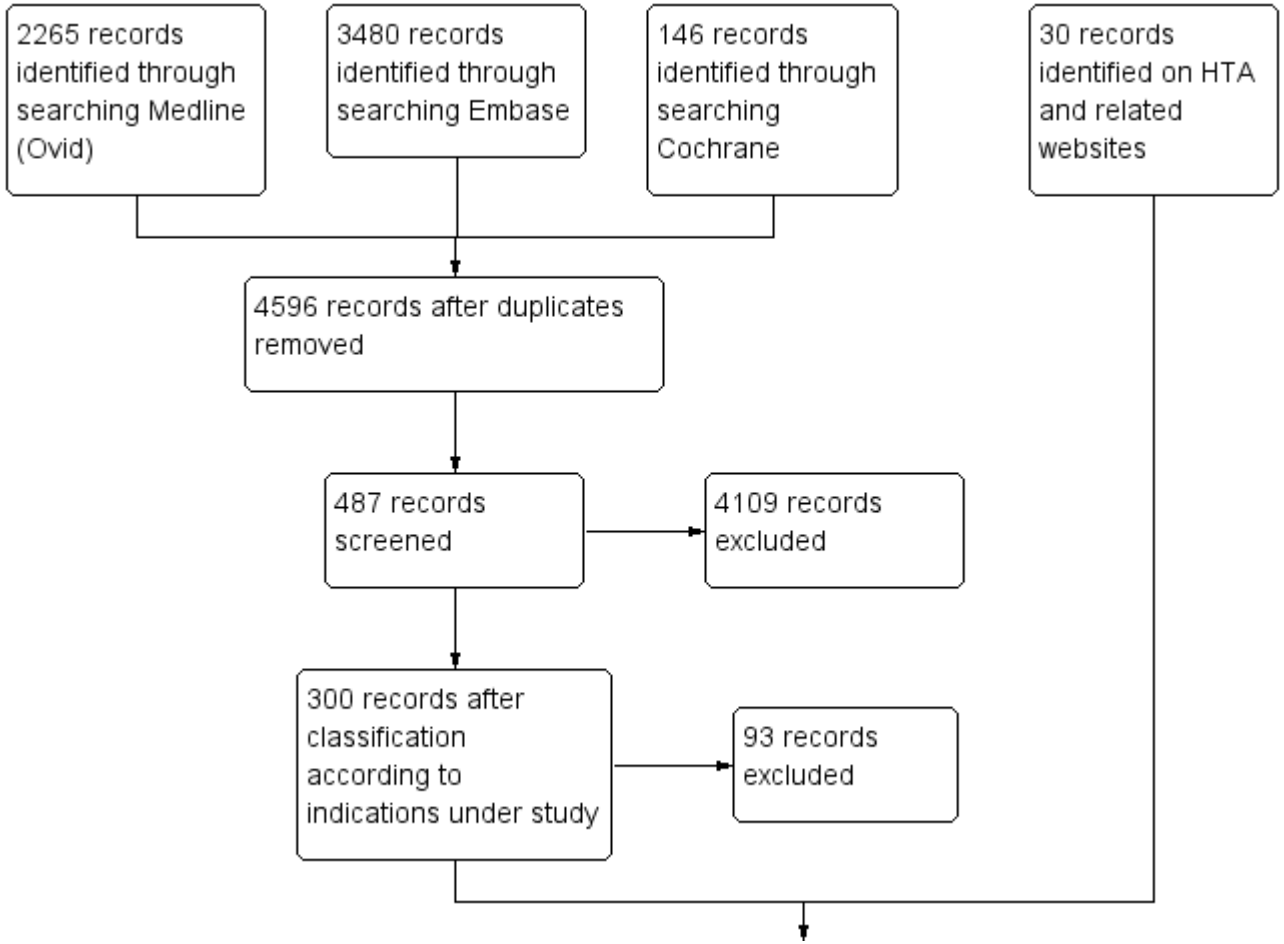
URL:	http://ClinicalTrials.gov/show/NCT02040467
Population :	Not mentioned
Start date :	December 2013
Estimated primary completion date:	January 2024
Title:	Proton Beam Radiation Therapy in Treating Patients With Low Grade Gliomas
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Adult Brain Tumor|Adult Brain Stem Glioma|Adult Diffuse Astrocytoma|Adult Ependymoma|Adult Grade II Meningioma|Adult Melanocytic Lesion|Adult Meningeal Hemangiopericytoma|Adult Mixed Glioma|Adult Oligodendroglioma|Adult Pineal Gland Astrocytoma|Adult Pineocytoma|Recurrent Adult Brain Tumor
Interventions:	Radiation: proton beam radiation therapy|Procedure: quality-of-life assessment|Other: questionnaire administration
URL:	http://ClinicalTrials.gov/show/NCT01024907
Population :	Adults
Start date :	July 2009
Estimated primary completion date:	July 2014
Title:	Risk-Adapted Therapy for Young Children With Embryonal Brain Tumors, Choroid Plexus Carcinoma, High Grade Glioma or Ependymoma
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Brain and Central Nervous System Tumors
Interventions:	Drug: Induction Chemotherapy|Drug: Low-Risk Therapy|Drug: High-Risk Therapy|Drug: Intermediate-Risk Therapy
URL:	http://ClinicalTrials.gov/show/NCT00602667
Population :	Children
Start date :	November 2007
Estimated primary completion date:	December 2015
Title:	PPCR: Registry for Pedi Patients Treated With Proton RT
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Pediatric Patients Treated With Proton Beam Radiation Therapy
Interventions:	Other: No intervention
URL:	http://ClinicalTrials.gov/show/NCT01696721
Population :	Adults
Start date :	July 2012
Estimated primary completion date:	December 2015
Title:	Proton Radiotherapy for Recurrent Tumors
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Tumours

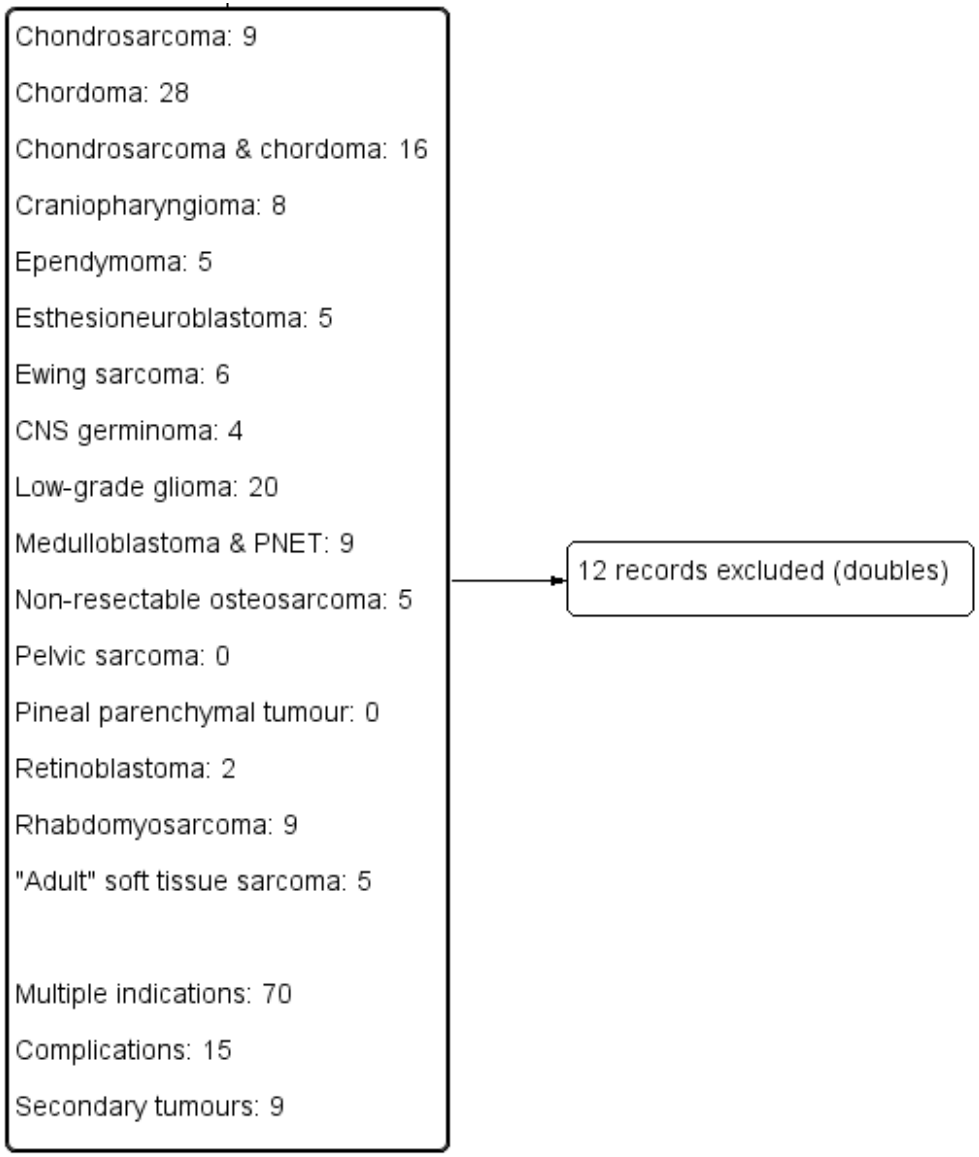
Interventions:	Proton Radiotherapy
URL:	http://clinicaltrials.gov/ct2/show/NCT01126476
Population :	Adults
Start date :	February 2010
Estimated primary completion date:	February 2015
Title:	Registry Study for Proton Therapy Clinical Outcomes and Long-Term Follow-up
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Cancer
Interventions:	
URL:	http://clinicaltrials.gov/ct2/show/NCT02070328
Population :	age not provided
Start date :	December 2013
Estimated primary completion date:	January 2022
Side effects	
Title:	Monitoring of Patients Treated With Particle Therapy Using Positron-Emission-Tomography (PET): The MIRANDA Study
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Particle Therapy
Interventions:	
URL:	http://ClinicalTrials.gov/show/NCT01528670
Population :	Adults
Start date :	January 2005
Estimated primary completion date:	September 2010
Title:	Data Collection of Normal Tissue Toxicity for Proton Therapy for Pediatrics
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Pediatric Cancer
Interventions:	Other: Data Collection|Other: Dose Distribution Data Collection
URL:	http://ClinicalTrials.gov/show/NCT01502150
Population :	Adults
Start date :	June 2005
Estimated primary completion date:	June 2020
Title:	Outcomes Study of Late Effects After Proton RT for Pediatric Tumors of the Brain, Head, and Neck
Recruitment:	Recruiting
Study Results:	No Results Available

Conditions:	Central Nervous System Tumors
Interventions:	
URL:	http://ClinicalTrials.gov/show/NCT01067196
Population :	Adults
Start date :	February 2010
Estimated primary completion date:	January 2021
Title:	Neurobehavioral Functioning in Pediatric Brain Tumor Patients After Proton Beam Radiation Treatment
Recruitment:	Active, not recruiting
Study Results:	No Results Available
Conditions:	Brain Tumor|Central Nervous System Neoplasms
Interventions:	
URL:	http://ClinicalTrials.gov/show/NCT01180881
Population :	Children and young adults
Start date :	October 2009
Estimated primary completion date:	March 2013
Title:	Data Collection of Normal Tissue Toxicity for Proton Therapy
Recruitment:	Recruiting
Study Results:	No Results Available
Conditions:	Cancer
Interventions:	
URL:	http://clinicaltrials.gov/ct2/show/NCT00991094
Population :	Adults
Start date :	May 2005
Estimated primary completion date:	September 2016

1.4. Flow chart for selection procedure

Figure 1 – Flow chart of study selection




Chondrosarcoma: 9
Chordoma: 28
Chondrosarcoma & chordoma: 16
Craniopharyngioma: 8
Ependymoma: 5
Esthesioneuroblastoma: 5
Ewing sarcoma: 6
CNS germinoma: 4
Low-grade glioma: 20
Medulloblastoma & PNET: 9
Non-resectable osteosarcoma: 5
Pelvic sarcoma: 0
Pineal parenchymal tumour: 0
Retinoblastoma: 2
Rhabdomyosarcoma: 9
"Adult" soft tissue sarcoma: 5
Multiple indications: 70
Complications: 15
Secondary tumours: 9
12 records excluded (doubles)

2. QUALITY APPRAISAL

2.1. Quality appraisal tools

For the assessment of the quality of comparative observational studies the Cochrane Collaboration's tool for assessing risk of bias (Table 3) was used with the addition of two extra items that account for the potential bias due to the selection of the study cohorts or the lack of randomisation: 'Concurrency of the intervention and comparator group' and 'Comparability of the intervention and comparator group'. For the first item low risk of bias was assigned if the participants in the intervention and comparator group were enrolled and followed-up concurrently (i.e. in parallel). For the second item low risk of bias was assigned in case of a matched study design and/or appropriate adjustment for confounders in the analysis.

Table 3 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors

Domain	Support for judgement	Review authors' judgement
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

2.2. Study selection and quality appraisal

2.2.1. Skull base chondrosarcoma & skull base and (para)spinal chordoma

2.2.1.1. Study selection

This part on study selection contains records on paediatric skull base and (para)spinal chordoma as well as records on paediatric skull base chondrosarcoma because most studies cover the two pathologies together. After screening titles and abstracts, 53 records covering skull base and (para)spinal chordoma and/or skull base chondrosarcoma as single indication were retained. Among those, three publications (probably all narrative reviews) were not retrieved[1-3]. In addition, 14 records covering multiple indications under study (among which skull base and (para)spinal chordoma and skull base chondrosarcoma in children or both children and adults) and 4 records covering complications were retained. No documents from HTA agencies' websites were retained.

Based on full-text evaluation, 2 primary studies were included [4, 5]. The rationale for exclusion of the reviews is presented in Table 4 and for exclusion of the other primary studies in Table 5.

Table 4 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Abubakar DS, et al. 2014 Paediatr. Child Health - Current perspectives on childhood brain tumours: a review	Narrative review
Almefty K, et al. 2007 Cancer 110(11):2457-2467 - Chordoma and chondrosarcoma: Similar, but quite different, skull base tumors	Narrative review
Alonso-Basanta M, et al. 2011 Otolaryngol. Clin. North Am. 44(5):1173-1183 - Proton Beam Therapy in Skull Base Pathology	Narrative review
Amichetti M, et al. 2009 Neurosurgical Review 32(4):403-416 - Proton therapy in chordoma of the base of the skull: a systematic review	All primary studies included in this review were published before 2007 and hence adopted in the previous KCE report (exception: Hoch et al. 2006, which is a clinicopathologic study focusing on histologic features)
Amichetti M, et al. 2010 Neurosurg. Rev. 33(2):155-165 - A systematic review of proton therapy in the treatment of chondrosarcoma of the skull base	Included studies were published before 2007; none included children only
Amichetti M, et al. 2012 Curr. Crug Ther. 7(4):235-247 - Current concepts on the management of chordoma	Narrative review
Amichetti M, et al. 2012 Radiation Oncology 7(210):- Radiosurgery with photons or protons for benign and malignant tumours of the skull base: a review	No systematic review
Bilsky MH, et al. 2008 Neurosurg. Clin. North Am. 19(1):119-123 - Radiation for Primary Spine Tumors	Narrative review
Bloch O, et al. 2013 Neurosurg. Clin. North Am. 24(1):89-96 - Skull Base Chondrosarcoma. Evidence-Based Treatment Paradigms	Narrative review
Brada M, et al. 2009 Cancer J. 15(4):319-324 - Current clinical evidence for proton therapy	Primary studies included in this review and published before 2007 were adopted in the previous KCE report (exception: Hoch et al. 2006, which is a clinicopathologic study focusing on histologic features); those published from 2007 on were adopted in the present report as primary studies
Casali PG, et al. 2007 Curr. Opin. Oncol. 19(4):367-370 - Chordoma	Narrative review
Chan AW, et al. 2008 J. Surg. Oncol. 97(8):697-700 - Proton radiation therapy for head and neck cancer	Narrative review

Reference	Reason(s) for exclusion
Chugh R, et al. 2007 Oncologist 12(11):1344-1350 - Chordoma: The nonsarcoma primary bone tumor	Narrative review
De Ruysscher D, et al. 2012 Radiother Oncol 103(1):5-7 - Charged particles in radiotherapy: a 5-year update of a systematic review	Primary studies included in this review and published before 2007 were adopted in the previous KCE report (exception: Hoch et al. 2006, which is a clinicopathologic study focusing on histologic features); those published from 2007 on were adopted in the present report as primary studies
Di Maio S, et al. 2011 J Neurosurg 115(6):1094-105 - Current comprehensive management of cranial base chordomas: 10-year meta-analysis of observational studies	Me(di)an age in included studies ranged between 38.3-53 y.o.; no separate results for children
Fukumitsu N 2012 Isrn Otolaryngology Print 965204(- Particle beam therapy for cancer of the skull base, nasal cavity, and paranasal sinus	Narrative review
Gelderblom H, et al. 2008 Oncologist 13(3):320-329 - The clinical approach towards chondrosarcoma	Narrative review
Habrand JL, et al. 2009 Cancer Radiother 13(6-7):550-5 - La protontherapie en radiotherapie pediatrique	Narrative review
Habrand JL, et al. 2013 Cancer Radiother 17(5-6):400-6 - Evolution des indications cliniques en hadrontherapie 2008-2012	Narrative review
Huh WW, et al. 2011 Cancer Treat. Rev. 37(6):431-439 - Pediatric sarcomas and related tumors of the head and neck	Narrative review
Koutourousiou M, et al. 2011 Otolaryngol. Clin. North Am. 44(5):1155-1171 - Skull base chordomas	Narrative review
Kraft G 2009 Med Monatsschr Pharm 32(9):328-34 - Tumortherapie mit Schwerionenstrahlen	Narrative review
Ladra MM, et al. 2014 Cancers 6(1):112-127 - Proton radiotherapy for pediatric sarcoma	Narrative review
Loeffler JS, et al. 2013 Nat Rev Clin Oncol 10(7):411-24 - Charged particle therapy-optimization, challenges and future directions	Narrative review
Macdonald OK, et al. 2009 Semin. Spine Surg. 21(2):121-128 - Radiotherapy for Primary and Metastatic Spinal Tumors	Narrative review
Mavrogenis AF, et al. 2012 Orthopedics 35(3):e379-e390 - Chondrosarcomas revisited	Narrative review
Mottard S, et al. 2010 Orthop. Trauma 24(5):332-341 - (ii) Chondrosarcomas	Narrative review
Nguyen QN, et al. 2008 Curr. Oncol. Rep. 10(4):338-343 - Emerging role of proton beam radiation therapy for chordoma and chondrosarcoma of the skull base	Narrative review

Reference	Reason(s) for exclusion
Ogino T 2012 Int. J. Clin. Oncol. 17(2):79-84 - Clinical evidence of particle beam therapy (proton)	Summary of clinical outcomes from systematic reviews
Olsen DR, et al. 2007 Radiother Oncol 83(2):123-32 - Proton therapy - a systematic review of clinical effectiveness	Systematic review already included in the previous KCE report. Dates of publication for the 6 studies included range from 1995 to 2003.
Sciubba DM, et al. 2008 Neurosurg. Clin. North Am. 19(1):5-15 - Chordoma of the Spinal Column	Narrative review
Stacchiotti S, et al. 2011 Curr. Oncol. Rep. 13(4):323-330 - Systemic therapy options for unresectable and metastatic chordomas	Narrative review
Timmermann B 2010 Klin. Padiatr. 222(3):127-133 - Proton beam therapy for childhood malignancies: Status report	Narrative review
Walcott BP, et al. 2012 Lancet Oncol. 13(2):e69-e76 - Chordoma: Current concepts, management, and future directions	Narrative review

Table 5 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Ares C, et al. 2009 Int. J. Radiat. Oncol. Biol. Phys. 75(4):1111-1118 - Effectiveness and Safety of Spot Scanning Proton Radiation Therapy for Chordomas and Chondrosarcomas of the Skull Base: First Long-Term Report	Only 3 children with chondrosarcoma and 3 children with chordoma included
Chen YL, et al. 2013 Spine 38(15):E930-E936 - Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas	Probably no children included (unclear data on age of the sample)
Choi GH, et al. 2010 Child's Nerv. Syst. 26(6):835-840 - Pediatric cervical chordoma: Report of two cases and a review of the current literature	Only 2 patients
Cloyd JM, et al. 2009 Spine J. 9(11):928-935 - En bloc resection of primary tumors of the cervical spine: report of two cases and systematic review of the literature	Only adults included
DeLaney TF, et al. 2009 Int. J. Radiat. Oncol. Biol. Phys. 74(3):732-739 - Phase II Study of High-Dose Photon/Proton Radiotherapy in the Management of Spine Sarcomas	Only adults included
Demizu Y, et al. 2009 Int. J. Radiat. Oncol. Biol. Phys. 75(5):1487-1492 - Analysis of Vision Loss Caused by Radiation-Induced Optic Neuropathy After Particle Therapy for Head-and-Neck and Skull-Base Tumors Adjacent to Optic Nerves	No separate results per indication; patients' age ranged between 15-85 y.o.
Deraniyagala RL, et al. 2014 J. Neurolog. Surg. Part B Skull Base 75(1):53-57 - Proton therapy for skull base chordomas: An outcome study from the University of Florida proton therapy institute	Only adults included

Reference	Reason(s) for exclusion
Foweraker KL, et al. 2007 Clin Oncol (R Coll Radiol) 19(7):509-16 - High-dose radiotherapy in the management of chordoma and chondrosarcoma of the skull base and cervical spine: Part 1--Clinical outcomes	Only adults included
Fuji H, et al. 2011 Skull Base 21(3):201-206 - Feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base	Mixture of children and adults
Grossbach A, et al. 2011 Neurosurgery 69(6):E1327-E1332 - Multicentric chordoma: A case report and review of the literature	Only 2 (adult) cases and narrative review
Holzmann D, et al. 2010 Minimally Invasive Neurosurg. 53(5-6):211-217 - The transnasal transclival approach for clivus chordoma	Only adults included
Hsu W, et al. 2011 Neurosurgery 68(4):E1160-E1164 - Clear-cell chondrosarcoma of the lumbar spine: Case report and review of the literature	Only 1 (adult) case and narrative review
Korchi AM, et al. 2013 Can. J. Neurol. Sci. 40(6):800-806 - Radiologic patterns of necrosis after proton therapy of skull base tumors	Only 2 cases with chondrosarcoma and 3 with chordoma
Mandonnet E, et al. 2008 Child's Nerv. Syst. 24(6):699-706 - Spectrum of skull base tumors in children and adolescents: A series of 42 patients and review of the literature	Only 3 patients with chordoma and 2 patients with chondrosarcoma
McDonald MW, et al. 2013 Int. J. Radiat. Oncol. Biol. Phys. 87(5):1107-1114 - Proton therapy for reirradiation of progressive or recurrent chordoma	Only adults included
Menezes AH, et al. 2014 J. Neursurg. Pediatr. 13(3):260-272 - Primary atlantoaxial bone tumors in children: Management strategies and long-term follow-up: Clinical article	Only two out of five cases with chordoma received proton-beam radiation
Mima M, et al. 2014 Br. J. Radiol. 87(1033):- Particle therapy using carbon ions or protons as a definitive therapy for patients with primary sacral chordoma	Only adults included
Miyawaki D, et al. 2009 Int. J. Radiat. Oncol. Biol. Phys. 75(2):378-384 - Brain Injury After Proton Therapy or Carbon Ion Therapy for Head-and-Neck Cancer and Skull Base Tumors	Age ranged between 23-81 y.o.; no separate results per indication
Nikoghosyan AV, et al. 2010 BMC cancer 10(606 - Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study	Study protocol
Nikoghosyan AV, et al. 2010 BMC cancer 10(607 - Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study	Study protocol
Pehlivan B, et al. 2012 Int. J. Radiat. Oncol. Biol. Phys. 83(5):1432-1440 - Temporal lobe toxicity analysis after proton radiation therapy for skull base tumors	Only 3 children with chondrosarcoma and 3 with chordoma
Roda RH, et al. 2009 J. Clin. Neurosci. 16(9):1220-1221 - Epilepsy and temporal lobe injury after skull base proton beam therapy	Only 1 child with chondrosarcoma and 1 with chordoma

Reference	Reason(s) for exclusion
Rutz HP, et al. 2007 Int. J. Radiat. Oncol. Biol. Phys. 67(2):512-520 - Extracranial chordoma: Outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation	Only 3 children included
Rutz HP, et al. 2008 Int. J. Radiat. Oncol. Biol. Phys. 71(1):220-225 - Postoperative Spot-Scanning Proton Radiation Therapy for Chordoma and Chondrosarcoma in Children and Adolescents: Initial Experience at Paul Scherrer Institute	Same cases were included in Rombi et al.
Schulz-Ertner D 2009 Cancer J. 15(4):306-311 - The clinical experience with particle therapy in adults	Only adults included
Seizeur R, et al. 2010 Rev. Neurol. 166(3):305-313 - Chondrosarcomas of skull base treatment	Only adults included
Sen C, et al. 2010 J Neurosurg 113(5):1059-71 - Clival chordomas: clinical management, results, and complications in 71 patients	Mixture of children and adults
Srivastava A, et al. 2013 J. Rad. Res. 54(SUPPL.1):i43-i48 - Quality of life in patients with chordomas/chondrosarcomas during treatment with proton beam therapy	Only adults included
Staab A, et al. 2011 Int. J. Radiat. Oncol. Biol. Phys. 81(4):e489-e496 - Spot-scanning-based proton therapy for extracranial chordoma	Mixture of children and adults
Wagner TD, et al. 2009 Int. J. Radiat. Oncol. Biol. Phys. 73(1):259-266 - Combination Short-Course Preoperative Irradiation, Surgical Resection, and Reduced-Field High-Dose Postoperative Irradiation in the Treatment of Tumors Involving the Bone	Mixture of children and adults
Yasuda M, et al. 2012 Neurosurg. Rev. 35(2):171-182 - Chordomas of the skull base and cervical spine: Clinical outcomes associated with a multimodal surgical resection combined with proton-beam radiation in 40 patients	Mixture of children and adults
Yoneoka Y, et al. 2008 Acta Neurochir (Wien) 150(8):773-8; discussion 778 - Cranial base chordoma--long term outcome and review of the literature	Mixture of children and adults

2.2.1.2. Quality appraisal

Quality appraisal of selected primary studies

Quality appraisal of selected primary studies was not performed as they were both retrospective case series.

2.2.2. Craniopharyngioma

2.2.2.1. Study selection

After screening titles and abstracts, 8 records covering craniopharyngioma were retained (see appendix, Figure 1). In addition, 11 records covering multiple indications under study (among which craniopharyngioma) were retained and 2 records covering complications of proton beam therapy. Moreover, 1 additional article published in July (and hence not included in our initial search) was suggested by one of the external experts and was also included[6]. No additional documents on craniopharyngioma were retrieved from HTA agencies' websites.

Based on full-text evaluation, 3 primary studies were included[6-8]. The rationale for exclusion of the other reviews is presented in Table 6 and for exclusion of the other primary studies in Table 7.

Table 6 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Abubakar DS, et al. 2014 Paediatr. Child Health - Current perspectives on childhood brain tumours: a review	Narrative review
Aggarwal A, et al. 2013 Pituitary 16(1):26-33 - Radiotherapy for craniopharyngioma	Narrative review
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Gridley DS, et al. 2010 Expert Rev. Neurother. 10(2):319-330 - Proton-beam therapy for tumors of the CNS	Narrative review
Habrand JL, et al. 2009 Cancer Radiother 13(6-7):550-5 - La protonthérapie en radiotherapie pédiatrique	Narrative review
Habrand JL, et al. 2013 Cancer Radiother 17(5-6):400-6 - Evolution des indications cliniques en hadrontherapie 2008-2012	Narrative review
Iannalfi A, et al. 2013 Clin. Oncol. 25(11):654-667 - Radiotherapy in craniopharyngiomas	Included studies on PBT (Fitzek 2006 and Luu 2006) adopted a mixed population of children and adults (when age at PBT was considered)
Kortmann RD 2011 Frontiers in Endocrinology 2(100):- Different approaches in radiation therapy of craniopharyngioma	Narrative review
Loeffler JS, et al. 2013 Nat Rev Clin Oncol 10(7):411-24 - Charged particle therapy--optimization, challenges and future directions	Narrative review

Merchant TE 2009 Cancer J. 15(4):298-305 - Proton beam therapy in pediatric oncology	Narrative review
Merchant TE 2013 Semin. Radiat. Oncol. 23(2):97-108 - Clinical controversies: Proton therapy for pediatric tumors	Narrative review
Muller HL 2013 Pituitary 16(1):56-67 - Childhood craniopharyngioma	Narrative review
Stieber VW 2008 J. Neuro-Ophthalmol. 28(3):222-230 - Radiation therapy for visual pathway tumors	Narrative review
Timmermann B 2010 Klin. Padiatr. 222(3):127-133 - Proton beam therapy for childhood malignancies: Status report	Narrative review

Table 7 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Amsbaugh MJ, et al. 2012 Pract. Radiat. Oncol. 2(4):314-318 - Spot scanning proton therapy for craniopharyngioma	Case report
Beltran C, et al. 2012 Int. J. Radiat. Oncol. Biol. Phys. 82(2):e281-e287 - On the benefits and risks of proton therapy in pediatric craniopharyngioma	Dosimetric study design
Combs SE, et al. 2013 Acta Oncol. 52(7):1504-1509 - Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base	No results or details on treatment documented for the 5 patients with craniopharyngioma
Suneja G, et al. 2013 Pediatr. Blood Cancer 60(9):1431-1436 - Acute toxicity of proton beam radiation for pediatric central nervous system malignancies	Only 4 patients with craniopharyngioma included
Viswanathan V, et al. 2011 Endocr Pract 17(6):891-6 - Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors	No results reported separately for the 7 children with craniopharyngioma; unclear whether the 7 children with craniopharyngioma received PBT alone or PBT + conventional RT

2.2.2.2. Quality appraisal

Quality appraisal of selected primary studies

Quality appraisal was only performed for the comparative study (Bishop et al. 2014) and not for the retrospective case series.

Table 8 – Risk of bias summary of included primary study

Domains	Options	Bishop 2014
Domain 1: Selection bias		
1. Can selection bias sufficiently be excluded?	Yes/No/Insufficient info to assess	No
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	Yes/No/Insufficient info to assess	Yes
Domain 2: Detection bias		
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Yes/No/Insufficient info to assess	Insufficient info to assess
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes/No/Insufficient info to assess	No
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	Yes/No/Insufficient info to assess	Yes
6. Is the assessment of outcome made blind to exposure status?	Yes/No/Insufficient info to assess	No
If no to question 6, does this have an impact on the assessment of the outcome?	Yes/No/ Not possible in this type of exposure /Insufficient info to assess	Insufficient info to assess
7. Is the follow-up sufficiently long to measure all relevant outcomes?	Yes/No/Insufficient info to assess	No
Domain 3: Attrition bias		
8. Can selective loss-to-follow-up be sufficiently excluded?	Yes/No/Insufficient info to assess	Insufficient info to assess

2.2.3. Ependymoma

2.2.3.1. Study selection

After screening titles and abstracts, 5 records covering ependymoma were retained (see appendix, Figure 1). In addition, 2 records covering multiple indications under study (among which ependymoma) were retained, but not further discussed in this chapter as they are reported in the Glioma chapter and concern only 4 patients with ependymoma.

Based on full-text evaluation, 3 primary studies were included[9-11] but as all patients included in the MacDonald 2008 publication[11] were also comprised in the MacDonald 2013 report[10], the former was excluded. The rationale for exclusion of the reviews is presented in Table 9 and for exclusion of the other primary studies in Table 10.

Table 9 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Abubakar DS, et al. 2014 Paediatr. Child Health - Current perspectives on childhood brain tumours: a review	Narrative review
Allen AM, et al. 2012 Radiother. Oncol. 103(1):8-11 - An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee	Narrative review
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Gridley DS, et al. 2010 Expert Rev. Neurother. 10(2):319-330 - Proton-beam therapy for tumors of the CNS	Narrative review
Hardy P, et al. 2008 J. Radiother. Pract. 7(1):9-18 - What are the potential benefits and limitations of particle therapy in the treatment of paediatric malignancies?	No evidence tables; no quality appraisal of included studies
MacDonald SM, et al. 2010 Child's Nerv. Syst. 26(3):285-291 - Proton beam therapy following resection for childhood ependymoma	Narrative review
Merchant TE 2009 Cancer J. 15(4):298-305 - Proton beam therapy in pediatric oncology	Narrative review
Merchant TE 2013 Semin. Radiat. Oncol. 23(2):97-108 - Clinical controversies: Proton therapy for pediatric tumors	Narrative review
Patel TR, et al. 2012 Hematol. Oncol. Clin. North Am. 26(4):757-777	Narrative review
Timmermann B 2010 Klin. Padiatr. 222(3):127-133 - Proton beam therapy for childhood malignancies: Status report	Narrative review

Table 10 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Barney CL, et al. 2014 Neuro-Oncology 16(2):303-309 - Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Only 2 patients with ependymoma
Kuhlthau KA, et al. 2012 J Clin Oncol 30(17):2079-86 - Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy	Health related QoL at the start of the treatment; results not controlled for type of treatment (e.g. whether chemo was included) or type of PBT (craniospinal irradiation vs. partial brain irradiation)
MacDonald, S. M., S. Safai, et al. (2008). "Proton Radiotherapy for Childhood Ependymoma: Initial Clinical Outcomes and Dose Comparisons." Int. J. Radiat. Oncol. Biol. Phys. 71(4): 979-986.	All patients included in MacDonald 2013
Sabin ND, et al. 2013 AJNR Am J Neuroradiol 34(2):446-50 - Imaging changes in very young children with brain tumors treated with proton therapy and chemotherapy	Only 4 patients with ependymoma
Ray GL, et al. 2013 Pediatr. Blood Cancer 60(11):1839-1841 - Definitive treatment of leptomeningeal spinal metastases in children	No results reported separately by indication
Suneja G, et al. 2013 Pediatr. Blood Cancer 60(9):1431-1436 - Acute toxicity of proton beam radiation for pediatric central nervous system malignancies	No results reported separately by indication
Viswanathan V, et al. 2011 Endocr Pract 17(6):891-6 - Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors	Only 2 patients with ependymoma

2.2.3.2. Quality appraisal

Quality appraisal of selected primary studies

Quality appraisal of the selected studies was not performed as only case series were included.

2.2.4. Esthesioneuroblastoma

2.2.4.1. Study selection

After screening titles and abstract, 5 records covering esthesioneuroblastoma were retained (see appendix, Figure 1). In addition, 3 records covering multiple indications under study (among which esthesioneuroblastoma) and 3 records covering side effects after proton beam therapy were retained. No documents from HTA agencies' websites were retained.

Based on full-text evaluation, 2 primary studies were included. The rationale for exclusion of the other studies is presented in Table 11 and Table 12.

Table 11 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Cianchetti M, et al. 2012 International journal of otolaryngology 325891- Sinonasal malignancies and charged particle radiation treatment: a systematic literature review	No quality assessment (only included study on esthesioneuroblastoma is Zenda et al. 2011, which was also excluded (cf. infra))

Table 12 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Demizu Y, et al. 2009 Int. J. Radiat. Oncol. Biol. Phys. 75(5):1487-1492 - Analysis of Vision Loss Caused by Radiation-Induced Optic Neuropathy After Particle Therapy for Head-and-Neck and Skull-Base Tumors Adjacent to Optic Nerves	Only 4 patients with ONB treated with proton; no separate results per indication; patients' age ranged between 15-85 y.o.
Hojo H, et al. 2012 J. Radiat. Res. 53(5):704-709 - Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies	Adults (in scope for this indication: children); no separate results per indication (ONB: 20/65 patients)
Koto M, et al. 2013 Radiother. Oncol. - Risk factors for brain injury after carbon ion radiotherapy for skull base tumors	Only 4 patients with esthesioneuroblastoma
Miyawaki D, et al. 2009 Int. J. Radiat. Oncol. Biol. Phys. 75(2):378-384 - Brain Injury After Proton Therapy or Carbon Ion Therapy for Head-and-Neck Cancer and Skull Base Tumors	Only 4 patients with ONB treated with proton; no separate results per indication; patients' age ranged between 23-81 y.o.
Nichols AC, et al. 2008 Skull Base 18(5):327-336 - Esthesioneuroblastoma: The Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital experience with craniofacial resection, proton beam radiation, and chemotherapy	Cases also included in Herr et al., 2014 (which is included)
Nishimura H, et al. 2007 Int. J. Radiat. Oncol. Biol. Phys. 68(3):758-762 - Proton-Beam Therapy for Olfactory Neuroblastoma	Adults (in scope for this indication: children) (retrospective series of 14 cases)
Okano S, et al. 2012 Jpn. J. Clin. Oncol. 42(8):691-696 - Induction chemotherapy with docetaxel, cisplatin and s-1 followed by proton beam therapy concurrent with cisplatin in patients with t4b nasal and sinonasal malignancies	Adults (in scope for this indication: children); no separate results per indication (ONB: 7/13 patients); focus on induction chemotherapy
Resto VA, et al. 2008 Head Neck 30(2):222-229 - Extent of surgery in the management of locally advanced sinonasal malignancies	All patients older than 15 y.o. (in scope for this indication: children)

Reference	Reason(s) for exclusion
Zenda S, et al. 2011 Int. J. Radiat. Oncol. Biol. Phys. 81(5):1473-1478 - Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses	Adults (in scope for this indication: children); no separate results per indication (ONB: 9/39 patients)

2.2.4.2. Quality appraisal

Quality appraisal of selected primary studies (cohort studies)

Quality appraisal of the selected study was not performed as it was a retrospective case series.

2.2.5. Ewing sarcoma

2.2.5.1. Study selection

After screening titles and abstracts, 6 records covering Ewing sarcoma were retained (see appendix, Figure 1). In addition, 9 records covering multiple indications under study (among which Ewing sarcoma) were retained and 1 record covering complications of proton beam therapy. No additional documents on Ewing sarcoma were retrieved from HTA agencies' websites.

Based on full-text evaluation, 1 primary study[12] was included. The rationale for exclusion of the other reviews is presented in Table 13 and for exclusion of the other primary studies in Table 14.

Table 13 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Bolling T, et al. 2013 Clin. Oncol. 25(1):19-26 - Management of Bone Tumours in Paediatric Oncology	Narrative review
Chuba PJ 2013 J. Radiat. Oncol. 2(2):149-158 - Radiation therapy strategies and clinical trials in pediatric Ewing's sarcoma	Narrative review
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Habrand JL, et al. 2009 Cancer Radiother 13(6-7):550-5 - La protontherapie en radiotherapie pediatrique	Narrative review
Ladra MM, et al. 2014 Cancers 6(1):112-127 - Proton radiotherapy for pediatric sarcoma	Narrative review
Merchant TE, et al. 2014 Curr. Opin. Pediatr. 26(1):3-8 - Proton beam therapy: A fad or a new standard of care	Narrative review
Merchant TE 2013 Semin. Radiat. Oncol. 23(2):97-108 - Clinical controversies: Proton therapy for pediatric tumors	Narrative review
Macdonald OK, et al. 2009 Semin. Spine Surg. 21(2):121-128 - Radiotherapy for Primary and Metastatic Spinal Tumors	Narrative review

Table 14 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Barney CL, et al. 2014 Neuro-Oncology 16(2):303-309 - Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Only adults included
Gray ST, et al. 2009 Skull Base 19(6):409-416 - Efficacy of proton beam therapy in the treatment of Ewing's sarcoma of the paranasal sinuses and anterior skull base	Only 2 patients included
Mandonnet E, et al. 2008 Child's Nerv. Syst. 24(6):699-706 - Spectrum of skull base tumors in children and adolescents: A series of 42 patients and review of the literature	Only 1 patient with Ewing sarcoma included, who was not treated with PBT
Hattangadi, J., B. Esty, et al. (2012). "Radiation recall myositis in pediatric Ewing sarcoma." Pediatr. Blood Cancer 59(3): 570-572.	Only 2 patients included
Iwata S, et al. 2013 Int. J. Clin. Oncol. 18(6):1114-1118 - Efficacy of carbon-ion radiotherapy and high-dose chemotherapy for patients with unresectable Ewing's sarcoma family of tumors	All patients were treated with carbon-ion therapy
Viswanathan V, et al. 2011 Endocr Pract 17(6):891-6 - Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors	Only 1 patient with Ewing sarcoma
Xie CF, et al. 2010 Chin 29(4):420-4 - Extraskeletal Ewing's sarcoma: a report of 18 cases and literature review	No patient treated with PBT

2.2.5.2. Quality appraisal

The quality appraisal was not performed for the Rombi et al.[12] study as it is a retrospective case series.

2.2.6. CNS Germinoma

2.2.6.1. Study selection

After screening titles and abstracts, 4 records covering CNS germinoma were retained (see appendix, Figure 1). In addition, 6 records covering multiple indications under study (among which CNS germ cell tumours) were retained and 2 records covering complications and quality of life impact of proton beam therapy. No documents on CNS germinoma were retrieved from HTA agencies' websites.

Based on full-text evaluation, only 1 primary study was included. The rationale for exclusion of the other studies is presented in Appendix, Table 6 and Table 16.

Table 15 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Gezondheidsraad 2009 Health Technology Assessment Database 1):- Proton radiotherapy	Databases not mentioned; no evidence tables; no quality appraisal of included studies
Gridley DS, et al. 2010 Expert Rev. Neurother. 10(2):319-330 - Proton-beam therapy for tumors of the CNS	Narrative review
Kortmann RD 2014 Expert Rev. Anticancer Ther. 14(1):105-119 - Current concepts and future strategies in the management of intracranial germinoma	Narrative review
Kun LE, et al. 2009 Pediatr. Radiol. 39(SUPPL. 1):S65-S70 - Radiation therapy for children: Evolving technologies in the era of ALARA	Narrative review
Patel TR, et al. 2012 Hematol. Oncol. Clin. North Am. 26(4):757-777	Narrative review

Table 16 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Barney CL, et al. 2014 Neuro-Oncology 16(2):303-309 - Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Only adults included (in scope for this indication: children; disease entity in the pediatric population may differ from the adult population[a])
Diluna ML, et al. 2009 J. Neuro-Oncol. 95(3):437-443 - Primary, non-exophytic, optic nerve germ cell tumors	Only 2 patients with CNS germ cell tumours
Kuhlthau KA, et al. 2012 J Clin Oncol 30(17):2079-86 - Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy	Health related QoL at the start of the treatment; results not controlled for type of treatment (e.g. whether chemo was included) or type of PBT (craniospinal irradiation vs. partial brain irradiation)
Suneja G, et al. 2013 Pediatr. Blood Cancer 60(9):1431-1436 - Acute toxicity of proton beam radiation for pediatric central nervous system malignancies	No results separately per indication
Viswanathan V, et al. 2011 Endocr Pract 17(6):891-6 - Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors	Only 1 patient with CNS germ cell tumours

[a] http://clinicaltrials.gov/show/NCT01049230

2.2.6.2. Quality appraisal

Quality appraisal of the selected study was not performed as it was a retrospective case series.

Grade profiles

Table 17 – Grade profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival 100%	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low
Progression-free survival 95%	1	-2	-1	-1	-1	0	1: Serious methodological limitations 2: Only one study 3: Data not separately presented for germinoma and NGGCT 4: Low sample size	Very low
Local recurrence rate Germinoma: 0/13 NGGCT: 1/9 (peritoneal)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low
Distal recurrence rate Germinoma: 0/13 NGGCT: 1/9 (peritoneal)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

2.2.7. Low-grade glioma

2.2.7.1. Study selection

After screening titles and abstract, 20 records covering glioma were retained (see appendix, Figure 1). An additional paper was obtained through the update of the search which was performed in September 2014[13]. In addition, 17 records covering multiple indications under study (among which glioma) and 2 records covering complications and quality of life impact of proton therapy were retained.

Based on full-text evaluation, 2 primary studies were included[13, 14]. The rationale for exclusion of the other reviews is presented in Table 18 and for exclusion of the other primary studies in Table 19.

Table 18 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Abubakar DS, et al. 2014 Paediatr. Child Health - Current perspectives on childhood brain tumours: a review	Narrative review
Combs SE, et al. 2007 BMC Cancer 7(- Radiotherapeutic alternatives for previously irradiated recurrent gliomas	Narrative review
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Gezondheidsraad 2009 Health Technology Assessment Database 1):- Proton radiotherapy	Databases not mentioned; no evidence tables; no quality appraisal of included studies
Gridley DS, et al. 2010 Expert Rev. Neurother. 10(2):319-330 - Proton-beam therapy for tumors of the CNS	Narrative review
Habrand JL, et al. 2009 Cancer Radiother 13(6-7):550-5 - La protontherapie en radiotherapie pediatrique	Narrative review
Hadziahmetovic M, et al. 2011 Future Oncol. 7(10):1169-1183 - Recent advancements in multimodality treatment of gliomas	Narrative review
Kortmann RD 2011 Onkologe 17(1):37-43 - Radiotherapy of brain gliomas in adulthood	Narrative review
Loeffler JS, et al. 2013 Nat Rev Clin Oncol 10(7):411-24 - Charged particle therapy--optimization, challenges and future directions	Narrative review
Mahajan A 2013 J. Radiat. Oncol. 2(2):129-133 - Pediatric low-grade glioma	Narrative review
Mannina E, et al. 2014 Pract. Radiat. Oncol. 4(1):50-54 - Steroid-induced adaptive proton planning in a pediatric patient with low grade glioma: A case report and literature review	Full text not retrieved
Merchant TE 2009 Cancer J. 15(4):298-305 - Proton beam therapy in pediatric oncology	Narrative review

Reference	Reason(s) for exclusion
Minturn JE, et al. 2013 Curr. Treat. Options Neurol. 15(3):316-327 - Gliomas in children	Narrative review
Oh DS, et al. 2012 Curr. Drug Discov. Technol. 9(4):268-279 - Targeted radiotherapy for malignant gliomas	Narrative review
Patel TR, et al. 2012 Hematol. Oncol. Clin. North Am. 26(4):757-777	Narrative review
Semenova J 2009 J Pediatr Oncol Nurs 26(3):142-149 - Proton beam radiation therapy in the treatment of pediatric central nervous system malignancies: a review of the literature	Narrative review
Sminia P, et al. 2012 Cancers 4(2):379-399 - External beam radiotherapy of recurrent glioma: Radiation tolerance of the human brain	Narrative review
Stieber VW 2008 J. Neuro-Ophthalmol. 28(3):222-230 - Radiation therapy for visual pathway tumors	Narrative review
Taw BBT, et al. 2012 Neurosurg. Clin. North Am. 23(2):259-267 - Radiation Options for High-Grade Gliomas	Narrative review
Timmermann B 2010 Klin. Padiatr. 222(3):127-133 - Proton beam therapy for childhood malignancies: Status report	Narrative review

Table 19 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Barney CL, et al. 2014 Neuro-Oncology 16(2):303-309 - Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Only 1 adult with glioma included
Combs SE, et al. 2010 BMC cancer 10(533 - Randomised phase I/II study to evaluate carbon ion radiotherapy versus fractionated stereotactic radiotherapy in patients with recurrent or progressive gliomas: the CINDERELLA trial	Study protocol
Combs SE, et al. 2010 BMC cancer 10(478 - Randomized phase II study evaluating a carbon ion boost applied after combined radiochemotherapy with temozolomide versus a proton boost after radiochemotherapy with temozolomide in patients with primary glioblastoma: the CLEOPATRA trial	Study protocol
Combs SE, et al. 2013 Acta Oncol. 52(7):1504-1509 - Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base	Patients with glioma treated with carbon ion only (results of the 2 above study protocols)
Combs SE, et al. 2013 Radiother. Oncol. 108(1):132-135 - Comparison of carbon ion radiotherapy to photon radiation alone or in combination with temozolomide in patients with high-grade gliomas: Explorative hypothesis-generating retrospective analysis	Post-hoc analysis of Mizoe 2007 using carbon ion in adults
Hauswald H, et al. 2012 Radiat. Oncol. 7(1):- First experiences in treatment of low-grade glioma grade I and II with proton therapy	Adults and children included; no separate results for children
Kahn J, et al. 2011 Int. J. Radiat. Oncol. Biol. Phys. 81(1):232-238 - Long-term outcomes of patients with spinal cord gliomas treated by modern conformal radiation techniques	Adults and children included; no separate results for children

Reference	Reason(s) for exclusion
Kuhlthau KA, et al. 2012 J Clin Oncol 30(17):2079-86 - Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy	Health related QoL at the start of the treatment; results not controlled for type of treatment (e.g. whether chemo was included) or type of PBT (craniospinal irradiation vs. partial brain irradiation)
Matsuda M, et al. 2011 Br. J. Radiol. 84(SPEC. ISSUE 1):S54-S60 - Prognostic factors in glioblastoma multiforme patients receiving high-dose particle radiotherapy or conventional radiotherapy	Only adults included
Matsumura A, et al. 2009 Appl. Radiat. Isot. 67(7-8 SUPPL.):S12-S14 - Current practices and future directions of therapeutic strategy in glioblastoma: Survival benefit and indication of BNCT	Unclear reporting of data (no patient characteristics, no detailed info on treatment nor on results)
Maucort-Boulch D, et al. 2010 Cancer Radiotherapie 14(1):34-41 - Rationale for carbon ion therapy in high-grade glioma based on a review and a meta-analysis of neutron beam trials	Comparison between neutron and carbon ion therapy (no proton therapy)
Mizoe JE, et al. 2007 Int J Radiat Oncol Biol Phys 69(2):390-6 - Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy	Only adults included; treatment with carbon ion
Mizumoto M, et al. 2013 Strahlenther. Onkol. 189(8):656-663 - Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy: Technical considerations based on experience at a single institution	No patient with glioma included
Mizumoto M, et al. 2010 Int. J. Radiat. Oncol. Biol. Phys. 77(1):98-105 - Phase I/II Trial of Hyperfractionated Concomitant Boost Proton Radiotherapy for Supratentorial Glioblastoma Multiforme	Only adults included
Rieken S, et al. 2011 Int. J. Radiat. Oncol. Biol. Phys. 81(5):e793-e801 - Assessment of early toxicity and response in patients treated with proton and carbon ion therapy at the Heidelberg ion therapy center using the raster scanning technique	Only 4 patients treated with proton beam therapy
Suneja G, et al. 2013 Pediatr. Blood Cancer 60(9):1431-1436 - Acute toxicity of proton beam radiation for pediatric central nervous system malignancies	No results separately per indication
Viswanathan V, et al. 2011 Endocr Pract 17(6):891-6 - Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors	Only 4 patients with glioma
Wind JJ, et al. 2012 Neurosurg. Clin. North Am. 23(2):247-258 - The Role of Adjuvant Radiation Therapy in the Management of High-Grade Gliomas	Patients treated with carbon ion only

2.2.7.2. Quality appraisal

Quality appraisal of the selected studies was not performed as it were retrospective case series.

2.2.8. Medulloblastoma & PNET

2.2.8.1. Study selection

After screening titles and abstract, 9 records covering medulloblastoma were retained (see appendix, Figure 1). In addition, 12 records covering multiple indications under study (among which medulloblastoma) were retained and 4 records covering complications of proton beam therapy. No additional documents on medulloblastoma were retrieved from HTA agencies' websites.

Based on full-text evaluation, 3 primary studies were included[15-17]. The rationale for exclusion of the other reviews is presented in Table 20 and for exclusion of the other primary studies in Table 21.

Table 20 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Abubakar DS, et al. 2014 Paediatr. Child Health - Current perspectives on childhood brain tumours: a review	Narrative review
Bartlett F, et al. 2013 Clin. Oncol. 25(1):36-45 - Medulloblastoma	Narrative review
Bourdeaut F, et al. 2011 Curr. Opin. Oncol. 23(6):630-637 - Medulloblastomas: Update on a heterogeneous disease	Narrative review
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Fossati P, et al. 2009 Cancer Treat. Rev. 35(1):79-96 - Pediatric medulloblastoma: Toxicity of current treatment and potential role of protontherapy	Narrative review
Gezondheidsraad 2009 Health Technology Assessment Database 1):- Proton radiotherapy	Databases not mentioned; no evidence tables; no quality appraisal of included studies
Gridley DS, et al. 2010 Expert Rev. Neurother. 10(2):319-330 - Proton-beam therapy for tumors of the CNS	Narrative review
Gudrunardottir T, et al. 2014 Child's Nerv. Syst. 1-12 - Treatment developments and the unfolding of the quality of life discussion in childhood medulloblastoma: a review	Narrative review
Hardy P, et al. 2008 J. Radiother. Pract. 7(1):9-18 - What are the potential benefits and limitations of particle therapy in the treatment of paediatric malignancies?	No evidence tables; no quality appraisal of included studies
Loeffler JS, et al. 2013 Nat Rev Clin Oncol 10(7):411-24 - Charged particle therapy--optimization, challenges and future directions	Narrative review

Reference	Reason(s) for exclusion
Merchant TE 2009 Cancer J. 15(4):298-305 - Proton beam therapy in pediatric oncology	Narrative review
Merchant TE 2013 Semin. Radiat. Oncol. 23(2):97-108 - Clinical controversies: Proton therapy for pediatric tumors	Narrative review
Semenova J 2009 J Pediatr Oncol Nurs 26(3):142-149 - Proton beam radiation therapy in the treatment of pediatric central nervous system malignancies: a review of the literature	Narrative review
Von Hoff K, et al. 2012 Curr. Treat. Options Neurol. 14(4):416-426 - Medulloblastoma	Narrative review

Table 21 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Barney CL, et al. 2014 Neuro-Oncology 16(2):303-309 - Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Only adults included
Brown AP, et al. 2013 Int. J. Radiat. Oncol. Biol. Phys. 86(2):277-284 - Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma	Only adults included
Krause M, et al. 2014 Strahlenther Onkol 190(1):111-2 - Geringere Akuttoxizitat bei Erwachsenen mit Medulloblastom durch kraniospinale Strahlentherapie mit Protonen	Only adults included
Kuhlthau KA, et al. 2012 J Clin Oncol 30(17):2079-86 - Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy	Health related QoL at the start of the treatment; results not controlled for type of treatment (e.g. whether chemo was included) or type of PBT (craniospinal irradiation vs. partial brain irradiation)
Ray GL, et al. 2013 Pediatr. Blood Cancer 60(11):1839-1841 - Definitive treatment of leptomeningeal spinal metastases in children	No results reported separately by indication
Sabin ND, et al. 2013 AJNR Am J Neuroradiol 34(2):446-50 - Imaging changes in very young children with brain tumors treated with proton therapy and chemotherapy	Only 1 patient with medulloblastoma and 1 patient with PNET
Suneja G, et al. 2013 Pediatr. Blood Cancer 60(9):1431-1436 - Acute toxicity of proton beam radiation for pediatric central nervous system malignancies	No results reported separately by indication
Viswanathan V, et al. 2011 Endocr Pract 17(6):891-6 - Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors	Unclear number of patients in group PBT and in group PBT + conventional RT for each tumour type

2.2.8.2. Quality appraisal

Quality appraisal of selected primary studies was not performed as they were all case-series.

2.2.9. Non-resectable osteosarcoma

2.2.9.1. Study selection

After screening titles and abstract, 5 records covering osteosarcoma were retained (see appendix, Figure 1). In addition, 5 records covering multiple indications under study (among which non-resectable osteosarcoma) were retained and 1 record covering side effects after proton radiotherapy for non-resectable osteosarcoma. No studies on secondary malignancies were retained. No documents on non-resectable osteosarcoma were retrieved from HTA agencies' websites.

Based on full-text evaluation, only one study on proton beam therapy (Ciernik et al., 2011[18]) and one on carbon ion therapy (Matsunobu et al., 2012[19]). The rationale for exclusion of the other studies is presented in Table 22 and Table 23.

Table 22 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Ando K, et al. 2013 Cancers 5(2):591-616 - Current therapeutic strategies and novel approaches in osteosarcoma	Narrative review
Bolling T, et al. 2013 Clin. Oncol. 25(1):19-26 - Management of Bone Tumours in Paediatric Oncology	Narrative review
Huh WW, et al. 2011 Cancer Treat. Rev. 37(6):431-439 - Pediatric sarcomas and related tumors of the head and neck	Narrative review
Katonis P, et al. 2013 Clin. Med. Insights: Oncol. 7:199-208 - Spinal osteosarcoma	Narrative review
Ladra MM, et al. 2014 Cancers 6(1):112-127 - Proton radiotherapy for pediatric sarcoma	Narrative review
Macdonald OK, et al. 2009 Semin. Spine Surg. 21(2):121-128 - Radiotherapy for Primary and Metastatic Spinal Tumors	Narrative review

Table 23 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Barney CL, et al. 2014 Neuro-Oncology 16(2):303-309 - Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Only adults included (in scope for this indication: children)
Blattmann C, et al. 2010 BMC Cancer 10- Non-randomized therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with non-resectable osteosarcoma	Study protocol
Rieken S, et al. 2011 Int. J. Radiat. Oncol. Biol. Phys. 81(5):e793-e801 - Assessment of early toxicity and response in patients treated with proton and carbon ion therapy at the Heidelberg ion therapy center using the raster scanning technique	Only 1 patient with osteosarcoma in the study

2.2.9.2. Quality appraisal

Quality appraisal of selected primary studies

Quality appraisal of selected studies was not performed as it were retrospective case series.

2.2.10. Pelvic sarcomas

2.2.10.1. Study selection

After screening titles and abstract, no records covering pelvic sarcomas were retained (see appendix, Figure 1). Two records covering multiple indications under study (among which pelvic sarcomas) were retained. No documents on pelvic sarcomas were retrieved from HTA agencies' websites.

Based on full-text evaluation, no studies were included; the rationale for the exclusions is presented in Table 24.

Table 24 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Hardy P, et al. 2008 J. Radiother. Pract. 7(1):9-18 - What are the potential benefits and limitations of particle therapy in the treatment of paediatric malignancies?	No evidence tables; no quality appraisal of included studies
Merchant TE 2013 Semin. Radiat. Oncol. 23(2):97-108 - Clinical controversies: Proton therapy for pediatric tumors	Narrative review

2.2.11. Pineal parenchymal tumours

2.2.11.1. Study selection

After screening titles and abstract, no records covering pineal parenchymal tumours were retained (see appendix, Figure 1). Four records covering multiple indications under study (among which pineal parenchymal tumours) and 1 record on complications after PBT were retained. No documents on pineal parenchymal tumours were retrieved from HTA agencies' websites.

Based on full-text evaluation, no studies were included; the rationale for the exclusions is presented in Table 25 and Table 26.

Table 25 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Abubakar DS, et al. 2014 Paediatr. Child Health - Current perspectives on childhood brain tumours: a review	Narrative review
Gridley DS, et al. 2010 Expert Rev. Neurother. 10(2):319-330 - Proton-beam therapy for tumors of the CNS	Narrative review
Hardy P, et al. 2008 J. Radiother. Pract. 7(1):9-18 - What are the potential benefits and limitations of particle therapy in the treatment of paediatric malignancies?	No evidence tables; no quality appraisal of included studies

Table 26 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Barney CL, et al. 2014 Neuro-Oncology 16(2):303-309 - Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Adults (in scope for this indication: children)
Suneja G, et al. 2013 Pediatr. Blood Cancer 60(9):1431-1436 - Acute toxicity of proton beam radiation for pediatric central nervous system malignancies	Only 1 patient with pinealoblastoma

2.2.12. Retinoblastoma

2.2.12.1. Study selection

After screening titles and abstract, 2 records covering retinoblastoma were retained (see appendix, Figure 1). In addition, 5 records covering multiple indications under study (among which retinoblastoma) were retained and 1 record covering secondary malignancies after proton radiotherapy for retinoblastoma. No studies on side-effects or on the quality of life impact of proton radiotherapy were retained. No documents on retinoblastoma were retrieved from HTA agencies' websites.

Based on full-text evaluation, only the study covering secondary malignancies after proton radiotherapy for retinoblastoma was included (Sethi, 2014). The rationale for exclusion of the other studies is presented Table 27 and Table 28.

Table 27 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Gezondheidsraad 2009 Health Technology Assessment Database 1):- Proton radiotherapy	Databases not mentioned; no evidence tables; no quality appraisal of included studies
Habrand JL, et al. 2013 Cancer Radiother 17(5-6):400-6 - Evolution des indications cliniques en hadrontherapie 2008-2012	Narrative review
Hardy P, et al. 2008 J. Radiother. Pract. 7(1):9-18 - What are the potential benefits and limitations of particle therapy in the treatment of paediatric malignancies?	No evidence tables; no quality appraisal of included studies
Semenova J 2009 J Pediatr Oncol Nurs 26(3):142-149 - Proton beam radiation therapy in the treatment of pediatric central nervous system malignancies: a review of the literature	Narrative review

Table 28 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Chang JW, et al. 2011 Korean J Ophthalmol 25(6):387-393 - The clinical outcomes of proton beam radiation therapy for retinoblastomas that were resistant to chemotherapy and focal treatment	3 patients (resistant to chemotherapy and focal treatment[b])
Munier FL, et al. 2008 Clin. Exp. Ophthalmol. 36(1):78-89 - New developments in external beam radiotherapy for retinoblastoma: From lens to normal tissue-sparing techniques	3 patients treated with salvage proton beam therapy; 1 patient with adjuvant proton beam therapy

[b] In 2/3 patients the end result was recurrence and enucleation of the eye

2.2.12.2. Quality appraisal

Quality appraisal of selected primary studies

Table 29 – Risk of bias summary of included primary studies

Domains	Options	Sethi 2014[20]
Domain 1: Selection bias		
Can selection bias sufficiently be excluded?	Yes/No/Insufficient info to assess	Insufficient info to assess
Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	Yes/No/Insufficient info to assess	No
Domain 2: Detection bias		
Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Yes/No/Insufficient info to assess	Yes
Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes/No/Insufficient info to assess	Yes
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	Yes/No/Insufficient info to assess	Insufficient info to assess
Is the assessment of outcome made blind to exposure status?	Yes/No/Insufficient info to assess	No
If no to question 6, does this have an impact on the assessment of the outcome?	Yes/No/ Not possible in this type of exposure /Insufficient info to assess	No
Is the follow-up sufficiently long to measure all relevant outcomes?	Yes/No/Insufficient info to assess	Yes
Domain 3: Attrition bias		
Can selective loss-to-follow-up be sufficiently excluded?	Yes/No/Insufficient info to assess	Insufficient info to assess

2.2.13. Rhabdomyosarcoma

2.2.13.1. Study selection

After screening titles and abstracts, 9 records covering rhabdomyosarcoma were retained (see appendix, Figure 1). In addition, 15 records covering multiple indications under study (among which rhabdomyosarcoma) and 1 record covering complications and quality of life impact of proton therapy were retained.

Based on full-text evaluation 3 primary studies were included. The rationale for exclusion of the reviews is presented in Table 30 and for exclusion of the other primary studies in Table 31.

Table 30 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Allen AM, et al. 2012 Radiother. Oncol. 103(1):8-11 - An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee	Narrative review
Cotter SE, et al. 2012 Technol. Cancer Res. Treat. 11(3):267-278 - Proton radiotherapy for solid tumors of childhood	Narrative review
Finger PT 2009 Surv. Ophthalmol. 54(5):545-568 - Radiation Therapy for Orbital Tumors: Concepts, Current Use, and Ophthalmic Radiation Side Effect	Narrative review
Gezondheidsraad 2009 Health Technology Assessment Database 1):- Proton radiotherapy	Databases not mentioned; no evidence tables; no quality appraisal of included studies
Gosiengfiao Y, et al. 2012 Pediatr. Drugs 14(6):389-400 - What is new in rhabdomyosarcoma management in children?	Narrative review
Gunduz K, et al. 2008 Expert Rev. Ophthalmol. 3(1):63-75 - Diagnosis and management of malignant tumors of the eyelid, conjunctiva and orbit	Narrative review
Habrand JL, et al. 2009 Cancer Radiother 13(6-7):550-5 - La protontherapie en radiotherapie pediatrique	Narrative review
Hardy P, et al. 2008 J. Radiother. Pract. 7(1):9-18 - What are the potential benefits and limitations of particle therapy in the treatment of paediatric malignancies?	Search date not mentioned; no evidence tables; no quality appraisal of included studies
Huh WW, et al. 2011 Cancer Treat. Rev. 37(6):431-439 - Pediatric sarcomas and related tumors of the head and neck	Narrative review
Jurdy L, et al. 2013 Saudi J. Ophthalmol. 27(3):167-175 - Orbital rhabdomyosarcomas: A review	Narrative review
Ladra MM, et al. 2014 Cancers 6(1):112-127 - Proton radiotherapy for pediatric sarcoma	Narrative review

Loeffler JS, et al. 2013 Nat Rev Clin Oncol 10(7):411-24 - Charged particle therapy--optimization, challenges and future directions	Narrative review
Merchant TE, et al. 2014 Curr. Opin. Pediatr. 26(1):3-8 - Proton beam therapy: A fad or a new standard of care	Narrative review
Stehr M 2009 Curr. Opin. Urol. 19(4):402-406 - Pediatric urologic rhabdomyosarcoma	Narrative review
Terezakis SA, et al. 2013 Clin. Oncol. 25(1):27-35 - Radiotherapy for Rhabdomyosarcoma: Indications and Outcome	Narrative review
Timmermann B 2010 Klin. Padiatr. 222(3):127-133 - Proton beam therapy for childhood malignancies: Status report	Narrative review

Table 31 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Ge X, et al. 2013 Asian Pac J Cancer Prev 14(8):4641-6 - Multidisciplinary collaborative therapy for 30 children with orbital rhabdomyosarcoma	No patient with rhabdomyosarcoma treated with proton
Heinzelmann F, et al. 2011 Strahlenther. Onkol. 187(11):715-721 - Comparison of different adjuvant radiotherapy approaches in childhood bladder/prostate rhabdomyosarcoma treated with conservative surgery	Only one patient with rhabdomyosarcoma included
Mandonnet E, et al. 2008 Child's Nerv. Syst. 24(6):699-706 - Spectrum of skull base tumors in children and adolescents: A series of 42 patients and review of the literature	6 patients with rhabdomyosarcoma included but none treated with PBT
Mizumoto M, et al. 2013 Strahlenther. Onkol. 189(8):656-663 - Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy: Technical considerations based on experience at a single institution	Only 2 patients with rhabdomyosarcoma
Resto VA, et al. 2008 Head Neck 30(2):222-229 - Extent of surgery in the management of locally advanced sinonasal malignancies	Only 2 patients with rhabdomyosarcoma
Viswanathan V, et al. 2011 Endocr Pract 17(6):891-6 - Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors	Only 3 patients with rhabdomyosarcoma

2.2.13.2. Quality appraisal

Quality appraisal of selected primary studies was not performed as they were all retrospective case-series.

2.2.14. (Para-)spinal 'adult type' soft tissue sarcoma

2.2.14.1. Study selection

After screening titles and abstract, 5 records covering ((para)spinal adult-type) soft tissue sarcomas were retained (see appendix, Figure 1). Five records covering multiple indications under study (among which ((para)spinal adult-type) soft tissue sarcomas) and 1 record on complications after PBT were retained. No documents on soft tissue sarcomas were retrieved from HTA agencies' websites.

Based on full-text evaluation, no studies were included; the rationale for the exclusions is presented in Table 32 and Table 33.

Table 32 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Badellino F, et al. 2008 Surg. Oncol. Clin. North Am. 17(3):649-672 - Treatment of Soft Tissue Sarcoma: A European Approach	Narrative review
Brada M, et al. 2009 Cancer J. 15(4):319-324 - Current clinical evidence for proton therapy	Included primary study (Timmermann et al. 2007) already adopted in the present report as primary study
Huh WW, et al. 2011 Cancer Treat. Rev. 37(6):431-439 - Pediatric sarcomas and related tumors of the head and neck	Narrative review
Ladra MM, et al. 2014 Cancers 6(1):112-127 - Proton radiotherapy for pediatric sarcoma	Narrative review
Mendenhall WM, et al. 2009 Am. J. Clin. Oncol. Cancer Clin. Trials 32(4):436-442 - The management of adult soft tissue sarcomas	Narrative review

Table 33 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Fayda M, et al. 2009 J Craniomaxillofac Surg 37(1):42-8 - The role of surgery and radiotherapy in treatment of soft tissue sarcomas of the head and neck region: review of 30 cases	Only adults
Resto VA, et al. 2008 Head Neck 30(2):222-229 - Extent of surgery in the management of locally advanced sinonasal malignancies	Only adults; STS of the sinonasal region
Schneider RA, et al. 2013 Strahlenther. Onkol. 189(12):1020-1025 - Small bowel toxicity after high dose spot scanning-based proton beam therapy for paraspinal/retroperitoneal neoplasms	Only 1 child included and not clear if it had a soft tissue arcoma or another neoplasm
Timmermann B, et al. 2007 Int. J. Radiat. Oncol. Biol. Phys. 67(2):497-504 - Spot-scanning proton therapy for malignant soft tissue tumors in childhood: First experiences at the Paul Scherrer Institute	Only 3 patients with (para)spinal non-rhabdomyosarcoma STS
Weber DC, et al. 2007 Int. J. Radiat. Oncol. Biol. Phys. 69(3):865-871 - Spot Scanning Proton Therapy in the Curative Treatment of Adult Patients With Sarcoma: The Paul Scherrer Institute Experience	Only adults

Reference	Reason(s) for exclusion
Yoon SS, et al. 2010 Ann. Surg. Oncol. 17(6):1515-1529 - Proton-Beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas	Only adults

2.3. Evidence tables by indication

2.3.1. Skull base chondrosarcoma & skull base and (para)spinal chordoma

Table 34 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with skull base and (para)spinal chordoma and skull base chondrosarcoma

Rombi et al. 2013[5]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Data collection was supported by Oncosuisse grant 01694-04-2005 - Competing interest: none
• Setting	Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland
• Sample size	26 patients (CH: n=19, CS: n=7)
• Duration and follow-up	Patient enrolment period: June 2000 – June 2010 Mean follow-up: 46 months (range: 4.5-126.5 months)
• Statistical analysis	Kaplan-Meier method to estimate failure free survival and overall survival
Patient characteristics	
• Eligibility criteria	Histologically proven diagnosis of CH or CS
• Exclusion criteria	No criteria mentioned
• Patient & disease characteristics	Median age: 13.2 y.o. (range: 3.7-20.8 y.o.) Tumour location: for CH: skull base (n=12), axial skeleton (n=7); for CS: skull base (n=5), axial skeleton (n=2) CS: 4/7 patients had high grade CS (mesenchymal type in 2 patients)
Interventions	
• Intervention group	*Surgery* • CH: gross total resection (n=4), subtotal resection (n=14), biopsy (n=1)

Rombi et al. 2013[5]	
	• CS: gross total resection (n=2), subtotal resection (n=4), biopsy (n=1) • Single surgery (n=10), multiple surgeries (for residual disease or tumour progression, n=16) *Radiotherapy* • Spot-scanning proton radiation therapy • Mean total dose: CH: 74 Gy(RBE)(range: 73.8-75.6), CS: 66 Gy(RBE) (range: 54-72) *Chemotherapy* • CS: 3/7 patients
• Control group	NA
• **Results for patients with CH**	
• 5-year overall survival	89% (no CI reported)
• Recurrence rate	2/19 (11%) failures (1 alive and 1 dead)
• 5-year local control rate	81% (no CI reported)
• Complication rate	*Note: only reported for the whole sample (CH and CS together)* Acute toxicity: 12/26 (grade 2), 0/26 (grade 3); late toxicity: 5/26 (grade 2), 0/26 (≥Grade 3)
• Secondary malignancy	No secondary malignancy observed during the follow-up
• Quality of life	Not reported
• **Results for patients with CS**	
• 5-year overall survival	75% (no CI reported)
• Recurrence rate	1/7 (14%) (1 dead due to local failure)
• 5-year local control rate	80% (no CI reported)
• Complication rate	*Note: only reported for the whole sample (CH and CS together)* Acute toxicity: 12/26 (grade 2), 0/26 (grade 3) Late toxicity: 5/26 (grade 2), 0/26 (≥Grade 3)
• Secondary malignancy	No secondary malignancy observed during the follow-up
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Relatively small number of patients

Rombi et al. 2013[5]	
	• Retrospective design • Case series, hence no comparison group • No clear exclusion criteria • Long period of enrolment (10 years) • Short follow-up (range: 4.5-126.5 months)

Habrand et al. 2008[4]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Sources of funding not mentioned - Competing interest: none
• Setting	Center for Proton Therapy, Orsay, France
• Sample size	30 patients: 26 CH, 3 low grade CS, 1 aggressive chondroma (AC)
• Duration and follow-up	Patient enrolment period: July 1996 – July 2006 Mean follow-up: 26.5 months (range: 5-102 months)
• Statistical analysis	Kaplan-Meier method to estimate failure free survival and overall survival
Patient characteristics	
• Eligibility criteria	No criteria mentioned
• Exclusion criteria	No criteria mentioned
• Patient & disease characteristics	Median age:_13.5 y.o. (range: 6-17 y.o.); gender: male/female ratio: 1.6/1 (only reported for patients with CH) Tumour location: for CH: skull base (n=13 + 1 with AC), cervical canal (n=1), skull base and spinal extension (n=12); for CS: skull base (n=3)
Interventions	
• Intervention group	*Surgery* • Surgical resection (all), repeated 1-5 times (for pathologic diagnosis and removal of as much tumor as possible). *Postoperative radiotherapy* • Proton beam therapy + photon (n=29); proton beam therapy (n=1)

Habrand et al. 2008[4]	
	• Mean total dose: 68.3 CGE (range: 54.6 – 71 CGE); mean dose in patients with CS lower than mean dose in patients with CH (65.3 vs. 69.1 CGE)
• Control group	NA
Results ***Note*: only results for 26 patients with CH reported as there were only 3 children with CS**	
• 5-year overall survival	Chordoma: 81% (95% CI: 56-100%)
• 5-year progression-free survival	Chordoma: 77% (95% CI: 59-95%)
• Recurrence rate	5/26 (19%) with recurrent local disease
• Complication rate	Acute toxicity: minor or mild (n=28); none (n=2) Reported acute toxicities: mucositis (n=10), epidermitis (n=14), headaches (n=10), nausea (n=9) and focal alopecia (n=23) Late toxicity: evaluable in 23/30 patients Reported late toxicities: grade 3 auditory toxicity (unilateral hypoacousia, n=2; in 1 of them it was present before RT), grade 3-4 visual toxicity (unilateral blindness, n= 4, present in all 4 before RT), grade 0-2 (minor or mild) side-effects (n=7, mainly related to partial pituitary dysfunction after RT)
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Relatively small number of patients, too few patients with CS • Retrospective design • Case series, hence no comparison group • Central pathologic review not performed systematically • No clear inclusion criteria • No clear exclusion criteria • Combined therapy: PBT + photon RT in most children • Long period of enrolment (10 years) • Short follow-up (range: 5-102 months)

2.3.2. Craniopharyngioma

Table 35 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with craniopharyngioma

Bishop et al. 2014[6]	
Methods	
• Design	Comparative study; retrospective study
• Source of funding and competing interest	*Sources of funding:* Supported by the Cancer Center Support (Core) Grant CA016672 to the University of Texas M. D. Anderson Cancer Center. *Competing interest:* None mentioned.
• Setting	Two settings in Houston (Texas, US): • The University of Texas MD Anderson Cancer Center • Methodist Hospital
• Sample size	52 paediatric craniopharyngioma patients
• Duration and follow-up	Patient enrolment period: 1996-2012 Follow-up: PBT cohort (n=21): median: 33.1 months (range: 10.5-65.6 months) IMRT cohort (n=31): median: 106.1 months (range: 8.9-185.3 months).
• Statistical analysis	Descriptive statistics for baseline characteristics; Fisher's exact test for categorical data; Kaplan-Meier method for overall survival and cystic and nodular progression-free survival times; log-rank tests to assess the equality of the survival function across groups; Cox proportional hazard model to assess the effect of patient, tumor, and other factors on the endpoints; backwards multivariate model with all factors found to have a p value of ≤.25; Wald test to assess the influence of covariates on the model.
Patient characteristics	
• Eligibility criteria	• Histologic confirmation of craniopharyngioma • Patient age ≤ 18 years at time of radiotherapy • Treatment with IMRT or PBT from 1996 through 2012
• Exclusion criteria	Not reported
• Patient & disease characteristics	PBT and IMRT cohorts were similar with regard to: • Sex distribution: female 57% vs. 55%; p=1.00 • Age at diagnosis (median): 9.1 y.o. vs. 8.8 y.o.; p=1.00

Bishop et al. 2014[6]	
	• Tumour size (median): 4.5 cm vs 3.6 cm; p= 0.19 • Number of surgeries (p=0.749) o 1 surgery: 71% vs. 55% o 2 surgeries: 19% vs. 29% o 3 surgeries: 10% vs. 13% o 4 surgeries: 0% vs. 3% • Radiation intent (p=0.586) o Postoperative (after either a subtotal resection or a gross total resection): 38% vs. 48% o Definitive (if only biopsy or cyst drainage had been done previously): 19% vs. 10% o Salvage (for disease that recurred after previous interventions): 43% vs. 42% Statistically significant differences between PBT and IMRT cohorts: • Median follow-up: 33.1 months (range: 10.5-65.6 months) vs. 106.1 months (range: 8.9-185.3 months); p<0.001 • Extent of first surgery (p=0.032): o Cyst drainage, fenestration, shunting: 33% vs. 61% o Subtotal resection (STR): 43% vs. 35% o Gross total resection: 24% vs. 3%
Interventions	
• Intervention group	*Proton beam therapy:* • Median RBE dose: 50.4 Gy (RBE) (range: 50.4-54 Gy) at 1.8 Gy per fraction • Most of the PBT was delivered with passive scatter technique (n=18) *Note*: from 2007 on (when PBT was available) all patients received PBT *Surgery:* Cf. supra
• Control group	*IMRT :* Median dose: 50.4 Gy (range: 50.4-54 Gy) at 1.8 Gy per fraction *Surgery:* Cf. supra
Results	
• 3-year overall survival	PBT: 94.1% vs. IMRT: 96.8%; p= 0.742

Bishop et al. 2014[6]	
	At the time of analysis: 4 patients had died (causes: cyst progression after STR (n=1), treatment related morbidity (uncontrolled diabetes insipidus and postoperative neurologic injury) (n=3)) – unclear to which treatment group they belonged
• 3-year cystic failure-free survival (CFFS)	PBT: 67.0% vs. IMRT: 76.8%; p= 0.994 but more of the IMRT group had late cystic growth (> 3 months after RT): 10-year CFFS rate: 67.8%
• 3-year nodular failure-free survival (NFFS)	PBT: 91.7% vs. IMRT: 96.4%; p= 0.546
• Recurrence rate	Not reported
• Cyst dynamics (after RT)	• Early cyst growth (≤ 3 months after RT): PBT: 19% vs. IMRT: 42%; p= 0.082 (*Note*: early cyst growth was transient in 82% (14/17)) • Late cyst growth (> 3 months after RT): PBT: 19% vs. IMRT: 32%; p= 0.353 • Cyst growth requiring intervention: PBT: 14% vs. IMRT: 10% (no p-value provided)
• Complication rate	• No exact complication rate is mentioned; >50% of patients had some perioperative morbidity • Toxicities newly acquired from start of radiation: o Vascular injuries: PBT: 10% vs. IMRT: 10%; p= 1.00 o Visual dysfunction: PBT: 5% vs. IMRT: 13%; p= 0.637 o Hypothalamic obesity: PBT: 19% vs. IMRT: 29%; p= 0.523 o Panhypopituitarism: PBT: 33% vs. IMRT: 55%; p= 0.162 o Other endocrinopathies (growth hormone deficits, hypothyroidism, adrenal insufficiency, sexual hormone deficiencies): PBT: 43% vs. IMRT: 23%; p= 0.139 *Note: Extent of surgery before RT dit not correlate with post-operative endocrine (p=0.096) or visual (p=0.064) complications*
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Retrospective design

Bishop et al. 2014[6]	
	• Significant shorter follow-up for the PBT group as PBT was only available from 2007 on • Extent of surgery significantly different between treatment groups • No randomization, no allocation concealment, no blinding • No clear exclusion criteria • Long patient enrolment period • Periodic imaging during the RT to ensure that the tumours is covered adequately by the prescribed dose throughout the entire treatment course occurred only in 44% of the cohort (PBT: n=19, IMRT: n=5) because most patients had been treated before the importance of interval imaging was reported. • Neurocognitive toxicity was not reported as formal testing was not done in all patients • Variable treatment schemes (i.e. surgery) • Unclear which complications were radiation/PBT induced • No information on which treatment group the 4 deceased subjects belonged to • No information on the methods and intervals of follow-up

Laffond et al. 2012[7]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	*Sources of funding:* Supported partly by the Hôpital National de Saint Maurice *Competing interest:* None mentioned
• Setting	Institut Curie Proton therapy centre in Orsay (France)
• Sample size	34 patients eligible, but 5 were lost to follow-up; results are reported on 29 patients
• Duration and follow-up	Patient enrolment period: 1995-2007 Follow-up: NA QoL assessment after a mean interval of 4 years 1 month (SD= 2.9; range: 1 year 8 months – 14 years) after the end of PBT
• Statistical analysis	Descriptive statistics Spearman correlation coefficients and ANOVA for relationship between outcomes and demographic/medical variables
Patient characteristics	
• Eligibility criteria	All patients treated for childhood craniopharyngioma, using PBT (used exclusively or combined with photon radiotherapy) in a single centre, between 1995 and 2007 (at least 1 year prior to the start of the study), either initially after sub-total surgery or at relapse/regrowth (following total or sub-total surgery).
• Exclusion criteria	Patients aged over 18 at the time of diagnosis or who had not reached 1 year post-treatment at the start of the study.
• Patient & disease characteristics	Mean age at diagnosis: 7 years 10 months (SD= 4.1; range: 1 year 10 months-15 years 10 months); mean age at time of the QoL assessment: 14 years (SD=4.1; range: 7 years 1 month – 24 years) Gender: males:15/29 Pre-existing conditions at diagnosis: hydrocephalus (n=10), hypothalamic involvement (n=23)
Interventions	
• Intervention group	*Surgery:* • Surgical resection: 28/29 o Complete resection (n=6) vs partial or sub-total resection (n=22) o Residual lesion involving hypothalamus (n=19) o Number of surgeries: one (n=18), two (n=5), three (n=3) and four (n=2) • Ommaya reservoir: 1/29

Laffond et al. 2012[7]	
	Proton beam therapy • After the first sub-total surgery (as part of a conservative approach; n=16); after relapse (n=13) • PBT alone (n=20); PBT combined with photon (n=9) • Dose range: 54-55.2 Gy
• Control group	NA
Results	
• Overall survival	Not reported
• Disease-free survival	Not reported
• Response rate	Not reported
• Recurrence rate	Not reported
• Complication rate	• No exact complication rate is mentioned • At the time of the QoL assessment (i.e. 1 year 8 months – 14 years after PBT) following late toxicities were reported by the patients: o Epilepsy: n=4 o Hemiparesis: n=3 o Recurrent headaches: n=15 o Visual impairment (reduced acuity and/or field loss): n=23 o Pituitary dysfunction: n=28 o Obesity (BMI > 97th percentile): n=17 o Hypothalamic syndrome: n=18 o Daily fatigue: n=21 o Mood disorders: mean MDI[c] T-score 49.1 (SD=13.3) o Depressive symptoms: o Slight-to-moderate: n=8 o Modere-to-severe: n=3
• Secondary malignancy	Not reported

[c] Multiscore Depression Inventory for children

Laffond et al. 2012[7]	
• Quality of life	• QoL measured by Kidscreen-52 questionnaire[d] o self-report: range from 43.05 to 51.14, which is in favour of an overall percieved satisfactory QoL. o proxy (reported by parents): range from 36.19 to 51.2 • Executive functioning in everyday life: BRIEF[e] global executive composite score (n=20): 52.2 (SD= 12.9)
Limitations and other comments	
• Limitations	• Retrospective design • Small sample size • 5/34 patients (15%) lost to follow-up • No control group • Long period of enrolment • Unclear what the correlation is between medical outcome and QoL • Unclear which complications were radiation/PBT induced • Results not separately reported for children who had PBT alone vs. PBT in combination with photon RT • Because characteristics of non respondents are not studied, the generalizability of the results may be limited

Winkfield et al. 2009[8]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Sources of funding not mentioned – Competing interest: none declared
• Setting	Massachusetts General Hospital, Boston, US
• Sample size	24 paediatric patients
• Duration and follow-up	Patient enrolment period: January 2001 – August 2007 Median follow-up: 40.5 months (range: 6 – 78 months)

[d] For more information see http://www.kidscreen.org/english/questionnaires/kidscreen-52-long-version/

[e] Behaviour Rating Inventory of Executive Function

Winkfield et al. 2009[8]	
• Statistical analysis	Descriptive statistics
Patient characteristics	
• Eligibility criteria	Paediatric patients with biopsy-proven craniopharyngioma treated with PBT in Massachusetts General Hospital
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Mean age at RT: 8.4 y.o. (range: 3 - 14 y.o.) Gender: male: 14/24 Histologic type: adamantinomatous (n=18), classification not reported (n=6) Cystic component: n=19 (bilobed: n=4, multicystic: n=3, complex (i.e. mixed solid and cystic component): n=4, complex/multicystic: n=1); median cyst volume: 6.3 cm^3 (range: 1.8-29.8)
Interventions	
• Intervention group	*Surgery*: • Gross total resection (n=4), subtotal resection (n=16), cyst drainage with biopsy (n=4) • Repeat resection due to recurrence: n=8 (3 surgical excisions: n=2) *Proton beam therapy* • Total dose (range): 52.2 – 54 Gy equivalents (GyE) in 1.8 GyE/fraction
• Control group	NA
Results	
• Overall survival	Not reported
• Disease-free survival	Not reported
• Response rate	Not reported
• Local control rate	At a median follow-up of 40.5 months (range: 6-78 months): 100%
• Cyst dynamics (during RT)	Among 19 patients with cystic component, only 17 patients had repeat imaging during RT: • 6/17 (35%) required intervention because of changes in cyst dimensions: o Cyst growth beyond the original treatment field, requiring enlargement of the treatment plan (n=4) o Decrease in cyst size, requiring reduction of the treatment plan (n=1) o Cyst drainage to avoid enlargement of the treatment field (n=1) *Note*: A patient with stable cyst volumes during proton RT required cyst drainage 8 weeks after RT completion for symptomatic hemianopsia.

Winkfield et al. 2009[8]	
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Retrospective design • No control group • No exclusion criteria mentioned • Variable surgical treatment • Small sample size

2.3.3. Ependymoma

Table 36 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with ependymoma

MacDonald et al. 2013[10]	
Methods	
• Design	Case series; retrospective study.
• Source of funding and competing interest	*Sources of funding:* • One author was a clinical research fellow by a grant from Doris Duke Charitable Foundation to Harvard Medical School • Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, *Competing interest:* • One author was on the medical advisory board of ProCure until 2008 and has stock options in ProCure
• Setting	Massachusetts General Hospital, Boston, US
• Sample size	70 paediatric patients (< 21 y.o.)
• Duration and follow-up	Patient enrolment period: October 2000 – February 2011 Follow-up (of 63 patients still alive): median: 46 months (range: 12 months – 11.7 years)
• Statistical analysis	Kaplan-Meier for overall survival, progression-free survival and disease-free survival ANOVA for change in IQ and SIB-R[f]

[f] Scales of Independent Behaviour-Revised (SIB-R) is a standardized questionnaire completed by the parents that assesses the adaptive skills and functional independence.

MacDonald et al. 2013[10]	
Patient characteristics	
• Eligibility criteria	All paediatric patients (<21 y.o.) with intracranial ependymoma treated with proton therapy
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Age (median): 38 months (range: 3 months-20 years); Gender : male: n=33; Tumour localisation: infratentorial tumours (n=51), supratentorial tumours (n=19); tumour grade: differentiated (classic) ependymoma (n=37), anaplastic ependymoma (n=33)
Interventions	
• Intervention group	*Surgery:* • Subtotal resection (n=23), Gross total surgery (n=46), near total resection (n=1) • Number of surgeries: 1 surgery (n=54), 2 surgeries (n=14), 3 surgeries (n=2) *Chemotherapy*: • n=21 *Proton beam therapy (offered upon local recurrence; as first radiation treatment)* • Dose (median): 55.8 Gy (range: 50.4-60.0 Gy) in fractions of 1.8 Gy relative biological equivalents • Time to RT from most recent surgery (median): 49 days (range: 30 days – 9 months) • Duration of RT (median): 43 days (range: 34 days – 54 days)
• Control group	NA
Results	
• Overall survival rate	3-year overall survival rate: 95%
• Progression-free survival	3-year progression free survival: 76%
• Recurrence rate	Local control rate At 3 years: 83% At 5 years: 77% Distal control rate At 3 years: 86% At 5 years: 83% Disease progression after a median follow-up of 18 months (range: 5.3 – 68.1 months): 18/70 Local recurrence: 8/18 Distant recurrence: 8/18 Synchronous local and distant: 2/18
• Complication rate	*Note: following outcomes were only assessed in a subset of the original sample* Endocrine outcomes

MacDonald et al. 2013[10]	
	• Laboratory evidence of central hypothyroidism: 1/32 patients with a median follow-up of 42 months for thyroid hormone • Growth hormone deficiency: 2/25 patients with a median follow-up of 42 months for growth hormone • Deficient levels of insuline-like growth factor (IGF-1): 9/25 (not on replacement therapy) • Highly variable changes in height recorded in 57 patients with a median follow-up of 41 months : ranging from loss of 94 percentiles to a gain of 74 percentiles (median: loss 2.6 percentiles) Auditory outcomes • Hearing loss: 2/23 patients (infratentorial tumours)with a median follow-up of 27 months ; both patients had recieved higher doses of radiation to their cochlea than the average median dose because of tumour extension into the foramen of Luschka Neurocognitive assessment • Mean total MDI/IQ[g]: 108.5 at baseline vs. 111.3 at follow-up (p=0.475), in 14 patients (mean time interval: 2.05 y (range: 1-4.5 y)) • No statistically significant differences in change over time were observed between patients under and over 3 y.o. • Mean SIB-R[h] standard score: 100.1 at baseline vs. 111.8 at follow-up (p=0.809), in 28 patients (mean time interval: 2.21 y (range: 1-5.9 y)) No statistically significant differences were observed between patients under and over 3 y.o Other toxicities • Cervical subluxation: 2/70 • Postradiotherapy cavernomas : 2/70 • Brainstem compression (due to residual disease adjacent to the brainstem): 1/70
• Secondary malignancies	No cases of secondary malignancies identified

Limitations and other comments	
• Limitations	• No control group • Retrospective design • No exclusion criteria mentioned

g MDI (Mental Development Index) or IQ adjusted according to the patient's age

h SIB-R: Scale of Independent Behaviour-Revised

MacDonald et al. 2013[10]	
	• Long enrolment period • Variable treatment schemes • Unclear which complications were radiation/PBT induced • Complications only assessed in a subset of the original sample • No information on the methods and intervals of follow-up

Amsbaugh et al. 2012[9]	
Methods	
• Design	Case series; data collected as part of an ongoing prospective clinical trial.
• Source of funding and competing interest	Sources of funding not mentioned – Competing interest: none declared
• Setting	University of Texas MD Anderson Cancer Center, Texas, US
• Sample size	8 children
• Duration and follow-up	Patient enrolment period: October 2006 – September 2010 Follow-up: mean: 26 months (range: 7-51 months); 1 month after PBT and then every 3-6 months
• Statistical analysis	Kaplan-Meier for overall survival, event-free survival and local control rates
Patient characteristics	
• Eligibility criteria	Patients aged between 1 to 18 years, diagnosed with a spinal ependymoma by pathology and received surgery before PBT
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Age at diagnosis (mean): 9.7 (range: 1.2-16.5) y.o. Gender: male: n=6 Tumour grade: WHO Grade[i] I n=6/8, among which 4 myxopapillary ependymomas and WHO Grade II (n=2); tumour localization: thoracic n=2, lumbar n=5, cervical n=1.

[i] The WHO classification of tumours of the Central Nervous System is based on a grading system from I to IV (Grade I tumours are slow-growing, nonmalignant, and associated with long-term survival. Grade II tumours are relatively slow-growing but sometimes recur as higher grade tumours. They can be nonmalignant or malignant. Grade III tumours are malignant and often recur as higher grade tumours. Grade IV tumours reproduce rapidly and are very aggressive malignant tumours). For more details see WHO Classification of Tumours of the Central Nervous System[21]

Amsbaugh et al. 2012[9]	
Interventions	
• Intervention group	*Surgery:* • Subtotal resection: 1 surgery (n=3), 2 surgeries (n=3), 3 surgeries (n=1); gross total surgery: 1 surgery (n=1); *Chemotherapy*: • n=2 (temozolomide; in 1 patient diagnosed with WHO grade II disease) *Photon therapy*: • n=1 *Proton beam therapy* • Mean total dose: 51.1 CGE • Total dose: 45 CGE (n=1); 46.8 CGE (n=1); 50.4 CGE (n=2); 54 CGE (n=4); time interval between diagnosis and proton therapy, range: 8-132 months
• Control group	NA
Results	
• Overall survival	After a mean follow-up of 26 months: 100%
• Event-free survival	After a mean follow-up of 26 months: 100%
• Local control	After a mean follow-up of 26 months: 100%
• Complication rate	Acute side effects: total number of patients not mentioned Reported acute side effects (according to CTC severity grading scale[j]): • Erythema: Grade I (n=4), Grade II (n=2) • Dry skin: Grade I (n=4), Grade II (n=1) • Fatigue: Grade I (n=3) • Weakness in extremities: Grade I (n=1) • Abdominal discomfort: Grade I (n=1; possibly due to chemotherapy)

j CTCAE Version 4 (version 3 used by the authors): Common Terminology Criteria for Adverse Events is a standard classification and severity grading scale for adverse events from 1 to 5. **Grade 1** – Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. **Grade 2** – Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.). **Grade 3** – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). **Grade 4** – Life-threatening consequences; urgent intervention indicated. **Grade 5** Death related to Adverse Events. For more information see Common Terminology Criteria for Adverse Events[22]

Amsbaugh et al. 2012[9]	
	• Diarrhea: Grade I (n=1; possibly due to chemotherapy) • Spinal range of motion limitation (not affecting daily living) Late side effects: not reported (too short follow-up)
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• **Limitations**	• Small number of patients • Case series • No control group • No exclusion criteria mentioned • Variable treatment schemes • Short follow-up

2.3.4. Esthesioneuroblastoma

Table 37 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with esthesioneuroblastoma

Herr et al. 2014[23]	
Methods	
• Design	Case series (chart review); retrospective
• Source of funding and competing interest	None reported
• Setting	Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital, Boston, US (tertiary referral centre)
• Sample size	22
• Duration and follow-up	Patient enrolment period: 1997-2013 Follow-up: mean: 73 months (range: 24-183 months)
• Statistical analysis	Kaplan Meier (end point for survival: death from any cause; end point for DFS: disease recurrence)
Patient characteristics	
• Eligibility criteria	Diagnosis of esthesioneuroblastoma (based on endoscopic intranasal biopsy)

Herr et al. 2014[23]	
• Exclusion criteria	None reported
• Patient & disease characteristics	Median age: 45.5 y.o. (range: 11-77 y.o.); female: 50% Kadish classification: 10/22 Kadish stage B; 12/22 Kadish stage C TNM staging: 14/22 with advanced tumours (stage T3 or T4); 3/22 had regional metastases
Interventions	
• Intervention group	Treatment schemes: • Patients enrolled 1997-2000 (n=3): induction chemotherapy (2 cycles of etoposide and cisplatin every 3 weeks; 1 patient: additional 2 cycles of carboplatin and etoposide)(and because there was no disease response in any case after chemo alone) followed by upfront craniofacial resection followed by PBT • Patients enrolled 2000-2013 (n=14): upfront craniofacial resection followed by adjuvant PBT • Patients enrolled 2000-2013 (n=5): upfront craniofacial resection followed by adjuvant PBT + concurrent chemotherapy (cisplatin and etoposide or carboplatin alone) • In addition: selective neck dissection in 3 patients with cervical lymph node involvement Irradiation of the primary site • Median total dose: 66.5 cobalt grey equivalent (CGE)(range: 54-70; on average 1.85 CGE per fraction over 35 fractions) • No breaks as a result of acute toxicity Irradiation of the neck (bilaterally): 8/22 patients – combination of photon and proton beam therapy • 3/8 with cervical lymph node metastases: range of therapeutic proton beam irradiation: 60-66 Gy • 5/8 (bilateral elective neck irradiation): 60 CGE of proton beam radiation to the upper neck and 50 Gy of external photons to the lower neck
• Control group	NA
Results	
• Overall survival	5-year overall survival rate: 95.2% (95% CI: 70.7-99.3%)
• Disease free survival	5-year disease free survival: 86.4% (95% CI: 63.4-95.4%)
• Recurrence	Local and/or regional and/or regional recurrence: at a mean of 73.4 months (range: 13-145 months) after diagnosis: 6/22 (27%) Note: • 5/9 patients with positive surgical margins recurred • 2/3 patients with regional recurrence (neck) had no elective neck irradiation

Herr et al. 2014[23]	
	• 3/3 patients with initial induction chemotherapy recurred Location of recurrences: CNS, spine, neck, parotis, vertebrae, rib
• Complication rate	13/22 (59%) had several mild to severe complications due to late-radiation toxicity (e.g. 1 patient with blindness in the ipsilateral eye as a result of radiation-induced optic neuritis, 4 patients with persistent sinocutaneous fistulas, 3 patients with infections at the anterior skull base) 13/22 (59%) experienced a total of 25 complications from all modalities of therapy • 8/22 had in total 11 ocular complications (e.g. epiphora (i.e. excessive tear production), transient cranial nerve VI palsy, persistent diplopia, blindness in the ipsilateral eye as a result of radiation-induced optic neuritis) • 2/22 had in total 5 CNS complications (e.g. recurrent seizures, postoperative cerebrospinal fluid leak and symptomatic pneumocephalus, asymptomatic postoperative pneumocephalus) • 8/22 had in total 9 wound healing complications • Several (no exact number reported) infectious complications
• Secondary malignancy	Not reported
Limitations and other comments	
• Limitations	• Retrospective design • Case series • No clear inclusion and exclusion criteria • No separate results for children and adults • Small sample size • Treatment schemes were variable • The analysis did not control for Kadish classification, nor for other confounding factors • Short follow-up, especially given the late occurrence of recurrences • No information on the methods and intervals of follow-up

2.3.5. Ewing sarcoma

Table 38 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with Ewing sarcoma

Rombi et al. 2012[12]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Supported in part by the Federal Share of program income earned by Massachusetts General Hospital on National Institutes of Health Grant #C06 CA059267 – Competing interest: none declared
• Setting	Francis H. Burr Proton Therapy Center at Massachusetts General Hospital, Boston, US
• Sample size	30 children with Ewing sarcoma
• Duration and follow-up	Patient enrolment period: 2003 - 2009 Follow-up: median: 38.4 months (range: 17.4 months -7.4 years)
• Statistical analysis	Kaplan-Meier for overall survival, event-free survival, disease-specific survival and local control rates Gray's method for cumulative incidence of second malignancies
Patient characteristics	
• Eligibility criteria	Patients 21 years of age and younger with Ewing sarcoma
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Median age at treatment: 10 y.o. (range: 1.8-21 y.o.) Gender: male n=14 Tumour localisation: pelvis (n=4), trunk (n=15 among which 14 vertebral body or sacrum), head-and-neck region (n=4), base of skull or cranium (n=7)
Interventions	
• Intervention group	*Chemotherapy:* • Based on the AEWS (A-Ewing Sarcoma) 0031 and POG (Pediatric Oncology Group) 9354 protocol (n=30); *Surgery:* • Subtotal resection (n=9); near gross total resection (n=2); gross total resection (n=2); biopsy only (n=17) *Photon therapy*: • N=2; *Proton beam therapy:* • N=30 (n=3: PBT given as salvage after local or distant failure)

Rombi et al. 2012[12]	
	• Median total dose: 54 Gy (range: 45-59.4) delivered at 1.8 Gy (RBE[k]) per fraction
• Control group	NA
Results	
• 3-year overall survival	89% Cause of death: disease progression (n=3), acute myeloid leukaemia (n=1)
• 3-year event-free survival	60%
• 3-year disease-specific survival	68%
• Disease-free survival	After a median follow-up of 38.4 months: 21/30 (70%)
• Recurrence rate	Recurrence rate: 5/30 (17%) Local recurrence rate: 2/30 Distant recurrence rate: 1/30 Local and distal recurrence rate: 2/30
• 3-year local control rate	86%
• Complication rate	*Acute complication rate*: 30/30 • Skin reaction (as a result of PBT): n=30 o Grade 1 (erythema with or without dry desquamation): n=16 o Grade 2 (bright erythema or patchy moist desquamation): n=9 o Grade 3 (confluent moist desquamation) : n=5/30 • Hoarseness, swelling and confluent mucositis at radiation portal: n=1 (patient with base-of-tongue Ewing sarcoma) • Grade 2 kerato-conjunctivitis: n=1 (patient with orbital primary lesion) • Fatigue: n=21 o Grade 1 (mild over baseline): n=18 o Grade 2 (moderate, difficulty performing the activities of daily living): n=2 o Grade 3 (severe interfering with the activities of daily living): n=1 • Nausea: n=5

[k] RBE : Relative biological effectiveness

Rombi et al. 2012[12]	
	o Mild nausea: n=4 o Moderate nausea: n=1 • Anorexia: n=14 o Grade 1 (loss of appetite without alteration in eating habits): n=5 o Grade 2 (oral intake altered without significant weight loss or malnutrition: n=9 *Functional outcome:* • Scolioses/kyphoses: n=5 o Mild: n=3 o Moderate: n=1 o Severe: n=1 *Late sequelae:* no rate reported • PBT induced skin changes (mild hyperpigmentation or teleangiectasias): n=6 • Teleangiectasia of nasal cavity causing occasional mild nosebleeds: n=1 • Permanent alopecia: n=2 • Late effects on eyes: n=2 o Canalicular stenosis, epiphora and left lid paralytic lagophthalmos: n=1 o Chronic corneal ulcer: n=1 • Endocrine deficiencies: n=2 • Unilateral high frequency hearing loss: n=1
• Secondary malignancy	2-year cumulative incidence: 7% (95%CI: 1-19%) 3-year cumulative incidence: 15% (95%CI: 5-32%) 4/30 (13%) Acute myeloid leukemia: n=3 Myelodysplastic syndrome: n=1 Solid tumours: n=0
• Quality of life	Not reported

Rombi et al. 2012[12]	
Limitations and other comments	
• Limitations	• Case series • No control group • Retrospective design • No exclusion criteria mentioned • Variable treatment schemes • Short follow-up • No information on the methods and intervals of follow-up

2.3.6. CNS Germinoma

Table 39 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with CNS germinoma

MacDonald et al. 2014[24]	
Methods	
• Design	Case series; retrospective study.
• Source of funding and competing interest	No funding sources reported
• Setting	Francis H. Burr Proton Facility and Harvard Cyclotron, Massachusetts General Hospital, Boston, US
• Sample size	22 patients (Germinoma: n=13; non-germinomatous germ cell tumour (NGGCT): n=9)
• Duration and follow-up	Patient enrolment period: 1998 - 2007 Follow-up: median: 28 months (range: 13-97 months)
• Statistical analysis	Nothing mentioned
Patient characteristics	
• Eligibility criteria	Patients with CNS germ cell tumours (GCT)
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Median age: 11 y.o. (range: 6-20 y.o.); female: 50%; primary lesions: pineal gland (n=4), suprasellar region (n=10), multiple midline lesions (n=6), multiple sites of brain involvement (n=2)
Interventions	
• Intervention group	**Germinoma**: *Chemotherapy:*

MacDonald et al. 2014[24]	
	11/13: pre-radiation platinum-based *Proton beam therapy:* 5/13: craniospinal irradiation (range: 18.3-23.4 Gy (RBE)) with involved field boost (range: 18.3-23.4 Gy (RBE) – total dose range: 30.6-57.6 Gy (RBE) 7/13: whole ventricular radiotherapy (range: 19.5-23.4 Gy (RBE)) with involved field boost (range: 7.2-22 Gy (RBE) – total dose range: 30.6-45.4 Gy (RBE) 1/13: whole brain radiotherapy (25.5 Gy (RBE)) with involved field boost (19.8 Gy (RBE)) - total dose: 45.3 Gy (RBE) **NGGCT**: *Chemotherapy:* 9/9: pre-radiation chemotherapy (carboplatin, etoposide, ifofamide) *Surgery:* 1/9: postchemotherapy/preradiation surgery *Proton beam therapy:* 8/9: craniospinal irradiation (range: 21.6-36 Gy (RBE)) with involved field boost (range: 18-30.6 Gy (RBE) – total dose range: 45 – 57.6 Gy (RBE) 1/9: involved field boost – total dose: 50.4 Gy (RBE)
• Control group	none
Results	
• Overall survival	100%
• Progression-free survival	95%
• Local recurrence rate	Germinoma: 0/13 NGGCT: 0/9
• Distal recurrence rate	Germinoma: 0/13 NGGCT: 1/9 (peritoneal)
• Complication rate	Not reported
• Secondary malignancy	Not reported
Limitations and other comments	
• Limitations	• Small sample • Retrospective design • Case series • No clear inclusion and exclusion criteria

MacDonald et al. 2014[24]	
	• No information on statistical analysis; no confidence intervals presented • Variable treatment schemes • For some patients follow-up was very short (only 13 months) • No information on the methods and intervals of follow-up

2.3.7. Low-grade glioma

Table 40 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with low-grade glioma

Greenberger et al. 2014[13]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Sources of funding not mentioned - Competing interest: one author has a spouse on the Medical Advisory Board of Procure and has stock options. No other conflicts of interest are declared
• Setting	Harvard Cyclotron and Massachusetts General Hospital, Boston, US
• Sample size	32 paediatric patients with low-grade glioma of the brain (n=29) or spinal cord (n=3)
• Duration and follow-up	Patient enrolment period: 1995 - 2007 Median follow-up: 7.6 years (range: 3.2-18.2 years)
• Statistical analysis	Kaplan-Meier for overall and progression free survival, Student paired sample *t* test to assess change in neurocognitive from baseline to follow-up among subgroups.
Patient characteristics	
• Eligibility criteria	Patients ≤ 21 years of age at the time of diagnosis with low grade glioma with at least 3 years of follow-up
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Median age at treatment: 11.0 y.o (range: 2.7-21.5 y.o); male: 17/32; histology: WHO grade I (pilocytic astrocytoma; 19/32), WHO grade II (6/32), low grade without other specification (2/32), no pathology specified (5/32); location: infratentorial (11/32), supratentorial (18/32), spinal (3/32); neurofibromatosis type I (2/32).
Interventions	
• Intervention group	*Surgery:* • Resection (21/32), biopsy only (6/32), none (5/32) • Shunt(s) (6/32)

Greenberger et al. 2014[13]	
	Chemotherapy: • Number of regimens before RT: none (16/32), 1 regimen (6/32), 2 regimens (7/32), 3 regimens (3/32); *Proton beam therapy:* • Median dose: 52.2 Gy (RBE) (range: 48.6-54 Gy (RBE)) • Modality: PTB only (23/32), PTB in combination with photons (9/32) *Note: patients treated before 2002 received 20% of the treatment with 3-D conformal photons because the cyclotron was closed 1 day per week*
• Control group	NA
Results	
• Overall survival	8-year overall survival: 100%
• Disease-free survival	Not reported
• Progression-free survival	• 6-year progression-free survival: 89.7% • 8-year progression-free survival: 82.8% • 5 patients had progression despite treatment at 4.07, 4.10, 4.6, 7.9 and 8.7 years after RT: o Leptomeningeal biopsy revealed a pleomoprihc xanthroastrocytoma (which was initially diagnosed as optic nerve glioma) o Repeated biopsy revealed an anaplastic astrocytoma (which was initially diagnosed as grade 2 thalamic astrocytoma) o Failure biopsy confirmed diagnosis of pilocytic astrocytoma, but the specimen only had stroma without tumour cells o Asymptomatic enhancement of low-grade brainstem glioma o Asymptomatic enhancement of hypothalamic glioma
• Response rate	Not reported
• Complication rate	• No complication rate for the whole sample reported • Neurocognitive outcomes for 12 patients with both a baseline evaluation and at least 1 follow-up evaluation after PBT (this subset of patients received exclusively proton therapy) o Full-Scale IQ (n=11): Mean change between baseline and follow-up: -0.7 (SD: 9.2), p=0.80

Greenberger et al. 2014[13]	
	Mean change between baseline and follow-up in high-risk dose[l] (n=4): -10.3 (SD: 2.5), p=0.0038 o Verbal Comprehension Index (n=12) Mean change between baseline and follow-up: -0.5 (SD: 11.7), p=0.88 Mean change between baseline and follow-up in age at treament < 7 y.o (n =4): -11.5 (SD: 6.4), p=0.036 Mean change between baseline and follow-up in high-risk dose (n=4): -13.5 (SD: 3.3), p=0.0039 o Perceptual Reasoning Index (n=12) Mean change between baseline and follow-up: -0.17 (SD: 9.8), p=0.95 • Visiual symptoms: change between baseline and most recent follow-up after PTB o Decreased acuity: improvement (5/18), stable (10/18), deterioration (3/18) o Optic nerve pallor/atrophy: improvement (1/18), stable (16/18), deterioration (1/18) • Endocrine outcomes: o Suspected neuro-endocrine abnormalities before start of RT (due to tumour involving hypothalamic-pituitary axis): 9/29 o Incidence of endocrinopathycorrelated with a mean dose of ≥40 Gy (RBE) to the hypothalamus, pituitary or optic chiasm • Vasculopathy: 2/32 in whom moyamoya disease developed, requiring pial synangiosis
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Small number of patients that provided no sufficient statistical power to enable subgroup analysis • Retrospective design • No control group • No clear exclusion criteria • Variable treatment schemes • Patients treated before 2002 received 20% of the treatment with 3-D conformal photons because the cyclotron was closed 1 day per week • 95% CI not provided for overall survival and progression-free survival rate • Complications were assessed in subsets of the original sample

[l] High risk dose is defined as receiving at least 15 Gy (RBE) to 20% of the volume of the left temporal lobe or hippocampus

Bian et al. 2013[14]	
Methods	
• Design	Case series; prospective study
• Source of funding and competing interest	Sources of funding not mentioned - Competing interest not mentioned
• Setting	Anderson Cancer Centre, Houston, US
• Sample size	6 paediatric patients with disseminated pilocytic astrocytoma
• Duration and follow-up	Patient enrolment period: not mentioned Median follow-up: 24 months (range: 5-95 months)
• Statistical analysis	NA
Patient characteristics	
• Eligibility criteria	Patients with disseminated pilocytic astrocytomas confirmed by MRI evidence of leptomeningeal spread or tumour found at sites other than the primary disease location
• Exclusion criteria	NA
• Patient & disease characteristics	Median age: 7 y.o (range: 2-15 y.o.); male: 5/6; location of primary tumour: cerebellum (2/6), thalamus (1/6), hypothalamus (1/6), T1-7 (1/6), C3-7 (1/6); location of metastasis: thoracic and sacral spine (1/6), ventricular horns (1/6), upper lumbar spine (1/6), spine (1/6), lumbar spine (1/6), brain and spine (1/6); mean time to identification of disseminated disease: 12 months (range: 2-23 months)
Interventions	
• Intervention group	*Surgery:* • Treatment of primary tumour: subtotal resection (5/6), gross total resection (1/6) • Post-RT: subtotal resection (3/6) *Chemotherapy*: • Treatment of primary tumour: 2/6 • Post-RT: 1/6 *Proton beam therapy* • Passive scattering technique • CSI (4/6), spine-only (1/6), supratentorial local field (1/6) • Initial radiation dose: ranges from 30.6-48.6 Gy (RBE)

Bian et al. 2013[14]	
	• Boost: total dose ranges from 43.2 to 54 Gy (RBE)
• Control group	NA
Results	
• Overall survival	At a median follow-up of 24 months (range: 5-95 months): overall survival: 83.3% (5/6)
• Disease-free survival	Not reported
• Recurrence rate	Not reported
• Response rate	At a median follow-up of 24 months (range: 5-95 months): • Stable disease: 66.7% (4/6) • Progressive disease: 16.7% (1/6)
• Complication rate	Not reported
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Very small sample size • No control group • No clear exclusion criteria • Variable treatment schemes • Short follow-up • Patient enrolment period not mentioned • Not clear if the included gliomas were low or high grade

2.3.8. Medulloblastoma & PNET

Table 41 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with medulloblastoma/PNET

Sethi et al. 2014[17]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	*Sources of funding:* Supported by the Doris Duke Charitable Foundation (R.V.S.). Research was supported by the National Cancer Institute of the National Institutes of Health under Award Number P01CA021239 and the Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center. *Competing interest:* One author's spouse is on the medical advisory board of ProCure. All other authors deny any real or potential conflicts of interest.
• Setting	Massachusetts General Hospital, Boston, US
• Sample size	109 paediatric patients with medulloblastoma
• Duration and follow-up	Patient enrolment period: 2002 – 2011 Follow-up median: 38.8 months (range: 1.4-119.2 months)
• Statistical analysis	Descriptive methods: frequencies and medians
Patient characteristics	
• Eligibility criteria	Children with medulloblastoma treated with proton beam therapy treated in Massachusetts General Hospital.
• Exclusion criteria	Any patients who underwent involved-field-only or posterior fossa-only irradiation
• Patient & disease characteristics	Median age at diagnosis: 7.4 y.o. (range: 2.2 – 22.7 y.o.); gender: male: 64/109 Histology: classic (n=81), anaplastic (n=17), desmoplastic (n=10), anaplastic + desmoplastic (n=1) Staging: metastases at diagnosis (n=20) Risk classification: standard (n=74), high-risk (n=35)
Interventions	
• Intervention group	*Surgery*: • Gross total resection (n=80); subtotal resection (n=27); biopsy (n=2) *Chemotherapy*: • Variety of chemotherapeutic protocols (number of patients by chemotherapeutic protocol not reported) *Proton beam therapy*:

Sethi et al. 2014[17]	
	• Passively scattered protons with brass apertures and Lucite blocks custom-made for each field • Craniospinal irradiation dose: 18 Gy [RBE] (n=5), 22.5 Gy [RBE] (n=1), 23.4 Gy [RBE] (n=70), 27 Gy [RBE] (n=2), 30.6 Gy [RBE] (n=2), 34.2 Gy [RBE] (n=1), 36 Gy [RBE] (n=28); • Boost: o Involved-field only: n=70 o Whole posterior fossa: n=39
• Control group	NA
Results	
• Overall survival	At a median follow-up of 38.8 months (range: 1.4-119.2 months): 97/109 (89%; 12 of the 16 patients who experienced relapse died of disease)
• Disease-free survival	Not reported
• Recurrence rate	At a median follow-up of 38.8 months (range: 1.4-119.2 months): 16/109 (15%) Patterns of treatment failure: • Gender: 14/16 malesRisk classification: high-risk (10/16, i.e. 4 were anaplastic, 3 had undergone a subtotal resection and 5 had metastatic disease at presentation) • Histology: classic medulloblastoma (11/16), anaplastic medulloblastoma (4/16), desmoplastic medulloblastoma (1/16) • Localisation of failure: spine (6/16), supratentorial (4/16), supratentorial + spine (1/16), diffuse (3/16), tumour bed (1/16), tumour bed + spine (1/16) • Latest disease status: dead of disease (12/16), no evidence of disease (2/16), alive with disease (2/16)
• Complication rate	Not reported
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Retrospective design • Long period of enrolment • No control group • Variable treatment schemes

Sethi et al. 2014[17]	
	• Only recurrence reported; e.g. no data on complications, secondary malignancies, quality of life • Short follow-up (range: 1.4-119.2 months) • No information on the methods and intervals of follow-up

Jimenez et al. 2013[15]	
Methods	
• Design	Case series; retrospective study.
• Source of funding and competing interest	Sources of funding not mentioned – Competing interest: none declared
• Setting	Massachusetts General Hospital, Boston, US
• Sample size	15 paediatric patients with medulloblastoma or supratentorial primitive neuroectodermal tumours
• Duration and follow-up	Patient enrolment period: 2002 – 2010 Follow-up: median: 39 months (range: 3 – 102 months)
• Statistical analysis	Kaplan-Meier for overall survival and local failure Paired t test to compare variation in height and neuropsychological function before and after treatment
Patient characteristics	
• Eligibility criteria	All patients < 60 months at the time of diagnosis of either medulloblastoma or supratentorial primitive neuroectodermal tumours and treated with surgery, chemotherapy and 3-dimensional proton beam radiation
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Median age at diagnosis: 35 months (range: 23 - 55 months); gender: male: 6/15 Tumour type: medulloblastoma (n=12 among whom 4 patients with anaplastic subtype), supratentorial primitive neuroectodermal (n=3) Staging: M-stage positive disease (Chang classification): n=6 Location: supratentorial: n=3
Interventions	
• Intervention group	*Surgery*: • Gross total resection (n=11), subtotal resection (n=3), partial resection (n=1) • Surgical re-resection: n=1 (after maximal safe resection after initial surgery the patient experienced tumour regrowth after chemotherapy)

Jimenez et al. 2013[15]	
	Chemotherapy: • Children's Oncology Group (COG) or Head Start protocol • n=14 • Additionally: autologous hematopoietic stem cell transplantation (exact number of patients not mentioned) *Proton beam therapy* • Mean time from surgery to the initiation of radiation: 219 days (range: 50-301 days) • Craniospinal irradiation followed by involved-field radiation (IFRT): n=11; IFRT: n=4 • Dose: o Median craniospinal irradiation dose: 21.6 Gy (RBE) (range: 18 – 30.6 Gy [RBE]) o Median boost dose to a total of 54.0 Gy (RBE) (range: 39.6-54.0 Gy [RBE]) o Organs at risk: ▪ median dose to the left cochlea: 24.0 Gy (RBE) (range, 0-35.8 Gy [RBE]) ▪ median dose to the right cochlea: 24.5 Gy (RBE) (range, 0-34.3 Gy [RBE]) ▪ median dose to the pituitary: 23.9 Gy (RBE) (range, 0-45.9 Gy [RBE]) ▪ median dose to the hypothalamus: 24.6 Gy (RBE) (range, 0-39.6 Gy [RBE]) ▪ median dose to the thyroid: 0.1 Gy (RBE) (range, 0-1.7 Gy [RBE]).
• Control group	NA
Results	
• 3-year overall survival	85.6% (no reliable CI reported) At a median follow-up of 39 months (range: 3-102 months) 2 patients had died: • Local failure: n=1 • Non-disease related cause (i.e. medication misadministration): n=1
• Disease-free survival	At a median follow-up of 39 months (range: 3-102 months) 13/15 (87%) patients were alive without evidence of disease
• Recurrence rate	Not reported
• 3-year local failure	7.7% (95% CI: 0.4% – 30.6%)
• Response rate	Not reported
• Complication rate	No acute nor late complication rate reported *Note: 2 patients died before toxicity evaluation*

Jimenez et al. 2013[15]	
	• At a median follow-up from the completion of radiation of 38 months (range: 12 – 81 months): high-frequency sensorineural hearing loss: 9/13 o Right (no intervention): 1/13 o Bilateral: no intervention (2/13), hearing aids (3/13), FM amplifier (3/13) *Note: Six of these patients had hearing evaluations after chemotherapy and before radiation therapy. Of these, 5 exhibited bilateral sensorineural hearing loss before the initiation of radiation therapy.* • At a median follow-up from the completion of radiation of 40 months (range: 12 – 102 months): grade 2 endocrinopathy, requiring hormone replacement (evaluated in 12 of 13 nondeceased patients): 3/12 o Growth hormone deficiency: 1/13 o Growth hormone and thyroid-stimulating hormone deficiency: 1/13 o Growth hormone and adrenocorticotropic hormone deficiency and premature puberty: 1/13 • Vertical height impairment: when all 3 patients with documented GH deficiency were excluded from the analysis, there was no significant difference in age-adjusted height compared with baseline. • Neuropsychological function: *Note: this was only assessed in 8 patients; follow-up date were collected through testing in 5 children and through mailed SIB-R questionnaire in 3 children* At a median follow-up of 26 months from completion of treatment (range: 15-38 months), there were no significant differences between baseline and follow-up in mean IQ scores (n=5) or baseline and follow-up SIB-R (functional independence) scores (n=8). • Late grade 1 permanent alopecia: n=1 • Grade 2 cataract: n=1
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Retrospective design • Small number of patients • Results not separately reported by tumour type • Long period of enrolment • No control group

Jimenez et al. 2013[15]	
	• No clear exclusion criteria • Variable treatment schemes • Unclear which complications were radiation/PBT induced • Complications only assessed in a subgroup of the original sample • Short follow-up (range: 3-102 months)

Moeller et al. 2011[16]	
Methods	
• Design	Case series; prospective study
• Source of funding and competing interest	Sources of funding not mentioned – Competing interest: none declared
• Setting	MD Anderson Cancer Center, Houston, Texas, US
• Sample size	23 consecutive children enrolled, of whom 4 children were censored because of bilateral ototoxicity grades 3 or 4 before radiotherapy and 3 ears were censored because of unilateral ototoxicity grades 3 or 4 before radiotherapy, leaving 35 ears in 19 patients
• Duration and follow-up	Patient enrolment period: 2006 – 2009 Ototoxicity assessed at baseline and after a mean period of 11 months (range: 8-16 months)
• Statistical analysis	One-way ANOVA for changes in raw audiometric thresholds Spearman's correlations and univariate linear modelling for associations between clinical, demographic, treatment, and audiometric variables
Patient characteristics	
• Eligibility criteria	Children with resected and histologically-confirmed medulloblastoma
• Exclusion criteria	None mentioned
• Patient & disease characteristics	Median age at diagnosis: 6 y.o. (range: 3 - 16 y.o.); gender: male: 14/19 Risk classification: standard-risk (n=16), high-risk[m] (n=3)
Interventions	

[m] High risk disease is defined as age < 36 months at diagnosis, presence of postchirurgical residual tumour > 1.5 cm² as measured on MRI, metastatic disease, or anaplastic histology

Moeller et al. 2011[16]	
• Intervention group	Mean total duration of all chemotherapy and radiotherapy: 28 weeks *Surgery*: • N=19 • No details reported on the extent of the surgery *Chemotherapy*: • Platinum-based chemotherapy (n=19) • Median cumulative cisplatin dose 303 mg/m² (range: 298-330 mg/m²) • Following PBT (n=14), before PBT (principally to delay irradiation; n=5) *Proton beam therapy* • The tumour bed plus a CTV expansion: boosted to a total dose of between 54 and 55.8 CGE. • Mean CSI dose: standard-risk patients (n=16): 23.4 CGE, high-risk patients (n=3): 36 CGE • Mean cochlear dose: 30 CGE (range: 19-43 CGE)
• Control group	NA
Results	
• Overall survival	Not reported
• Disease-free survival	Not reported
• Recurrence rate	Not reported
• Progression-free survival	Not reported
• Secondary malignancy	Not reported
• Quality of life	Not reported
• Complication rate	Ototoxicity: (assessed at baseline and 1 year post-radiotherapy) • Following PBT: incidence of high grade (grade 3-4) ototoxicity: 5% • Recommendation of hearing amplification: n=3 • Clinically and statistically significant worsening of hearing threshold across all frequencies tested ($p<0.05$) • Modest threshold change in the audible speech range (0.5-6 kHz) *Note*: scatter plots of cochlear radiation dose versus ototoxicity revealed no obvious correlation between the two
Limitations and other comments	

Moeller et al. 2011[16]	
• Limitations	• Small sample • No control group • No clear exclusion criteria • Variable treatment schemes • Short follow-up (ototoxicity assessed 1 year after PBT, while considered a late side effect of RT, with a latency of approximately 4 years) • Only complications (i.e. ototoxicity) reported; e.g. no data on survival, secondary malignancies, quality of life

2.3.9. Non-resectable osteosarcoma

Table 42 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with non-resectable osteosarcoma

Ciernik et al. 2011[18]	
Methods	
• Design	Case series (chart review); retrospective
• Source of funding and competing interest	Supported in part by grant PO1CA021239 from the National Cancer Institute and in part by the Zurich Cancer League, Switzerland; no conflict of interest reported
• Setting	Massachusetts General Hospital, Boston, US
• Sample size	55 patients with non-resectable or incompletely resected osteosarcoma
• Duration and follow-up	Patient enrolment period: 1983-2009 Follow-up: median: 27 months (range: 0-196 months)
• Statistical analysis	Competing risks regression methodology
Patient characteristics	
• Eligibility criteria	Not clearly reported
• Exclusion criteria	Not clearly reported
• Patient & disease characteristics	Median age: 26.9 y.o. (range: 2-76 y.o.); male: female ratio: 5:6 Anatomical sites: head/cranium (n=22), spine (n=17), pelvis or sacrum (n=13), femur (n=1), hip (n=1), rib/chest wall (n=1) TNM staging: stage I (n=12), stage II (n=38), stage IV (n=5) Histology: osteoblastic (n=29), chondroblastic (n=21), osteosarcoma with giant cells (n=2), fibroblastic (n=2), myxoid (n=1) Grading: grade 1 (n=12), grade 2 (n=23), grade 3 (n=20)

Ciernik et al. 2011[18]	
Interventions	
• Intervention group	*Radiotherapy* • Before 2001: with 160 MV protons via a fixed beam line; after 2001: with 230 MV protons via a rotational gantry • Total dose: 50.4-59.4Gy (n=5), 60-70Gy (n=22), ≥70Gy (n=28) • Variable proportion of total dose delivered with protons: 100% (n=11), 50-99% (n=17), <30% (n=9); no information for 18 patients • Pre-operative RT in 7 patients (to minimize the risk of intraoperative tumour cell seeding) • Intra-operative treatment with electrons (6MV) in 2 patients (doses of 7.5-15Gy), with ^{90}Yplaques in 1 patient (to deliver a dose to the dura adjacent to disease invading the spinal canal) *Surgery:* • Partial resection/debulking (n=19), gross resection with positive margins (n=24), no surgery (n=12) *Chemotherapy:* • Some chemotherapy (n=31), intensive chemotherapy (n=19), no systemic treatment (n=5) • Neoadjuvant (n=48), adjuvant chemotherapy after RT (n=41), unknown chemotherapy status (n=6)
• Control group	NA
Results	
• Overall survival	2-year overall survival: 84% (95% CI: 69-92%) 5-year overall survival: 67% (95% CI: 47-80%) Note: 2 patients died because of therapy related causes (acute lymphatic leukaemia and squamous cell carcinoma of the maxilla); 2 patients died of non-cancer related disease
• Disease free survival	2-year disease free survival: 68% (95% CI: 53-80%) 5-year disease free survival: 65% (95% CI: 49-77%)
• Local & distant control rate	*Local control*: 3-year local control rate: 82% (95% CI: 68-90%) 5-year local control rate: 72% (95% CI: 52-84%) *Distant failure*: 11/55 (20%) patients had distant failure Note: 4/12 patients with local failure also had distant failure
• Complication rate	46/55 (84%) patients had a significant late treatment associated toxicity Grade 1 toxicity (n=12), Grade 2 toxicity (n=12; pain, paraesthesia, atrophy, ineffective gait and foot drop, radiation myelopathy, and distal neuropathy), Grade 3 and 4 toxicity (n=17; grade 3: severe pain requiring morphine-based

Ciernik et al. 2011[18]	
	medication, cranial nerve damage with diplopia, immobility of limb, severe bowel dysfunction with distal functional obstruction because of denervation and severe headaches; grade 4: loss of organ or complete loss of organ function) *Note: Complaints were possibly caused by radiation alone in some patients, whereas most cases of neuronal dysfunction were either pre-existing or possibly related to surgery.*
• Secondary malignancy	Not reported
Limitations and other comments	
• Limitations	• Retrospective design • Case series • No clear inclusion and exclusion criteria • No separate results for children and adults • Long enrolment • Variable treatment schemes • Variable proportion of total radiation dose delivered with protons; no information for 18 patients • Unclear which complications were radiation/PBT induced • Short follow-up • No information on the methods and intervals of follow-up

Table 43 – Evidence table of intervention studies regarding the effect of carbon ion radiotherapy in children with non-resectable osteosarcoma

Matsunobu et al. 2012[19]	
Methods	
• Design	Case series (chart review); retrospective
• Source of funding and competing interest	Supported by the Research Project with Heavy Ions at the National Institute of Radiological Sciences-Heavy Ion Medical Accelerator in Chiba (NIRS-HIMAC); no conflict of interest reported
• Setting	Research Center Hospital for Charged Particle Therapy, Chiba, Japan
• Sample size	78 patients with non-resectable osteosarcoma of the trunk
• Duration and follow-up	Patient enrolment period: 1996-2009 Follow-up: median: 24 months (range: 2-166 months), for the 30 survivors: 42 months (range: 14-166 months); monitoring with CT and MRI at least every 6 months
• Statistical analysis	Kaplan-Meier, log-rank test, Cox proportional hazards model
Patient characteristics	
• Eligibility criteria	Histologic confirmation by the central pathologist, tumours judged medically inoperable by referring surgeons, grossly measurable tumours ≤15 cm in greatest diameter, an Eastern Cooperative Oncology Group performance status[25n] of 0 to 2, no distant metastasis at initial referral for treatment, no prior radiation therapy at the same site (excluding radiation-associated sarcoma), no prior chemotherapy within 4 weeks before CIRT, no infection at the tumour site, and no intravascular tumour embolism.
• Exclusion criteria	Not clearly reported
• Patient & disease characteristics	Median age: 41 y.o. (range: 11-83 y.o.); gender: female: 37% Performance status: 1: n=46, 2: n=32 Tumour status: primary: n=74, metastatic: n=4 Anatomical sites: pelvis (n=61), spine or paraspinal region (n=15), mediastinum and chest wall (n=2) Radiation associated osteosarcoma: n=3 (1 patient who received radiotherapy for uterine cervical cancer 16 years ago, 1 patient who received radiotherapy for prostatic cancer 7 years ago, and 1 patient who received radiotherapy for plasmacytoma of the pubis 16 years ago) TNM staging: not reported Histology: osteoblastic (n=36), chondroblastic (n=16), fibroblastic (n=14), other or unclassified (n=12) Median CTV: 510 cm^3 (range: 60-2299 cm^3)

[n] Eastern Cooperative Oncology Group performance status: Grade 0: Fully active, able to carry on all pre-disease performance without restriction, Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work, Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours, Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair, grade 5: dead[25].

Matsunobu et al. 2012[19]	
Interventions	
• Intervention group	*Surgery:* • Surgical (partial) resection (n= 11; 9 developed local recurrence and 2 had residual tumours) *Chemotherapy:* • n=61 *Radiotherapy:* • Total dose: 52.8 GyE (n=3), 57.6 GyE (n=3), 64.0 GyE (n=8), 70.4 GyE (n=57), 73.6 GyE (n=7) • 16 fixed fractions over 4 weeks, once daily, 4 days per week • All patients could complete the planned CIRT without interruption
• Control group	NA
Results	
• Overall survival	Median survival: 28 months (range: 2-166 months) 2-year overall survival: 58% (95% CI: not reported) 5-year overall survival: 33% (95% CI: not reported) *Notes:* 48 patients died; 45 patients died of their disease, 3 patients died of other causes 12 patients survived >5 years; 9 patients remained continuously disease free, 3 patients died after 5 years
• Disease-specific survival rate	2-year disease-specific survival: 60% (95% CI: not reported) 5-year disease-specific survival: 34% (95% CI: not reported)
• Progression-free survival	2-year progression-free survival: 34% (95% CI: not reported) 5-year progression-free survival: 23% (95% CI: not reported)
• Response rate	*Local control*: 2-year local control rate: 73% (95% CI: not reported) 5-year local control rate: 62% (95% CI: not reported) Local recurrences: in 21/78 patients Median time to diagnosis of local recurrence: 15 months (range: 4-96 months) *Distant metastasis*: 41/78 patients had distant metastasis; most frequent site: lung (n=28)
• Complication rate	Number of patients with acute or late side effects: not reported No fatal toxicities during follow-up after CIRT

Matsunobu et al. 2012[19]	
	Reported side effects: Skin/soft tissue reactions: Grade 3 acute skin reactions: n=3 Grade 3 late skin/soft tissue reactions: n=4 Grade 4 late skin/soft tissue reactions requiring skin grafts: n=3 Functional deficits (of various degrees, depending on the location and extent of the tumour before CIRT): Permanent neurologic complications (for which radiotherapy was believed to be the sole cause): n=4 Bone fractures (requiring surgery): n=2 *Note:* Of 9 patients who were continuously disease free for >5 years, 8 were able to walk with or without the help of a cane, and 6 were free from pain killers
• Secondary malignancy	Not reported
Limitations and other comments	
• Limitations	• Retrospective design • Case series • No separate results for children and adults • Variable treatment schemes • Unclear which complications were CIRT induced • Short follow-up

2.3.10. Retinoblastoma

Table 44 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with retinoblastoma

Sethi et al. 2014[20]	
Methods	
• Design	Comparative study; retrospective study
• Source of funding and competing interest	Supported by the Federal Share of program income earned by Massachusetts General Hospital on grant C06 CA059267, Proton Therapy Research and Treatment Center.
• Setting	Harvard Cyclotron Laboratory or the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital (MGH), US
• Sample size	Proton cohort: 55; photon cohort: 31
• Duration and follow-up	Patient enrolment period: 1986-2011 Follow-up: Proton cohort: median: 6.9 yrs.; 18 pts had ≥ 10 years FU; median age at last FU: 8.5 y.o. Photon cohort: median: 13.1 yrs.; 18 pts had > 10 years FU; median age at last FU: 14.2 y.o.
• Statistical analysis	Fisher exact test and Wilcoxon rank sum test to compare characteristics between the proton and photon cohorts; Kaplan-Meier method to estimate cumulative incidence of secondary malignancy; the logrank test to compare the risk of secondary malignancy between the proton and photon cohorts
Patient characteristics	
• Eligibility criteria	Patients who received proton RT for retinoblastoma at the Harvard Cyclotron Laboratory or the Francis H. Burr Proton Therapy Center at MGH between 1986 and 2011; at least 6 months FU; no other inclusion criteria mentioned
• Exclusion criteria	Patients who received proton RT after prior photon RT (n= 3); patients with< 6 months of follow-up (n=3 in proton cohort and n=2 in the photon cohort)
• Patient & disease characteristics	Proton and photon cohorts were similar with regard to: • Sex distribution: female 56% vs. 45%; p=0.372 • Age at diagnosis (median): 7.5 months vs. 7.2 months; p=0.544 Statistically significant differences between proton and photon cohorts with regard to: • Proportion hereditary cases: 84% vs. 61%; p=0.035 • Proportion patients aged >1 y.o. at initiation of RT: 64% vs. 39%; p=0.042 • Proportion patients who received chemotherapy: 56% vs. 16%; p<0.001
Interventions	

Sethi et al. 2014[20]	
• Intervention group	*Chemotherapy:* • 31/55 (56%) *Proton beam therapy:* • Median RBE dose (Gy): 44.16 (range: 40-50)
• Control group	*Chemotherapy:* • 5/31 (16%) *Photon therapy:* • Median RBE dose (Gy): 45.0 (range: 34-82.6)
Results	
• Overall survival	No data reported (As survival rates for patients with retinoblastoma are very high, even among those with advanced disease, the impact of proton beam therapy on medium term survival is not really an issue of concern)
• Disease free survival	No data reported
• Recurrence	No data reported
• Complication rate	No data reported
• Secondary malignancy	Secondary malignancy: • PBT: 2% vs. photon: 13% 10-year cumulative incidence of secondary malignancy: • PBT: 5% vs. photon: 14%; p= 0.120 10-year cumulative incidence of RT-induced or in-field secondary malignancy: • PBT: 0% vs. photon: 14%; p= 0.015
• Quality of life	No data reported
Limitations and other comments	
• Limitations	• Significant differences between groups including year of treatment, hereditary status, receipt of chemotherapy, median follow-up, hence unclear comparability of PBT and photon group • No randomization, no allocation concealment, no blinding • Variable treatment schemes • Long enrolment • Confounding factors are not taken into account in the analysis • Insufficient info to assess whether some eligible subjects might have secondary tumours at the time of enrolment • Assessment of outcome is not made blind to exposure status

Sethi et al. 2014[20]	
	• Short follow-up (ie, 1.0 to 24.4 years in the proton cohort, 1.4 to 23.9 years in the photon cohort) for some patients • Insufficient info to assess whether selective loss-to-follow-up can be sufficiently excluded • Several malignancies were not included in the analysis (e.g. 1 pineoblastoma, 1 osteosarcoma and 2 bening neoplasms)

2.3.11. Rhabdomyosarcoma

Table 45 – Evidence table of intervention studies regarding the effect of proton beam therapy in children with rhabdomyosarcomas

Childs et al. 2012[26]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Sources of funding not mentioned - Competing interest: none declared
• Setting	Harvard Cyclotron Laboratory (n=8) and Francis H. Burr Proton Therapy Center at Massachusetts General Hospital (n=9), Boston, US
• Sample size	17 consecutive patients with parameningeal rhabdomyosarcoma
• Duration and follow-up	Patient enrolment period: 1996 - 2005 Median follow-up (for survivors): 5 years (range: 2-10.8 years)
• Statistical analysis	Kaplan-Meier method to estimate failure free survival and overall survival Log–rank test to compare the survival difference between patients with and without intracranial extension at diagnosis.
Patient characteristics	
• Eligibility criteria	Histologically confirmed parameningeal rhabdomyosarcoma
• Exclusion criteria	No criteria mentioned
• Patient & disease characteristics	Median patient age at diagnosis: 3.4 years (range: 0.4–17.7) Histology: Embryonal (n=11), alveolar (n=4), and undifferentiated (n=2) Intracranial extension: 10 patients IRS † clinical grouping: 15/17 IRS group III; 2/17 IRS group IV
Interventions	
• Intervention group	*Chemotherapy:*

Childs et al. 2012[26]	
	• n=11: vincristine, actinomycin, and cyclophosphamide (VAC) for 40 weeks (COG trial for children with intermediate-risk rhabdomyosarcoma, COG D9803) • n=2: VAC alternating with vincristine, topotecan,and cyclophosphamide for 40 weeks (experimental arm of COG D9803) • n=3: complex multiagent chemotherapy regimen including ifosfamide, vincristine, actinomycin, carboplatin, epirubicin, and etoposide for 27 weeks (Malignant Mesenchymal Tumors Study 98) • n=1: combination of VAC, topotecan, etoposide, ifosfamide, carboplatin, and adriamycin for 58 weeks before initiation of RT (which was delayed because of the patient's young age) *Proton therapy:* • Median prescribed dose: 50.4 cobalt gray equivalents (GyRBE) (range: 50.4–56.0 GyRBE) • Daily fractions: 1.8–2.0 GyRBE • All patients completed the planned course of RT *Notes:* o Patients treated at HCL (n=8) received 4 fractions per week o 7/8 patients treated at HCL had a mixed photon/proton plan (median photon dose: 9 Gy (range: 9-21.6 Gy) *Surgery:* • n=1: debulking of the nasopharyngeal mass, but gross residual disease remained • n=16: only incisional or fine-needle biopsy to obtain histologic diagnosis with no further attempts at resection
• Control group	NA
Results	
• 5-year overall survival	64% (95% CI: 37-82%); patients with intracranial extension (n=10): 60% (95% CI: 25-83%) vs. patients without intracranial extension (n=7): 71% (95% CI: 26-92%)
• 5-year failure free survival	59% (95% CI: 33-79%); patients with intracranial extension (n=10): 50% (95% CI: 18-75%) vs. patients without intracranial extension (n=7): 71% (95% CI: 26-92%)
• Recurrence	7/17 (41%) patients at a median of 10.5 months (range: 7-18.5 months) [local only (n=2), regional only (n=2), distant only (n=2), and local and distant (n=1)] *Notes*: • 6 of 7 patients with recurrence died 8-34 months after diagnosis • Median survival after initial local–regional recurrence: 10 months (range: 2–95 months) • Median survival after distant recurrence: 4 months (range: 1 week to 15 months)
• Complication rate	A complication rate for the whole sample was not reported. Late effects likely related to PBT: failure to maintain height velocity (n=3), endocrine deficits (n=2), mild facial hypoplasia (n=7), failure of permanent tooth eruption adjacent to the treatment field (n=3), dental caries adjacent to the treatment field (n=5), chronic nasal/sinus congestion (n=2).

Childs et al. 2012[26]	
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Small number of patients • Retrospective design • Case series, hence no comparison group • No clear inclusion and exclusion criteria • Treatment schemes were variable • Confounding factors are not taken into account in the analyses other than intracranial extension • Long period of enrolment (10 years) • Differential follow-up: 6/17 patients had structured follow-up (within 6 weeks of therapy completion and then at 6-month intervals for 2 years and at least annually thereafter); for 11/17 patients follow-up information was obtained through contacting referring specialists • Short follow-up (for some patients only 2 years)

† *Intergroup Rhabdomyosarcoma Study*

Cotter et al. 2011[27]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Sources of funding not mentioned - Competing interest: none declared
• Setting	Massachusetts General Hospital, Boston, US (tertiary referral centre)
• Sample size	7 consecutive patients with bladder/prostate rhabdomyosarcoma
• Duration and follow-up	Patient enrolment period: 2002 - 2008 Median follow-up: 27 months (10-90 months)
• Statistical analysis	Frequencies
Patient characteristics	
• Eligibility criteria	Paediatric bladder/prostate rhabdomyosarcoma (embryonal)

Cotter et al. 2011[27]	
• Exclusion criteria	No criteria mentioned
• Patient & disease characteristics	Median age at the time of treatment: 30 months (range:10–70 months) Tumour histology: embryonal (7/7) IRS † clinical grouping: Group II stage 2 (1/7), Group III stage 2 (2/7), Group III stage 3 (4/7)
Interventions	
• Intervention group	*Surgery:* • n=4: gross total resection (prior to radiotherapy) • n=3: either biopsy or partial resection *Chemotherapy:* • All patients: concurrent chemotherapy during radiation course and additional chemotherapy according to IRS V (www.childrensoncologygroup.org) protocols. • Note: n=1: salvage chemotherapy and radiation for recurrent disease *Proton therapy*: • Total dose: range: 36 - 50.4 CGE
• Control group	NA
Results	
• Overall survival	Not reported
• Disease-free survival	5/7 (71%; with intact bladders) at study completion
• Recurrence rate	Local recurrence rate: 1/7 (14%; recurrence in the bladder) Regional recurrence rate: 1/7 (14%; recurrence in the rectum and inguinal nodes)
• Complication rate	3/7 (43%)(cave: unclear which side effects were due to proton beam therapy) Reported side effects: urinary sphincter dysfunction (1/7), intermittent hematuria (1/7),enuresis/hydronephrosis/ vesicoureteral reflux (grade IV) (1/7) Note: there were no skeletal or gastrointestinal effects
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Small number of patients • Retrospective design • Case series, hence no comparison group

Cotter et al. 2011[27]	
	• Confounding factors are not taken into account in the analysis • No clear inclusion and exclusion criteria • Differential follow-up: structured follow-up for some patients; for others follow-up information was obtained through contacting referring specialists • Short follow-up (for some patients only 10 months)

† *Intergroup Rhabdomyosarcoma Study*

Timmermann et al. 2007[28]	
Methods	
• Design	Case series; retrospective study
• Source of funding and competing interest	Sources of funding not mentioned - Competing interest: none declared
• Setting	Paul Scherrer Institute, Switzerland
• Sample size	16 patients with soft tissue sarcomas; 12/16: rhabdomyosarcomas
• Duration and follow-up	Patient enrolment period: 1997-2005 Follow-up: range: 4.3 - 70.8 months
• Statistical analysis	Kaplan-Meier survival analysis
Patient characteristics	
• Eligibility criteria	Patients under 21 years of age with malignant soft tissue tumours in the region of head and neck, spine, and pelvis, treated with PBT
• Exclusion criteria	Non reported
• Patient & disease characteristics	Median age at diagnosis: 3.3 years (range: 0.9-12.1 years) Gender: female: 7/16 Histology-tumour sites: • 10 embryonal rhabdomyosarcomas: parameningeal (6/10); prostate (1/10); orbital (3/10) • 1 unclassified rhabdomyosarcoma: parapharyngeal (1/1) • 1 alveolar rhabdomyosarcoma: orbital (1/1) Postsurgical grouping (IRS†): • Embryonal rhabdomyosarcomas: Group III (9/10); Group IV (1/10)

Timmermann et al. 2007[28]	
	• Unclassified rhabdomyosarcoma: Group III (1/1) • Alveolar rhabdomyosarcoma: Group III (1/1)
Interventions	
• Intervention group	*Surgery:* • Unclear how many children had surgery and whether it was total or partial resection before or after proton beam therapy *Chemotherapy:* • n=14: chemotherapy before and during PBT • n=2: no chemotherapy (*note*: these were children with other diagnosis than RMS) *Proton beam therapy:* • Spot scanning proton therapy (n=16); intensity modulated proton therapy (n=3) • Median total dose: 50.0 CGE (range: 46-61.2); dose per fraction: 1.8-2.0 CGE • Median total duration: 42.5 days (range: 38-50); 4 days per week *Note*: from 2004 on: intensity-modulated proton therapy *Photon therapy*: • n= 2: treatment completion with 10.0-10.8 CGE
• Control group	NA
Results	
• Overall survival rate	At a median follow-up of 18.6 months: 10/12 (83%) patients (only patients with rhabdomyosarcoma considered) *Note*: estimated 1- and 2-year overall survival rate: 90.9% and 69.3% (for the whole sample)
• Progression-free survival	Not reported separately for children with rhabdomyosarcoma *Note*: estimated 1- and 2-year progression-free survival rate: 81.8% and 71.6% (for the whole sample)
• Response rate	After proton beam therapy: • Complete remission: 3/12 • Partial remission: 3/12 • Stable disease: 6/12 *Note*: only evaluable in 12/16 children (as in these children tumour residue was radiographically measurable)
• Recurrence rate	Local recurrence: 2/12 (17%) patients (only patients with rhabdomyosarcoma considered) *Note*: both children died
• Complication rate	Acute toxicity: Not reported separately for children with rhabdomyosarcoma

Timmermann et al. 2007[28]	
	Note: acute side effects were mild; grade 3 or 4 toxicity occurred only for bone marrow when parallel chemotherapy was applied (for the whole sample) Late side effects: 2/3 surviving children with RMS *Note:* Only 3 surviving children with RMS were followed for more than 1 year (for the others follow-up was too short to evaluate late sequelae) Reported side effects: caries (n=1), mild myopia (n=1) and orbital asymmetry (n=1)
• Secondary malignancy	Not reported
• Quality of life	Not reported
Limitations and other comments	
• Limitations	• Small number of patients • Retrospective design • Case series, hence no comparison group • No clear exclusion criteria • Variable proton beam therapy (3 patients received IMPBT) • Unclear how many children had surgery and whether it was total or partial resection before or after proton beam therapy • Short follow-up (for some patients only 4 months) • No information on the methods and intervals of follow-up • Toxicity was scored retrospectively in some and prospectively in other children • Confounding factors are not taken into account in the analyses

† *Intergroup Rhabdomyosarcoma Study*

2.4. Grade profiles & summary of findings tables

2.4.1. Skull base chondrosarcoma & skull base and (para)spinal chordoma

2.4.1.1. Grade profiles - Skull base chondrosarcoma & skull base and (para)spinal chordoma

Table 46 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with chordoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
5-year overall survival rate - PBT 89%	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low
5-year overall survival rate - photon & PBT 81%	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low
5-year progression free survival - photon & PBT 77%	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only two studies 4: Low sample size	Very low
Local and/or regional and/or regional recurrence rate – PBT 2/19 (11%)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low
Local recurrence rate – photon & PBT 5/26 (19%)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low
5-year local control rate – PBT 81%	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

Table 47 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with chondrosarcoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
5-year overall survival rate 75%	1	-2	-1	0	-2	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
Local recurrence rate 1/7 (14%)	1	-2	-1	0	-2	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
5-year local control rate 80%	1	-2	-1	0	-2	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

Table 48 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with chordoma & chondrosarcoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Complication rate – photon & PBT Acute toxicity: 28/30 (93%)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only two studies 4: Low sample size	Very low
Complication rate - PBT Acute toxicity: 12/26 (46%)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only two studies 4: Low sample size	Very low
Complication rate - PBT Late toxicity: 5/26 (19%)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only two studies 4: Low sample size	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:

Very low level of evidence

2.4.1.2. Summary of findings tables

Table 49 – Clinical evidence profile: Clinical effectiveness of proton beam and photon therapy in children with chordoma

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	With *PBT*		Risk with Control	Risk difference with *PBT* (95% CI)
5-year overall survival											
26 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	81%			
5-year progression free survival											
26 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	77%			
Recurrence rate											
26 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	5/26 (19%)			
Complication rate											
26 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	Acute toxicity: 28/30 (93%; including 3 cases with CS)			

[o] Small sample size, retrospective design, case series, no clear inclusion and exclusion criteria, combined therapy (PBT and photon) in most children, long period of enrolment, short follow-up

[p] Only 1 study retrieved

[q] Low sample size

Table 50 – Clinical evidence profile: Clinical effectiveness of spot-scanning proton beam therapy in children with chordoma

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With Control	Study event rates (%) With *PBT*	Relative effect (95% CI)	Anticipated absolute effects: Risk with Control / Risk difference with *PBT* (95% CI)
5-year overall survival										
19 (1 study)	Very serious risk of bias[r]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	CH : 89% (no CI reported)		
Recurrence rate										
19 (1 study)	Very serious risk of bias[r]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	2/19 (11%)		
5-year local control rate										
19 (1 study)	Very serious risk of bias[r]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	81% (no CI reported)		
Complication rate – chordoma & chondrosarcoma										
26 (1 study) (CH: n=19, CS: n=7)	Very serious risk of bias[r]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	(CH and CS together) Acute toxicity: 12/26 Late toxicity: 5/26		

[r] Small sample size, retrospective design, case series, no clear exclusion criteria, short follow-up

Table 51 – Clinical evidence profile: Clinical effectiveness of spot-scanning proton beam therapy in children with chondrosarcoma

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With *PBT*		Risk with Control	Risk difference with *PBT* (95% CI)
5-year overall survival											
7 (1 study)	Very serious risk of bias[r]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	75% (no CI reported)			
Recurrence rate											
7 (1 study)	Very serious risk of bias[r]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	1/7 (14%)			
5-year local control rate											
7 (1 study)	Very serious risk of bias[r]	Serious inconsistency[d]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	80% (no CI reported)			
Complication rate – chordoma & chondrosarcoma											
26 (1 study) (CH: n=19, CS: n=7)	Very serious risk of bias[r]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	(CH and CS together) Acute toxicity: 12/26 Late toxicity: 5/26			

2.4.2. Craniopharyngioma

2.4.2.1. Grade profiles - Craniopharyngioma

Table 52 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with craniopharyngioma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
3-year overall survival PBT: 94.1% vs. IMRT: 96.8%; p= 0.742	1	-2	-1	0	0	0	1: Very serious methodological limitations 2: Only one study	Very low
3-year cystic failure-free survival PBT: 67.0% vs. IMRT: 76.8%; p= 0.994	1	-2	-1	0	0	0	1: Very serious methodological limitations 2: Only one study	Very low
3-year nodular failure-free survival PBT: 91.7% vs. IMRT: 96.4%; p= 0.546	1	-2	-1	0	0	0	1: Very serious methodological limitations 2: Only one study	Very low
Cyst dynamics - Early cyst growth (≤ 3 months after RT) PBT: 19% vs. IMRT: 42%; p= 0.082	1	-2	-1	0	0	0	1: Very serious methodological limitations 2: Only one study	Very low
Cyst dynamics - Late cyst growth (> 3 months after RT) PBT: 19% vs. IMRT: 32%; p= 0.353	1	-2	-1	0	0	0	1: Very serious methodological limitations 2: Only one study	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:

Very low level of evidence

2.4.2.2. *Summary of findings tables*

Table 53 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with craniopharyngioma

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With PBT	With IMRT		Risk with Control	Risk difference with Intervention (95% CI)
3-year overall survival											
52 (1 study)	Very serious risk of bias[s]	Serious inconsistency[t]	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	94.1%	96.8%			
3-year cystic failure-free survival											
52 (1 study)	Very serious risk of bias[s]	Serious inconsistency[t]	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	67.0%	76.8%			
3-year nodular failure-free survival											
52 (1 study)	Very serious risk of bias[s]	Serious inconsistency[t]	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	91.7%	96.4%			
Cyst dynamics - Early cyst growth (≤ 3 months after RT)											
52 (1 study)	Very serious risk of bias[s]	Serious inconsistency[t]	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	19%	42%			
Cyst dynamics - Late cyst growth (> 3 months after RT)											
52 (1 study)	Very serious risk of bias[s]	Serious inconsistency[t]	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	19%	32%			

[s] No randomization, no allocation concealment, no blinding, significant differences between groups

[t] Only one study

2.4.3. Ependymoma

2.4.3.1. Grade profiles - Ependymoma

Table 54 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with ependymoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
3-year overall survival Intracranial ependymomas 95%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year progression-free survival Intracranial ependymomas 76%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year local control rate Intracranial ependymomas 83%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
5-year local control rate Intracranial ependymomas 77%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year distal control rate Intracranial ependymomas 86%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
5-year distal control rate Intracranial ependymomas 83%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

2.4.3.2. *Summary of findings tables*

Table 55 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with ependymoma

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With PBT		Risk with Control	Risk difference with PBT (95% CI)
3-year overall survival (intracranial ependymomas)											
70 (1 study)	Very serious risk of bias[u]	Serious inconsistency[v]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	95%			
3-year progression-free survival (intracranial ependymomas)											
70 (1 study)	Very serious risk of bias[u]	Serious inconsistency[v]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	76%			
3-year local control rate (intracranial ependymomas)											
70 (1 study)	Very serious risk of bias[u]	Serious inconsistency[v]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	83%			
5-year local control rate (intracranial ependymomas)											
70 (1 study)	Very serious risk of bias[u]	Serious inconsistency[v]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	77%			
3-year distal control rate (intracranial ependymomas)											
70 (1 study)	Very serious risk of bias[u]	Serious inconsistency[v]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	86%			

[u] Retrospective design, case series, no exclusion criteria, variable treatment schemes, very long period of enrolment, variable follow-up duration (from 12 months to 11.7 years)

[v] Only 1 study retrieved

5-year distal control rate (intracranial ependymomas)								
70 (1 study)	Very serious risk of bias[u]	Serious inconsistency[v]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	83%

2.4.4. Esthesioneuroblastoma

2.4.4.1. Grade profiles - Esthesioneuroblastoma

Table 56 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with esthesioneuroblastoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
5-year overall survival rate 95.2% (95% CI: 70.7-99.3%)	1	-2	-1	-1	-1	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults 4: Low sample size	Very low
5-year disease free survival 86.4% (95%: 63.4-95.4%)	1	-2	-1	-1	-1	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults 4: Low sample size	Very low
Local and/or regional and/or regional recurrence rate 6/22 (27%)	1	-2	-1	-1	-1	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults 4: Low sample size	Very low
Complication rate 13/22 (59%)	1	-2	-1	-1	-1	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults 4: Low sample size	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade

Very low level of evidence

2.4.4.2. *Summary of findings tables*

Table 57 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with esthesioneuroblastoma

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** With Control	**Study event rates (%)** With PBT	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with Control	**Anticipated absolute effects** Risk difference with PBT (95% CI)
5-year overall survival											
22 (1 study)	Very serious risk of bias[w]	Serious inconsistency[x]	Serious indirectness[Error! Bookmark not defined.]	Serious imprecision[z]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency, indirectness and imprecision	NA	95.2% (95% CI: 70.7-99.3%)			
Disease free survival											
22 (1 study)	Very serious risk of bias[w]	Serious inconsistency[x]	Serious indirectness[y]	Serious imprecision[z]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency, indirectness and imprecision	NA	86.4% (95% CI: 63.4-95.4%)			
Recurrence rate (Local and/or regional and/or distant)											
22 (1 study)	Very serious risk of bias[w]	Serious inconsistency[x]	Serious indirectness[y]	Serious imprecision[z]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency, indirectness and imprecision				NA	27%
Complication rate											
22 (1 study)	Very serious risk of bias[w]	Serious inconsistency[x]	Serious indirectness[y]	Serious imprecision[z]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency, indirectness and imprecision				NA	59%

[w] Small sample, retrospective design, case series, no clear inclusion and exclusion criteria, short follow-up, no information on the methods and intervals of follow-up, treatment schemes were variable, the analysis did not control for Kadish classification, nor for other confounding factors.
[x] Only 1 study retrieved
[y] No control group; children mixed with adults
[z] Low sample size

2.4.5. Ewing sarcoma

2.4.5.1. Grade profiles - Ewing sarcoma

Table 58 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with Ewing sarcoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
3-year overall survival 89%	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low
3-year disease-specific survival 68%	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low
3-year event-free survival 60%	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low
Recurrence rate 17%	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low
3-year local control 86%	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low
Complication rate 100% (acute complications)	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low
2-year cumulative incidence of secondary malignancy 7% (95%CI: 1-9%)	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low
3-year cumulative incidence of secondary malignancy 15% (95%CI: 5-32%)	1	-1	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: No control group	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:

Very low level of evidence

2.4.5.2. Summary of findings tables

Table 59 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with Ewing sarcoma

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With Control	Study event rates (%) With PBT	Relative effect (95% CI)	Anticipated absolute effects Risk with Control / Risk difference with PBT(95% CI)
3-year overall survival										
30 (1 study)	Very serious risk of bias[aa]	Serious inconsistency[bb]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	89%		
3-year event-free survival										
30 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	60%		
3-year disease-specific survival										
30 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	86%		
Recurrence rate										
30 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	17%		
3-year local control										

[aa] Case series, retrospective design, no clear exclusion criteria, long period of enrolment, short follow-up (mean 38.4 months)

[bb] Only 1 study retrieved

Quality assessment								Summary of Findings
30 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	86%
Complication rate								
30 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	100%
2-year cumulative incidence of secondary malignancy								
30 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	7% (95%CI: 1-19%)
3-year cumulative incidence of secondary malignancy								
30 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	15% (95%CI: 5-32%)

2.4.6. CNS Germinoma

2.4.6.1. Grade profiles - CNS germinoma

Table 60 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with CNS germinoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
3-year overall survival 89%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year disease-specific survival 68%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year event-free survival 60%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
Recurrence rate 17%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year local control 86%	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
Complication rate 100% (acute complications)	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
2-year cumulative incidence of secondary malignancy 7% (95%CI: 1-9%)	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year cumulative incidence of secondary malignancy 15% (95%CI: 5-32%)	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:

Very low level of evidence

2.4.6.2. *Summary of findings tables*

Table 61 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with CNS germ cell tumours

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With PBT**		**Risk with Control**	**Risk difference with PBT** (95% CI)
Overall survival											
22 (1 study)	Very serious risk of bias[cc]	Serious inconsistency[dd]	No serious indirectness	Serious imprecision[ee]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	100%			
Progression free survival											
22 (1 study)	Very serious risk of bias[cc]	Serious inconsistency[dd]	No serious indirectness	Serious imprecision[ee]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency, indirectness and imprecision	NA	95%			
Local recurrence rate											
22 (1 study)	Very serious risk of bias[cc]	Serious inconsistency[dd]	No serious indirectness	Serious imprecision[ee]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	0%			
Distal recurrence rate											
22 (1 study)	Very serious risk of bias[cc]	Serious inconsistency[dd]	No serious indirectness	Serious imprecision[ee]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	Germinoma: 0/13 NGGCT: 11% (1/9; peritoneal)			

[cc] Small sample, retrospective design, case series, no clear inclusion and exclusion criteria, no information on statistical analysis, no confidence intervals presented, for some patients follow-up was very short (only 13 months), no information on the methods and intervals of follow-up

[dd] Only 1 study retrieved

[ee] Small sample size

2.4.7. Low-grade glioma

2.4.7.1. Grade profiles - Low-grade glioma

Table 62 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with low-grade glioma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
8-year overall survival 100%	1	-2	-1	0	-2	0	1: Very serious methodological limitations 2: Only one study 4: 95% CI not provided	Very low
6-year progression-free survival 89.7%	1	-2	-1	0	-2	0	1: Very serious methodological limitations 2: Only one study 4: 95% CI not provided	Very low
8-year progression-free survival 82.8%	1	-2	-1	0	-2	0	1: Very serious methodological limitations 2: Only one study 4: 95% CI not provided	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

2.4.7.2. *Summary of findings tables*

Table 63 – Clinical evidence profile: Clinical effectiveness of proton therapy in children with low-grade glioma

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Hazard ratio** (95% CI)	**Anticipated absolute effects**	
							With photon	With *proton*		Risk with Control	Risk difference with *PBT* (95% CI)
8-year overall survival											
32 (1 study)	Very serious risk of bias[ff]	Serious inconsistency[gg]	No serious indirectness	Very serious imprecision[hh]	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	100%			
6-year progression-free survival											
32 (1 study)	Very serious risk of bias[ff]	Serious inconsistency[gg]	No serious indirectness	Very serious imprecision[hh]	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	89.7%			
8-year progression-free survival											
32 (1 study)	Very serious risk of bias[ff]	Serious inconsistency[gg]	No serious indirectness	Very serious imprecision[hh]	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	82.8%			

[ff] Small sample size, retrospective design, case series, no control group, no clear exclusion criteria, short follow-up, variable treatment schemes
[gg] Only one study
[hh] 95% CI not provided

2.4.8. Medulloblastoma & PNET

2.4.8.1. Grade profiles - Medulloblastoma/PNET

Table 64 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with medulloblastoma/PNET

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
3-year overall survival (Medulloblastoma & PNET) 85.6% (reported 95% CI not reliable)	1	-1	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
Recurrence rate (Medulloblastoma) 15% (16/109 patients)	1	-1	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
3-year local failure rate (Medulloblastoma & PNET) 7.7% (95% CI: 0.4 – 30.6%)	1	-1	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
Complication rate (i.e. high-grade ototoxicity at 1yr)(Medulloblastoma) 5% (No 95% CI reported)	1	-1	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Low sample size	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

2.4.8.2. *Summary of findings tables*

Table 65 – Clinical evidence profile: Clinical effectiveness of proton therapy in children with medulloblastoma and PNET

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	With *PBT*		Risk with Control	Risk difference with *PBT* (95% CI)
3-year overall survival (Medulloblastoma & PNET)											
15 (1 study)	Serious risk of bias[ii]	Serious inconsistency[jj]	No serious indirectness	Serious imprecision[kk]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	85.6% (no reliable 95% CI reported)			
Recurrence rate (Medulloblastoma)											
109 (1 study)	Serious risk of bias[ll]	Serious inconsistency[jj]	No serious indirectness	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	NA	15%			
3-year local failure rate (Medulloblastoma & PNET)											
15 (1 study)	Serious risk of bias[ii]	Serious inconsistency[jj]	No serious indirectness	Serious imprecision[kk]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	7.7% (95% CI: 4 - 30.6%)			
Complication rate (i.e. high-grade ototoxicity at 1yr)(Medulloblastoma)											
19 (1 study)	Serious risk of bias[mm]	Serious inconsistency[jj]	No serious indirectness	Serious imprecision[kk]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	5% (No 95% CI reported)			

[ii] Retrospective design, case series, no control group, short follow-up, variable treatment schemes
[jj] Only one study
[kk] Low sample size
[ll] Retrospective design, case series, no control group, no clear exclusion criteria, variable treatment schemes
[mm] Retrospective design, case series, no control group, short follow-up, variable treatment schemes

2.4.9. Non-resectable osteosarcoma

2.4.9.1. Grade profiles - Non-resectable osteosarcoma

Table 66 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with non-resectable osteosarcoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
2-year overall survival PBT: 84%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
5-year overall survival PBT: 67%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
2-year disease-free survival PBT: 68%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
5-year disease-free survival PBT: 65%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
3-year local control rate PBT: 82%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
5-year local control rate PBT: 72%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
Complication rate PBT: 46/55	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

Table 67 – Grade profile of intervention studies regarding the effect of carbon ion therapy in children with osteosarcoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
2-year overall survival CIRT: 58%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
5-year overall survival CIRT: 33%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
2-year disease-specific survival CIRT: 60%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
5-year disease-specific survival CIRT: 34%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
2-year progression-free survival CIRT: 34%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
5-year progression -free survival CIRT: 23%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
2-year local control rate CIRT: 73%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low
5-year local control rate CIRT: 62%	1	-2	-1	-1	0	0	1: Serious methodological limitations 2: Only one study 3: Children mixed with adults	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:
Very low level of evidence

2.4.9.2. *Summary of findings tables*

Table 68 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with non-resectable osteosarcoma

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Photon	CIRT		Risk with Control	Risk difference with CIRT (95% CI)
2-year overall survival											
55 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness[pp]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	84% (95% CI: 69-92%)			
5-year overall survival											
55 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness[pp]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	67% (95% CI: 47-80%)			
2-year disease-free survival											
55 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness[pp]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	68% (95% CI: 53-80%)			
5-year disease-free survival											
55 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness[pp]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	65% (95% CI: 49-77%)			
3-year local control rate											
55 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness[pp]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	82% (95% CI: 68-90%)			

[nn] Retrospective design, case series, no clear inclusion and exclusion criteria, no separate results for children and adults, variable treatment schemes, variable proportion of total radiation dose delivered with protons, short follow-up, no information on the methods and intervals of follow-up

[oo] Only one study

[pp] Children mixed with adults

Quality assessment							Summary of Findings	
5-year local control rate								
55 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness[pp]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	72% (95% CI: 52-84%)
Complication rate								
55 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness[pp]	No serious imprecision	Not detected	⊕⊖⊖⊖NA **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	46/55

Table 69 – Clinical evidence profile: Clinical effectiveness of carbon ion therapy in children with non-resectable osteosarcoma

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Photon	CIRT		Risk with Control	Risk difference with CIRT (95% CI)
2-year overall survival											
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	58%			
5-year overall survival											
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	33%			
2-year disease-specific survival											
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	60%			
5-year disease-specific survival											

Quality assessment								Summary of Findings
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	34%
2-year progression-free survival								
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	34%
5-year progression-free survival								
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	23%
2-year local control rate								
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	73%
5-year local control rate								
78 (1 study)	Very serious risk of bias[qq]	Serious inconsistency[rr]	No serious indirectness[ss]	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and indirectness	NA	62%

[qq] Retrospective design, case series, no separate results for children and adults, variable treatment schemes, unclear which complications were CIRT induced, short follow-up

[rr] Only one study

[ss] Children mixed with adults

2.4.10. Retinoblastoma

2.4.10.1. Grade profiles - Retinoblastoma

Table 70 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with retinoblastoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Secondary malignancy PBT: 2% vs. photon: 13%; p= 0.372	1	-2	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
10-year cumulative incidence of secondary malignancy PBT: 5% vs. photon: 14%; p= 0.120	1	-2	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low
10-year cumulative incidence of RT-induced or in-field secondary malignancy PBT: 0% vs. photon: 14%; p= 0.015	1	-2	-1	0	0	0	1: Serious methodological limitations 2: Only one study	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias

Overall grade:

Very low level of evidence

2.4.10.2. Summary of findings tables

Table 71 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with retinoblastoma

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With photon	Study event rates (%) With PBT	Relative effect (95% CI)	Anticipated absolute effects Risk with Control / Risk difference with PBT (95% CI)
Secondary malignancy										
86 (1 study)	Very serious risk of bias[tt]	Serious inconsistency[uu]	No serious indirectness	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	13%	2%		
10-year cumulative incidence of secondary malignancy										
86 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	14%	5%		
10-year cumulative incidence of RT-induced or in-field secondary malignancy										
86 (1 study)	Very serious risk of bias[nn]	Serious inconsistency[oo]	No serious indirectness	No serious imprecision	Not detected	⨁⊖⊖⊖ **VERY LOW** due to high risk of bias and inconsistency	14%	0%		

[tt] No randomization, no allocation concealment, no blinding, unclear comparability of PBT and photon group, significant differences between groups, insufficient info to assess whether some eligible subjects might have secondary tumours at the time of enrolment, insufficient info to assess whether selective loss-to-follow-up can be sufficiently excluded

[uu] Only one study

2.4.11. Rhabdomyosarcoma

2.4.11.1. Grade profiles - Rhabdomyosarcoma

Table 72 – Grade profile of intervention studies regarding the effect of proton beam therapy in children with rhabdomyosarcoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
5-year overall survival 64% (95% CI: 37-82%)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
5-year failure free survival 59% (95% CI: 33-79%)	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
Recurrence rate (parameningeal, parapharyngeal, orbital or prostate RMS) 2/12 patients	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
Recurrence rate (parameningeal RMS) 7/17 patients	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
Recurrence rate (bladder/prostate RMS) 2/7 patients	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low
Complication rate (bladder/prostate RMS) 3/7 patients	1	-2	-1	0	-1	0	1: Serious methodological limitations 2: Only one study 4: Very low sample size	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias
RMS: Rhabdomyosarcoma

Overall grade:

Very low level of evidence

2.4.11.2. Summary of findings tables

Table 73 – Clinical evidence profile: Clinical effectiveness of proton beam therapy in children with rhabdomyosarcoma

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With *PBT*		Risk with Control	Risk difference with *PBT* (95% CI)
5-year overall survival (parameningeal RMS)											
17 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	64% (95% CI, 37-82%)			
5-year failure free survival (parameningeal RMS)											
17 (1 study)	Very serious risk of bias[vv]	Serious inconsistency[ww]	No serious indirectness	Serious imprecision[xx]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	59% (95% CI: 33-79%)			
Recurrence rate (parameningeal RMS)											
17 (1 study)	Very serious risk of bias[o]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	7/17 patients			
Recurrence rate (parameningeal, parapharyngeal, orbital or prostate RMS)											
12 (1 study)	Very serious risk of bias[yy]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	2/12 patients			

[vv] Small sample size, retrospective design, case series, no clear inclusion and exclusion criteria, variable treatment schemes, long period of enrolment, differential follow-up, short follow-up (for some patients only 2 years)

[ww] Only 1 study retrieved

[xx] Low sample size

[yy] Small sample size, retrospective design, case series, no clear exclusion criteria, variable proton beam therapy (3 patients received IMPBT), unclear how many children had surgery and whether it was total or partial resection before or after proton beam therapy, short follow-up (for some patients only 4 months), no information on the methods and intervals of follow-up, toxicity was scored retrospectively in some and prospectively in other children

Quality assessment								Summary of Findings
Recurrence rate (bladder/prostate RMS)								
7 (1 study)	Very serious risk of bias[zz]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	2/7 patients
Complication rate (bladder/prostate RMS)								
7 (1 study)	Very serious risk of bias[zz]	Serious inconsistency[p]	No serious indirectness	Serious imprecision[q]	Not detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias, inconsistency and imprecision	NA	3/7 patients

[zz] Small sample size, retrospective design, case series, no clear inclusion and exclusion criteria, differential follow-up , short follow-up (for some patients only 10 months)

3. BELGIAN INCIDENCE DATA - DESCRIPTION OF THE SELECTION CRITERIA PER TUMOUR TYPE

Table 74 – Belgian incidence data (BCR): Selection criteria per tumour type

Tumour type	Tumour specific parameters used to retrieve the results
Skull base & (para)spinal chordoma	The query was performed with the following histology codes: '9370', '9371' and '9372'. Based on the ICD-O3, the localisation 'base of skull' cannot be defined as such (as a separate entity). Due to the problems in defining 'base of skull', no additional criteria for the primary localisation could be provided. The current query with the above histology codes resulted in 2 registrations in children (1 at the level of the skull and 1 at the level of the brain stem) and 1 registration in an adolescent (brain stem).
Skull base chondrosarcoma	The query was performed with the following histology codes: '9220', '9242', '9221', '9240', '9231' and '9243'. Based on the ICD-O3, the localisation 'base of skull' cannot be defined as such (as a separate entity). Due to the problems in defining 'base of skull', no additional criteria for the primary localisation could be provided. The current query with the above histology codes resulted in 4 registrations in children (3 at the level of the extremities and 1 at the level of the central axis) and 9 registrations in adolescents (5 at the level of the extremities, 2 at the level of the skull and 2 at the level of the chest).
Spinal & paraspinal 'adult' type soft tissue sarcoma	The query was performed with the histology codes '8800-9049' and '9120-9342' and behaviour '3' (N = 625), thus initially retaining all sarcomas. From this result, the following sarcomas were discarded ('non-adult type sarcoma' approach): => Wilms-tumour ('8960','8964') (N = 135) => Ewing's sarcoma ('9260') (N = 105) => Osteosarcoma ('9180-9195') (N = 126) + Chondrosarcoma (cf previous query) (N = 13) => Rhabdomyosarcoma ('non-adult' type: '8900', '8910', '8912') (N = 64) => Hepatoblastoma ('8970') (N = 16) => Embryonal sarcoma ('8991') (N = 6) => Congenital fibrosarcoma ('8814') (N = 5) => Desmoplastic small-round-cell tumour ('8806') (N = 4). 151 sarcomas were retained as intermediate result for the selection 'spinal & paraspinal'. Since the localisations 'spinal' and 'paraspinal' cannot be unambigously defined using ICD-O3, we attempted to retain all sarcomas at the level of the central axis. (Based on the existing ICD-O topography codes, 'C41.1', 'C41.2', 'C41.4', 'C47', 'C70', 'C71' and 'C72' were retained.)

Tumour type	Tumour specific parameters used to retrieve the results
Pelvic sarcoma	The query was performed with the histology codes '8800-9049' and '9120-9342' and behaviour '3', thus initially retaining all sarcomas. From this result, the primary localisations 'C41.4', 'C44.5', 'C48.1', 'C48.2', 'C48.8', 'C49.4', 'C49.5', 'C56.9' and 'C67' were retained. BEWARE: this selection includes also rhabdomyosarcoma and Ewing's sarcoma (see below).
Rhabdomyosarcoma	The query was performed with the histology codes '8900-8921' and behaviour '3'.
Ewing's sarcoma	The query was performed with the histology code '9260' and behaviour '3'.
Retinoblastoma	The query was performed with the histology codes '9510-9514' and behaviour '3'.
Optic pathway and other selected low grade glioma	Other selected low grade glioma (including optic pathway): all gliomas were initially retained for this tumour type (histology codes '9380-9480'), irrespective of its behaviour. All tumours with WHO grade 3-4 were excluded from the obtained result. The gliomas for which an unambigous grade could not be established, were included in the results. BEWARE: this selection includes also ependymomas and low grade cases of pineal parenchymal tumours and medulloblastomas (see below). Optic pathway: the previous selection of low grade gliomas was expanded with the precondition of 'C72.3' (optic nerve) as primary tumour localisation
Ependymoma	The query was performed with the histology codes '9391-9394'; both invasive and non-invasive diagnoses were retained.
Craniopharyngeoma	The diagnoses with histology codes '9350-9352' were retained.
Pineal parenchymal tumours ('not pineoblastoma')	According to the definition of ICCC3 (International Classification on Childhood Cancer), there are only 3 pineal parenchymal tumours (IIIe3), one of which is a pineoblastoma and 2 of which are 'not pineoblastomas'.
Esthesioneuroblastoma	The query was performed with the histology code '9522' and behaviour '3'.
Medulloblastoma / primitive neuroectodermal tumours (PNET)	The diagnoses with histology codes '9470', '9471', '9472', '9473' and '9474' were retained.
CNS Germ cell tumours	The selection criteria for germ cell tumours, described in the International Classification on Childhood Cancer (ICCC3 = Xa), were used.
Non-resectable osteosarcoma (C-ion therapy)	"Non-resectable osteosarcoma" as entity cannot be extracted from the Belgian Cancer Registry database. Therefore, the query was performed with the histology codes '9180', '9181', '9182', '9183', '9184', '9185', '9186', '9187', '9192', '9193', '9194' and '9195', and behaviour '3'.

*References: **ICD-O3**: International Classification of Diseases for Oncology (ICD-03), third edition; WHO, Geneva 2000. **ICCC-3:** Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, Third Edition. s.l. : Cancer, 2005. Vols. 103:1457-67.*

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