Appendix: Health Technology Assessment search strategy and methods

Medline

#1 "proton therapy"[Mesh]
#2 "Proton therapy"[title/abstract]
#3 "proton therapies"[title/abstract]
#4 "Proton Beam Therapy" [title/abstract]
#5 "Heavy Ion Radiotherapy"[Mesh]
#6 "Heavy Ion Radiotherapy"[title/abstract]
#7 "Carbon therapy" [title/abstract]
#8 "Proton Beam Therapy" [title/abstract]
#9 PBT [title/abstract]
#10 "proton beam radiation therapy" [title/abstract]
#11 PBRT[title/abstract]
#12 hadrontherapy[title/abstract]
#13 "proton beam radiation"[title/abstract]
#14 "proton radiation therapy"[title/abstract]
#15 (#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)
#16 "systematic review"[title/abstract]
#17 hta[title/abstract]
#18 "clinical trial"[title/abstract]
#19 trial[title/abstract]
#20 comparative[title/abstract]
#21 versus[title/abstract]
#22 metaanalysis[title/abstract]
#23 meta-analysis[title/abstract]
#24 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)
#15 AND #24

ITEMS: 499

EMBASE

#1 'proton therapy' (EMTREE term)
#2 'proton therapies':ti,ab,kw
#3 'proton beam therapy':ti,ab,kw
#4 'heavy ion radiotherapy':ti,ab,kw
#5 'ion therapy' (EMTREE term)
#6 'carbon therapy':ti,ab,kw
#7 'proton radiation therapy':ti,ab,kw
#8 'hadrontherapy':ti,ab,kw
OR 'proton beam radiation':ti,ab,kw

ITEMS: 303

Cochrane Library

Proton* AND (therapy OR beam OR irradiation OR radiation OR radiotherapy)

ITEMS: 102

TOTAL DEDUPLICATED: 798

PRISMA study flow diagram

(from Moher et al.)*

*Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.

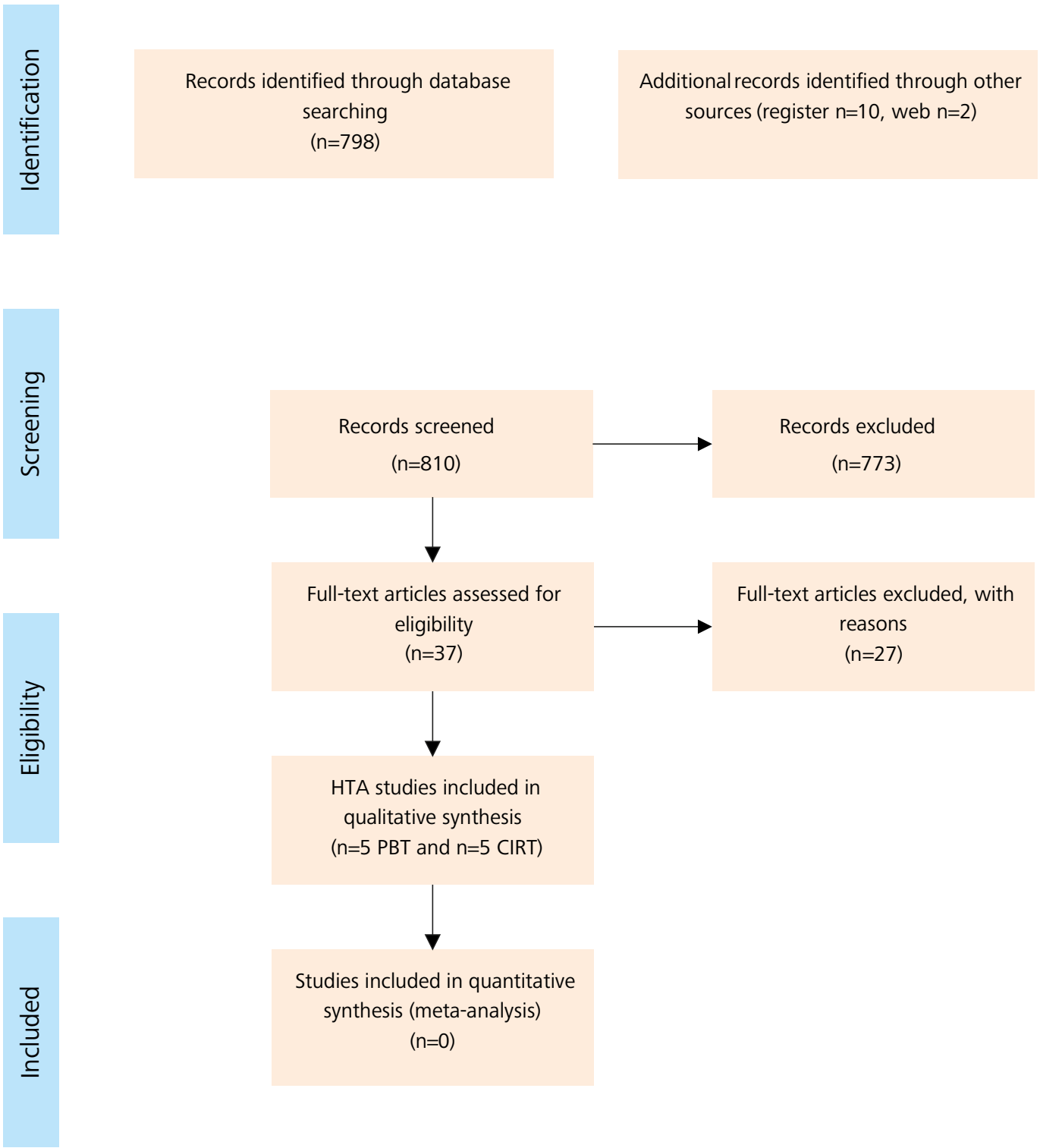

Table A1. HTA Reports - SOLID PAEDIATRIC TUMOURS

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Refers to the 2015 report on children (see conclusions) and confirms persisting uncertainty.	(KCE 2015) For chondrosarcoma, chordoma, ependymoma, esthesioneuroblastoma, Ewing sarcoma, CNS germinoma, glioma, medulloblastoma, non-resectable osteosarcoma (for PBT as well as CIRT) and rhabdomyo-sarcoma there is insufficient scientific evidence to support or to refute the use of PBT (or CIRT) in children. For pelvic sarcoma, pineal parenchymal tumour, PNET and (para-) spinal "adult type" soft tissue sarcoma there is no scientific evidence to support or to refute the use of PBT in children. For cranio-pharyngioma there is very low level scientific evidence that PBT compared with IMRT did not result in significant differences in overall survival, cystic failure-free survival, nodular failure-free survival, toxicity or cyst dynamics. For retino-blastoma it was concluded that there was very low level scientific evidence that PBT results in a lower risk of developing RT-induced in-field secondary malignancies, but as radiation induced solid malignancies develop a minimum of at least 5 to 10 years after treatment and for some children the follow-up was short, the results should be interpreted with caution.	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Page 41 of pdf. 1 prospective comparative cohort study of paediatric patients with medulloblastoma (n=88) found no difference in recurrence rate and Overall survival, but 3 patients treated with PBT developed secondaries. 1 comparative cohort study and two retrospective studies suggest PBT is associated with lower rates of adverse events	There are very few data on reduction in incidence of secondary tumours, which is the main reason justifying use of PBT (see also overlap with other topics)	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	No specific query (adults + children together). Refers to results from KCE 2015	The evidence revealed that the clinical effectiveness of PBT, alone or in combination with photon radiotherapy, was comparable to other types of radiotherapy in most types of cancer included in this overview (i.e., craniopharyngioma in children; giant-cell bone tumours, breast cancer, medulloblastoma, esophageal cancer, liver cancer, lung cancer, and most prostate cancer in adults; and some intramedullary spinal cord glioma in children and adults, analyzed together), with the exception of: greater benefits in meningioma and subgroups of malignant meningioma…; lower benefits in some intramedullary spinal cord glioma in both children and adults… The safety of PBT, alone or in combination with photon radiotherapy… was associated with: … lower harms in retinoblastoma in children … the quality of the included primary studies was mostly low or insufficient to make definitive conclusions about the benefits or harms of PBT	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	8 Comparative primary studies (1 prospective, 7 retrospective) assessing toxicity, AE and QoL; 1 study assessing PFS and 6 SRs assessing safety and effectiveness outcomes See summary extracted data presented from Table 1 (pdf p 5)	"Evidence from 6 systematic reviews (SRs) and 8 studies comparing PBRT with photon EBRT is at high risk of bias, though it suggests PBRT has potential or may provide survival comparable to photon EBRT while reducing adverse effects on QoL, IQ, hearing loss, and endocrine abnormalities. Better-quality studies with longer-term follow-up are needed to determine PBRT's actual benefits for pediatric brain tumors and effects on secondary malignancies".	5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	P.152 of pdf. 8 comparative studies (7 retrospective comparative cohorts, 1 prospective comparative cohorts) on brain tumour; 1 retrospective comparative study on head and neck and 1 retrospective comparative study on ocular tumour + several case series. All studies at moderately high / high risk of bias Appendix N11 (pdf p 296) 1 retrospective cohort study at moderately high RoB in children with ocular cancers PBT (n=16 eyes) vs. Photon or electron therapy (n=27 eyes) vs. Brachytherapy (n=4 eyes) 1 year OS Overall 97% (38/39). High toxicity with no difference between treatments 5 retrospective (n=268) and 1 prospective (n=57) case series at high RoB See specifically Appendix Table N 12 for orbital cancers (Pediatric Rhabdomyosarcoma) (pdf p 297)	Brain tumour: Benefits in terms of OS, PFS and recurrence generally similar between PBT and other forms of radiation therapy. Harms and toxicities appeared less with PBT but not statistically significant differences. Low level of evidence across all outcomes. Evidence for effectiveness and safety considered insufficient for all other tumours. Apparently high denominators hide the fact that these studies include a high number of different sarcomas and other paediatric cancers. This reduces the denominators for each type of sarcomas See also overlap with other topics Specific queries are needed to answer questions on specific cancers	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; IQ = intelligence quotient; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A1i. Ongoing studies - SOLID PAEDIATRIC TUMOURS

ID (Year) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
154 (2016) NCT02792582	Controlled non randomized	**Included**: craniopharyngioma patients up to 21 years old. **Excluded**: prior radio	140	Surgery	3 years Overall survival/ Progression free survival; adverse events; quality of life	5 years	2027	Recruiting	
NON COMPARATIVE STUDIES									
121 (2016) NCT02986048	Registry	**Included**: all patients treated with proton beam at the UH Proton Therapy Center; adults + children	999		Number of patients treated with PBT at UH Proton Therapy Center	10 years	2027	Recruiting	Mixed age
144 (2014) NCT02070328	Registry	**Included**: cancer patients who have received proton therapy; adult and children	300		6 months follow up	25 years	2022	Recruiting	Mixed age
149 (2014) NCT02040467	Registry	**Included**: all patients receiving proton beam radiation therapy; adults and children	3200		None	10 years	2024	Recruiting	Mixed age. Only collects Treatment-specific data
159 (2010) NCT01049230	Single arm	**Included**: central nervous System germ cell tumor, 3-25 years old, ECOG 0-2, life expectancy >1 year. **Excluded**: prior radio or chemo	45		Acute and late toxicity, PFS	2-3 years	2020	Active, not recruiting	
233 (2012) NCT01696721	Registry	**Included**: pediatric, adult (up to 21ys), treated with PBT, regardless of previous/current local or systemic treatments, or disease extent	5000	-	Toxicity: acute and late effects;	2 years	2022	Recruiting	registry of pediatric patients treated with PBT in the US
256 (2013) DRKS00005363	Registry	**Included**: pediatric with Indication for radiotherapy for whom proton beam therapy is conducted alternatively to conventional radiotherapy	N.A.	-	tumour control toxicity	N.A.	N.A.	Recruiting	The primary end point is the data collection
142 (2017) NCT03223766	Single arm (Cohort)	**Included**: children planned for PBT treatment or been treated with proton therapy at St. Jude Children's Research Hospital on or after November 18, 2015	1000		radiation associated grade 3 and grade 4 non-hematologic toxicities; incidence of necrosis, vasculopathy, and symptomatic and permanent neurologic deficits [at 1, 3, 5, and 10 years]; mortality and subsequent malignancies [5 and 10 years]	10 years	2037	Recruiting	
213 (2016) NCT02644993	Single arm (Cohort)	**Included**: children, patient who is planned to receive proton therapy at Samsung Medical Center. **Excluded**: no consent to partecipate	400		Quality of Life Questionnaire baseline (within 1 week before proton beam therapy completion), quality of life (3-6 months, 1, 3, 5, 10 years); Adverse event (3-6 months, 1, 3, 5, 10 years)	10 years	2025	Recruiting	
143 (2018) NCT03778294	Single arm	**Included**: newly diagnosed malignant grade IV glioma or glioblastoma; adults and children; ECOG 0-2	43		Overall survival at 1 year; progression free survival at 1 year; acute and late toxicity; Quality of Life	5 years	2021	Recruiting	
147 (2016) NCT02842723	Single arm	**Included**: paediatric craniopharyngioma; M children; Landsky performance status >60. **Excluded**: previous radio	33		local control rate at 3 years; visual pathway tolerance	3 years	2020	Active, not recruiting	
148 (2011) NCT01419067	Single arm	**Included**: craniopharyngioma patients up to 21 years old. **Excluded**: priori radio	112		5 years progression free and overall survival;	5 years	2021	Active, not recruiting	
165 (2015) NCT02559752	Single arm	**Included**: 4 to 21 years old with primary CNS tumor or diagnosis of metastatic disease to the CNS with an expected overall survival of >1 year. Planning to receive PBRT	80		Feasibility of obtaining serial computer-based neurocognitive testing as measured by an acceptance rate of 60% of eligible patients	2 years	2025	Recruiting	
171 (2014) NCT02112617	Single arm	**Included**: 6 months to 25 years; neuroblastoma or ganglioneuroblastoma or elevated urinary catecholamine metabolites; life expectancy >12 months; ECOG 0-2. **Excluded**: any prior therapeutic radiation therapy >500 cGy; chemotherapy completed more than 1 year before start of radiotherapy	30		Acute and late toxicity; OS; PFS	5-10 years	2028	Recruiting	Also including adults up to 25 yrs

Table A2. HTA Reports - TUMOURS OF THE CENTRAL NERVOUS SYSTEM

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Mentions retrospective cohort study of 32 gliomas of which 26 were low grade comparing PBT vs IMRT. At 5 year the 10 (6 low grade) exposed to PBT had worse mortality. No results stratified by grade of cancer. Two more retrospective studies including respectively 160 and 99 patients with oligodendrogliomas or astrocytomas did not find differences in safety between PBT and IMRT	"There is evidence of very low level (1 study, 32 patients) that proton treatment is associated with a worse survival than photon radiotherapy in patients with primary intramedullaryspinal cord gliomas. The data on recurrence are too imprecise to draw a firm conclusion."	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed	Only mentions in relation to burden estimation (116 cases/year).	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Four SRs reported of 6 retrospective studies, all of which judged of poor or very low quality and providing low strength evidence or no statistical assessment of evidence at all. Specifically, there were 1 study on 40 adults with medulloblastoma, 2 studies on 56 adults with meningioma, 1 study on 26 adults with recurrent malignant brain tumours, 1 study on 32 adults and children with intramedullary spinal cord glioma and 1 study on 52 children with craniopharyngioma. As for results of these studies, the CADTH authors state that: in adults with medulloblastoma, no statistically significant differences vs photon RT were shown for different efficacy outcomes, included 2-year overall survival, while statistically significantly lower risk of 1-month acute toxicity, including weight loss, esophagitis, and nausea or vomiting were shown. Among patients with malignant meningioma, PBT + photon RT, compared with photon RT alone, was associated with statistically significantly higher 5- or 8-year overall survival. However, the SR authors concluded there was insufficient evidence to make a definitive conclusion about the benefits of PBT alone, or combined with photon RT, for meningioma. In adults with recurrent malignant brain tumours, a poor-quality study reported no statistically significant differences in local recurrences over unknown duration or mortality after 11.6 months of median follow-up. In children and adults with intramedullary spinal cord glioma, a poor-quality study and low-strength evidence indicated no statistically significant differences in local recurrences over unknown duration between PBT and IMRT. However, PBT, compared with IMRT, was associated with statistically significantly lower chances of 5-year overall survival. In Children with craniopharyngioma, no statistically significant differences were found in 3-year overall or disease-free survival between PBT and IMRT	Findings from the clinical review, based mostly on low-quality evidence stemming from poor-quality, retrospective primary studies, suggest (as stated by CADTH authors) that the clinical effectiveness of PBT, alone or in combination with photon RT, is comparable to other types of RT in most of the types of cancer included in this overview. As for tumors of the SNC, CADTH highlights these exceptions: greater benefits in meningioma and subgroups of malignant meningioma; lower benefits in some intramedullary spinal cord glioma in both children and adults. The safety of PBT alone or in combination with photon RT, compared with other types of RT, varies by the type of cancer and is associated with: lower harms in retinoblastoma in children and medulloblastoma in adults; and both greater and lower harms in optic nerve sheath meningioma. Nevertheless, the authors of the SRs included in the overview caution that the quality of the included primary studies is mostly too low or insufficient to make definitive conclusions about the benefits or harms of PBT.	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	The report's only topic is cranio-spinal tumors. "Studies are at high risk of bias due to retrospective design, small sample sizes, single-center focus, and lack of high-quality randomized controlled trials. Patient populations and conditions (diseases and disease stages) were also mixed, and studies included data on patients treated in different years within the same facility or different facilities when treatment protocols evolved and changed, making pooling of data unfeasible in SRs." Authors searched on different types of gliomas and astrocitomas but concludes evidence is insufficient	"Despite the many studies and SRs, the evidence base has major limitations that place the evidence at high risk of bias. ….Longer-term follow-up studies in the form of randomized controlled trials are needed to assess PBRT's benefits compared to those of optimal photon EBRT".	5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	As the HTA authors state, eight cohort studies (11 publications) compared PBT with other treatment alternatives (primarily other forms of radiation therapy) in persons with pediatric brain tumors with a curative intent; all were considered to be at moderately high risk of bias. Across the four small comparative studies (6 publications) that provided data on effectiveness there were no statistically significant differences in OS at any time point which may be a reflection of sample sizes and/or residual confounding. (Low SOE) Across the seven comparative studies (10 publications) that reported on toxicities and harms, risk of hypothyroidism and other endocrine toxicities tended to be lower with PBT versus other forms of radiation, however statistical significance was not generally achieved, in part due to small sample sizes; the role of residual confounding may also contribute. (Low SOE)" A total of five retrospective comparative cohort studies were identified that compared PBT with photon radiation therapies in adult patients with various brain or spinal tumors. Three studies evaluated radiation therapies for curative intent and two for salvage therapy. All comparative cohort studies were considered to be at moderately high risk of bias. No differences have been shown on effectiveness and safety outcomes	Low quality evidence shows that for patients with high-grade glioblastoma, "PBT boost tended to result in lower OS but higher PFS probability versus photon alone; results were not statistically significant but may be clinically meaningful. In the large database study of primarily high-grade glioma, statistically higher 5-year overall survival was reported following PBT versus photon RT. Of note, the median follow-up period was significantly shorter in the PBT group (50.3 vs. 62.3 months). There is the potential for misclassification in database studies". As for safety, low and very low quality evidence showed that "PBT resulted in a lower frequency of mucositis (any grade); no other differences were seen in acute toxicity. Sample size may have played a role in these findings".	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A2i. Ongoing studies - TUMOURS OF THE CENTRAL NERVOUS SYSTEM

COMPARATIVE STUDIES									
25 (2019) **NCT 01795300**	RCT	**Included**: skull base meningioma, age ≥18, macroscopic tumor, Karnofsky Performance Score >60 **Excluded**: previous radiotherapy of the brain; atypical or anaplastic meningioma; optic nerve sheath meningioma	80	Carbon-ion therapy; Hypofractionated Photon Therapy; Conventional Photon Radiotherapy	Toxicity, Overall survival, PFS, QoL	1-3 years	2022	Not yet recruiting	
145 (2014) **NCT 02179086**	RCT	**Included**: grade IV glioblastoma; adults; KPS >=70 **Excluded**: distant disease; prior chemo or radio; severe comorbidities	606	Standard dose or escaleted dose photon therapy	5 years Overall Survival;5years Progression free survival; toxicity; neurocognitive function; Change in CD4 lymphopenia count	5 years	2026	Recruiting	4 arms trial
239 (2017) **NCT 03180502**	RCT	**Included**: grade II or III astrocytoma, oligodendroglioma or oligoastrocytoma, adults,KPS of >=70 **Excluded**: grade IV Disease, metastatic or multifocal disease; comorbidities; prior invasive malignancy; prior radio or chemo, concomitant use of cytotoxic chemo	120	photon-based IMRT	Local control, Overall survival, Progression-free survival Change in cognition; Incidence of adverse events Quality of Life	10 years	2025	Recruiting	Termozolomide in both arms
154 (2016) **NCT02792582**	Controlled non randomized	**Included**: craniopharyngioma patients up to 21 years old **Excluded**: prior radio	140	Surgery	3 years Overall survival/ Progression free survival; adverse events; quality of life	5 years	2027	Recruiting	
NON COMPARATIVE STUDIES									
31 (2010) **NCT 01165671**	RCT*	**Included**: unifocal, supratentorial primary glioblastoma; macroscopic tumor, prior photon irradiation, age >18, Karnofsky Performance Score ≥60 **Excluded**: previous radiotherapy of the brain or chemotherapy with DTIC or TMZ	150	Carbon-ion therapy	Overall survival, PFS, toxicity	1 year	2014	Unknown	No results posted
143 (2018) **NCT03778294**	Single arm	**Included**: adults + older adults, grade IV malignant glioma, ECOG 0, 1, 2 **Excluded**: grades I-III glioma; currently on avastin or and unable to undergo other potentially interfering drugs	43		Overall survival at 1 year; progression free survival at 1 year; acute and late toxicity; Quality of Life	1-5 years	2021	Recruiting	
155 (2011) **NCT01358058**	Single arm	**Included**: low grade and favorable Grade 3 gliomas; adults; life expectancy >5 years **Excluded**: prior chemo, radio; metastases	33		Progression free survival at 7 years; late toxicity; Overall survival	7 years	2020	Active, not recruiting	
159 (2010) **NCT01049230**	Single arm	**Included**: Central Nervous System germ cell tumor, 3-25 years old, ECOG 0-2, life expectancy >1 year **Excluded**: prior radio or chemo	45		Acute and late toxicity, PFS	2-3 years	2020	Active, not recruiting	
189 (2010) **NCT01199978**	Single arm	**Included**: adults with vestibular schwannoma or acoustic neuroma and life expectancy >5 years, Karnofsky performance status >60 **Excluded**: prior radiotherapy	30		Long-term hearing effects	3 years	2021	Recruiting	
203 (2012) **NCT01567787**	Single arm	Malignant peripheral nerve sheath tumors (MPNSTs) resected, subtotally resected or unresectable, adults **Excluded**: spinal instability, spinal cord compression with complete loss of function, previous radio	0		Local Control [7 years]; progression/palliation of pain, numbness, or weakness, adverse events, Quality of life [3, 6, 12, 24 and 60 months]; second malignant primaries (15 years)	5- 15 years	2015	Withdrawn (Feasibility issues)	
243 (2018) **DRKS00014873**	Single arm	**Included**: adults; diagnosis of a brain tumor or a tumor at the base of the skull **Excluded**: re-irradiation	100	-	Effect of radiation dose in proton beam therapy on endocrine function.	3 months - 5 years	Not reported	Recruiting	
190 (2018) **NCT03286335**	Single arm	**Included**: adults with benign or malignant brain tumor; Karnofsky performance status ≥60; life expectancy >6 months	100		Local control, acute and late toxicity, QoL	2 years	2024	Recruiting	
148 (2011) **NCT01419067**	Single arm	**Included**: craniopharyngioma; patients up to 21 years old **Excluded**: priori radiotherapy	112		5 years progression free and overall survival;	5 years	2021	Active, not recruiting	
165 (2015) **NCT02559752**	Single arm	**Included**: 4 to 21 years old with primary CNS tumor or diagnosis of metastatic disease to the CNS with an expected overall survival of >1 year. Planning to receive PBRT	80		Feasibility of obtaining serial computer-based neurocognitive testing as measured by an acceptance rate of 60% of eligible patients	2 years	2025	Recruiting	
171 (2014) **NCT02112617**	Single arm	**Included**: 6 months to 25 years; neuroblastoma or ganglioneuroblastoma or elevated urinary catecholamine metabolites; life expectancy >12 months; ECOG 0-2 **Excluded**: any prior therapeutic radiation therapy >500 cGy; chemotherapy completed more than 1 year before start of radiotherapy	30		Acute and late toxicity; OS; PFS	5-10 years	2028	Recruiting	Also including adults up to 25 yrs

*RCT comparing two hadrontherapies, thus not providing comparative data vs other treatments.

Table A3. HTA Reports - SARCOMAS

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Only mentions PBT treatment of Paraspinal or sacral, skull base chondrosarcoma/sarcoma as reimbursable in Belgium)	The authors state that high-quality evidence on the effectiveness of proton treatment is lacking. With the available evidence, it is impossible to conclude that proton treatment is better or worse than photon-based radiotherapy	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed	Cites supposed effectiveness of PBT on sarcomas but concludes evidence is insufficient for reimbursement	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Mentioned in search strategy but no data identified		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Reports 1 SR not finding any evidence on pelvic sarcomas in children and other types of sarcomas		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	No comparative studies were identified. Six small case series evaluated PBT for the treatment of pediatric soft tissue tumors (rhabdomyosarcoma) across various time frames	The authors state that there is insufficient evidence from six small case series to evaluate the effectiveness or safety PBT in in pediatric patients with soft-tissue tumors. (Insufficient SOE) No studies meeting inclusion criteria were identified that evaluated salvage therapy, differential effectiveness and safety or cost-effectiveness of PBT in this population.	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A3i. Ongoing studies - SARCOMAS

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
221 (2017) NCT02838602	RCT	**Included:** age ≥18 years; no severe comorbidity, life expectancy above 10 years; unresectable or inoperable or R2 resection of the tumor; radioresistant tumor according to the limitative list as following:adenoid cystic carcinoma of head and neck (larynx and trachea excluded); soft tissue sarcoma; rhabdomyosarcoma; retroperitoneal sarcoma;osteosarcoma (Ewing excluded); chondrosarcoma (except of skull base); axial skeleton chordoma (except of skull base); angiosarcoma; no skin involvement; ECOG Performance Status ≤2 or Karnovsky index ≥60 **Excluded**: previous irradiation in of the same tumor site; active metastatic disease; any contra-indication to undergo a radiation therapy by Xray or particle therapy; planned surgery or chemotherapy to take place after completion of radiotherapy; removable metallic material in the planning target volume; any history of another cancer in remission since less than 5 years	250	Radical radiotherapy by Xrays and / or carbon-ion therapy	progression free survival at 5 year Tolerance: Grades of the CTCAE-V4.02 classification (5 years) Overall survival (5 years) Quality of life EQ-5D questionnaire	5 years	November 2023	Recruiting	
228 (2012) NCT01659203	Comparative non-randomised,	**Included**: adults, primary soft tissue sarcoma of the retroperitoneum; Life expectancy of greater than 2 years **Excluded**: multifocal disease, lymph node or distant metastases; prior radio, chemo; uncontrolled comorbidity	80	IMRT	Local Control Rate; Overall survival; Progression-Free Survival; Response rate. Maximum tolerated dose (MTD)	2 years	Dec 2019	Recruiting	
NON COMPARATIVE STUDIES									
204 (2013) NCT01904565	Single arm	**Included**: unresectable soft tissue sarcoma (STS); extremity STS with stages T2 and G2 or 3 with M0; ECOG 0-1; adults	26		Acute and late morbidities/ local response (6 months); Local disease free survival [every 6 monthly up to max 48 months];	2 months / 4 years	2018	Unknown	Hyperthermia combined with Proton therapy
215 (2019) NCT03810651	Single arm	**Included**: adults+children, Wilms tumor or clear cell sarcoma of the kidney, stage III disease, focal or diffuse anaplasia, CCSK **Excluded**: prior radio or chemo	25		any non-hematologic toxicity within 90 days	90 days	2023	Recruiting	
195 (2013) NCT01819831	Single arm	**Included**: histologically proven primary soft tissue sarcoma of the upper extremity (including shoulder), lower extremity (including hip) or body trunk (excluding retroperitoneum); adults; ECOG 0-1 **Excluded**: sarcoma of the head, neck, intra-abdominal or retroperitoneal region, hand or foot	51		Late radiation toxicities (2 years), 1.Grade 3-5 adverse events (6 months); failure and death without disease progression (6 months); complication rates (6 months); radiation morbidity (2 yrs)	2 years	2026	Recruiting	
203 (2012) NCT01567787	Single arm	**Included**: malignant peripheral nerve sheath tumors (MPNSTs) resected, subtotally resected or unresectable, adults **Excluded**: spinal instability, spinal cord compression with complete loss of function, previous radio	0		Local Control [7 years]; Progression/palliation of pain, numbness, or weakness, adverse events, Quality of life [3, 6, 12, 24 and 60 months]; second malignant primaries (15 years)	5- 15 years	2015	Withdrawn (Feasibility issues)	
43 (2010) NCT01182753	RCT*	**Included**: low/intermediate grade chondrosarcoma with infiltration of the skull base; adults; Karnofsky performance score ≥60% **Excluded**: prior radiotherapy of skull base region; simultaneous chemotherapy or Immunotherapy; other malignancies with disease-free interval <5 years	154	Carbon ion	Local-Progression Free Survival; overall survival, progression free; metastasis free survival; Acute and late toxicity according to CTCAE V4.0 for acute side effects and RTOG/EORTC for late reaction; Patterns of recurrence and local control rate	5 years	2022	Recruiting	

*RCT comparing two hadrontherapies, thus not providing comparative data vs other treatments.

Table A4. HTA Reports - CHORDOMAS

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Cited only as reimbursable (both PBT and ion carbon therapy)		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed	In conclusion, since the quality of the existing data is inadequate, it is presently not relevant to propose treatment with PrT for: ■ Non-small-cell lung cancer; ■ Hepatocellular carcinoma; ■ Prostate cancer; ■ Esophageal cancer; ■ Breast cancer; ■ Re-irradiation cases.	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Mentions SR of 23 (n=650) of low quality studies in various tumours in children	Insufficient evidence to either support or refute [PBRT] in children.	5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Only case series or their metanalyses have been retrieved, specifically: one systematic review with a metanalysis of 17 case series including patients with chordoma of the Spine and Sacrum; one metanalysis of 9 case series including patients with chordoma after surgery; one systematic review with 23 studies in mixed populations of children, including chordoma patients; plus several single case series including chordoma patients	In patients with chordoma of the Spine and Sacrum, *indirect comparison of case series of Indirect comparison of case series of PBT vs. case series of photon RT vs. case series of Carbon Ion therapy was done* showing a trend towards optimal LC rates with primary RT for de novo chordoma only when the dose deliver is >70 Gy(RBE) in 16 fractions. However, such a treatment modality is also associated with higher toxicity rates and adverse effects As for children, there was insufficient evidence to either support or refute PBT	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A4i. Ongoing studies - CHORDOMAS

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
NON COMPARATIVE STUDIES									
199 (2016) **NCT02802969**	Single arm	**Included**: typical chordoma and chondroid chordoma of the skull base, spine or chordoma of sacral region; adults; ECOG 0-2 **Excluded**: metastatic patient, previous cancer, previous radiation therapy	64		Local tumour control at 36 months	3 years	2022	Recruiting	
235 (2013) **NCT01811394**	RCT*	**Included**: adults, Sacrococcygeal chordoma, adults. Karnofsky performance status ≥70%, Macroscopic tumour (MRI). **Excluded**: tumor extension in craniocaudal direction >16 cm, prior radiotherapy	100	Radiation: carbon ions	local progression free survival (LPFS), Overall survival (OS) incidence of Grade 3-5 toxicity (NCI-CTC-AE) and/ or discontinuation of the treatment for any reason; Quality of life	1 year	2022	Recruiting	RCT vs carbon ions
44 (2010) **NCT01182779**	RCT*	**Included**: Karnofsky Performance Score ≥60% Age between 18 and 80 years **Excluded**: prior RT of skull base region	319	carbon ions	local-progression free survival, Overall survival, Local control and patterns of recurrence (OS), toxicity	8 years	2023	Recruiting	RCT vs carbon ions

*RCT comparing two hadrontherapies, thus not providing comparative data vs other treatments.

Table A5. HTA Reports - TUMOURS OF THE HEAD & NECK REGION

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	No comparative studies were found for primary sinonasal tumours and recurrences of head & neck tumours	The authors state that high-quality evidence on the effectiveness of proton treatment is lacking. With the available evidence, it is impossible to conclude that proton treatment is better or worse than photon-based radiotherapy	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	The authors have retrieved a meta-analysis comparing the efficacy of treating nasal cavity and paranasal sinus cancer with PBT. The results from 13 cohorts of patients treated with charged particles (10 by PBT, n=286) and 30 cohorts treated with PhT (IMRT, RC3D, brachytherapy, n=1,186) drawn from non comparative studies were combined using random effects models. PrT provides a better overall survival rate at 5 years (RR: 1.51 [95% CI: 1.14-1.99]) compared to different PhT modalities, as well as a better disease-free survival rate at 5 years (RR: 1.44 [95% CI: 1.01-1.37]) compared to IMRT. Long-term locoregional control (greater than 5 years) is also better with PrT than with IMRT (RR: 1.26 [95% CI: 1.05-1.51]). These results in favor of PrT come from heterogeneous studies for which several confounding factors and biases were not taken into account in the analysis (adjustment for tumor grade and prognosis, selection bias patients). These data should therefore be confirmed by good quality comparative studies	The authors state that the methodological biases inherent in retrospective studies and non-controlled prospective studies limit the scope of the conclusions	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	No relevant SRs reporting on benefits were identified. One SR, containing a total of one unique primary study and 75 participants, contributed to the harms outcome data. The SR authors reported that PBT and carbon ion RT were similar in both unadjusted and adjusted rates of vision loss over unknown duration. However, statistical testing results were not always provided		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Reported of two systematic reviews of studies (not specified whether comparative and/or prospective) on mixed populations (including patients with head and neck cancers), assessing respectively quality of life (QOL) and patient reported outcomes (PRO), and cost effectiveness	The authors report the conclusions of authors of systematic reviews stating that, based on limited or greatly limited amounts of data, PBT provides favorable QOL/PRO profiles for select head/neck, and offers promising cost-effectiveness for high-risk head/neck cancers	5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	No comparative studies were identified. Six small case series evaluated PBT for the treatment of pediatric soft tissue tumors (rhabdomyosarcoma) across various time frames	The authors state that there is insufficient evidence from six small case series to evaluate the effectiveness or safety PBT in in pediatric patients with soft-tissue tumors. (Insufficient SOE) No studies meeting inclusion criteria were identified that evaluated salvage therapy, differential effectiveness and safety or cost-effectiveness of PBT in this population.	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A5i. Ongoing studies - TUMOURS OF THE HEAD & NECK REGION

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
135 (2013) NCT 01893307	RCT	**Included**: squamous cell carcinoma of the oropharynx Stage III-IV A,B); adults; ECOG 0-2 **Excluded**: previous radio; comorbidity; metastasis	360	IMRT	Late Grade 3-5 Toxicity (90 days; 2 years); Progression Free Survival	3 years	2024	Recruiting	
160 (2019) NCT03829033	RCT	**Included**: adults with squamous cell carcinoma of the tonsil T1-2 (p16-positive or p16-negative) N0-1 M0 (p16-positive)/N0-N2b M0 (p16-negative). ECOG 0-1 **Excluded**: previous surgery or radiotherapy in the head and neck region	100	Photon	Acute and late toxicity	7 weeks, 5 years	2028	Recruiting	
214 (2017) NCT 03164460	RCT	**Included**: adults, recurrent head and neck cancer, not eligible for surgery, (ECOG)=0, 1, or 2; 1-3 sites of recurrence. **Excluded**: widely metastatic disease, significant uncontrolled co-morbidities	100	MRT/IMPT	grade 3+ toxicity (2 years), local failure free survival (2 years), acute toxicity (90 days- 2 years), Progression free survival /Overall survival (2 years)	2 years	2023	Recruiting	
221 (2017) NCT02838602	RCT	**Included:** age ≥18 years; no severe comorbidity, life expectancy above 10 years; Unresectable or inoperable or R2 resection of the tumor; radioresistant tumor according to the limitative list as following:adenoid cystic carcinoma of head and neck (larynx and trachea excluded); soft tissue sarcoma; rhabdomyosarcoma; retroperitoneal sarcoma;osteosarcoma (Ewing excluded); chondrosarcoma (except of skull base); axial skeleton chordoma (except of skull base); angiosarcoma; no skin involvement; ECOG Performance Status ≤2 or Karnovsky index ≥60 **Excluded**: previous irradiation in of the same tumor site; active metastatic disease; any contra-indication to undergo a radiation therapy by Xray or particle therapy; planned surgery or chemotherapy to take place after completion of radiotherapy; removable metallic material in the planning target volume; any history of another cancer in remission since less than 5 years	250	Radical radiotherapy by Xrays and / or carbon-ion therapy	progression free survival at 5 year Tolerance: Grades of the CTCAE-V4.02 classification (5 years) Overall survival (5 years) Quality of life EQ-5D questionnaire	5 years	November 2023	Recruiting	
229 (2016) NCT 02923570	RCT	**Included**: adults, salivary gland cancer without the presence of extracapsular extension and/or positive surgical margin; skin cancer; melanoma; Karnofsky performance status ≥70 **Excluded**: prior head or neck irradiation; Non-resectable disease; use of chemotherapy	132	IMRT	Safety: number of patients with grade 2 or greater acute mucositis	1 year	2021	Recruiting	
163 (2016) NCT02663583	Comparative non randomised	**Included**: adults with previously untreated Oropharyngeal SCC (Clinical Stage I-Va). ECOG 0-2	44	TransOral Robotic Surgery	Functional outcome measured by using longitudinal digital wristband activity monitoring and PRO	6 months	2020	Recruiting	
183 (2011) NCT01586767	Comparative non randomised	**Included**: adults with adenoid cystic carcinoma; squamous cell carcinoma; sinonasal carcinoma; mucoepidermoid carcinoma; schneiderian carcinoma; myoepithelial carcinoma; esthesioneuroblastoma; melanoma. ECOG 0-1	90	IMRT	Local control rate, OS, QoL, acute and late toxicity	2-5 years	2021	Recruiting	
NON COMPARATIVE STUDIES									
132 (2016) NCT02736786	Single arm	**Included**: oropharyngeal cancer resected using transoral surgery with positive lymphadenopathy requiring adjuvant radiation therapy, T1-2 N1-3 M0 disease; adults	67		2 years Local Control Rate	2 years	2020	Recruiting	
151 (2012) NCT01627093	Single arm	head and neck cancer treated or undergoing treatment with PBT; adults	450		Overall Survival	7 years	2026	Active, not recruiting	
152 (2018) NCT03513042	Single arm	**Included**: unresected invasive HNSCC Squamous cell carcinoma located in the head and neck; adults; life expectancy of at least 3 months **Excluded**: metastases; prior radio, chemo, surgery; comorbidities	40		3 years overall survival/ disease specific survival/ disease free survival/ tumour response	3 years	2023	Not yet recruiting	
178 (2018) NCT03450967	Single arm	**Included**: adults with head and neck squamous cell carcinoma, with inoperable or metastatic disease; ECOG 0-1	27		Response rate	2 years	2021	Not yet recruiting	Durvalumab Plus Tremelimumab Combined With Proton Therapy
217 (2017) NCT03183271	Single arm	**Included**: adults, primary epithelial malignant or neuroendocrine tumour, Inoperable, locally advanced stage,Seated in rhinopharynx, nasal and paranasal sinuses, hypopharynx, larynx, oral cavity and oropharynx **Excluded**: metastasis, previous radiotherapy,	24		Local response (90 days), Acute toxicity (90 days), Local control (5 years), Disease free survival (5 years), Overall survival (5 years), Late toxicity (5 years)	5 years	2016	Completed No results posted	PBT boost
219 (2019) NCT03981068	Single arm	adults, loco-regional recurrence or new primary head and neck cancer, Inoperable or salvage surgery with R1/R2 resection, extranodal extension (ENE) or extensive soft tissue infiltration, Absence of distant metastasis, Life expectancy of >=1 year, PS<=2, EXCLUDED: radical surgery (R0), lymphoma or malignant melanoma	20		grade >=3 toxicity (3 years), Side effects, any grade (5 years), Quality of life and PROM (6 months), Loco-regional control (LRC) (5 years), overall survival (5 years)	5 years	2025	not yet recruiting	

Table A6. HTA Reports - PRIMARY CUTANEOUS MELANOMA

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Assessed uveal melanoma by reporting results of a systematic review including 27 primary studies (n=8,809) comparing protons (mostly), helium ions, and carbon ions with brachytherapy. Local recurrence rates, retinopathy and cataract were significantly lower with hadrontherapy whereas no significant difference has been observed in mortality rate and enucleation rate. However, the report suggests caution given the low level of evidence (15/27 uncontrolled studies) and the high risk of bias attributable to, among other things, unequal distribution of patients between treatment groups and non-adjustment of results for confounding factors.	Eye tumors (including uveal melanoma) can be treated by photonic radiosurgery with a good success rate.	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Mentions 2 SR reporting on local recurrences and mortality among PBT, iodine-125 brachytherapy, and ruthenium-106 brachytherapy in adults with choroidal melanoma from a single poor-quality, non-randomized study. The SR authors reported a statistically significantly lower rate of local recurrence but a higher mortality rate, with no statistical testing results, with PBT compared with either brachytherapy, all over unknown duration It is also reported one SR on late recurrences among PBT, iodine-125 brachytherapy, and helium ion RT in adults with uveal melanoma from a single low-quality, non-randomized study. The SR authors reported no five- or 15-year late recurrences after PBT or helium ion RT, but some late recurrences with iodine-125 brachytherapy. No statistical testing results were provided	Findings from the clinical review suggest that the clinical effectiveness of PBT, alone or in combination with photon RT, is comparable to other types of RT in most of the types of cancer included in this overview,. As for eye cancer (with no distinction for ocular melanoma) both greater and lower benefits are reported. The authors of the SRs included in the overview caution that the quality of the included primary studies is mostly too low or insufficient to make definitive conclusions about the benefits or harms of PBT	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Orbital melanomas (choroid, iris, fundus, fovea etc – appendix M): 14 retrospective case series (n=11522), all at high RoB; 3 retrospective cohort studies at moderately high RoB (n=453); 3 comparative cohort studies (unclear design - n=2855) at moderately high RoB		10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A6i. Ongoing studies - PRIMARY MELANOMA – INCLUDING CUTANEOUS AND OCULAR MELANOMA

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
229 (2016) NCT02923570	RCT	**Included**: adults, salivary gland cancer without the presence of extracapsular extension and/or positive surgical margin; skin cancer; melanoma; Karnofsky performance status ≥70 **Excluded**: prior head or neck irradiation; non-resectable disease; use of chemotherapy	132	IMRT	Safety: number of patients with grade 2 or greater acute mucositis	1 year	2021	Recruiting	
183 (2011) NCT01586767	Comparative non randomised	Adults with adenoid cystic carcinoma; squamous cell carcinoma; sinonasal carcinoma; mucoepidermoid carcinoma; schneiderian carcinoma; myoepithelial carcinoma; esthesioneuroblastoma; melanoma. ECOG 0-1	90	IMRT	Local control rate, OS, QoL, acute and late toxicity	2-5 years	2021	Recruiting	
NON COMPARATIVE STUDIES									
192 (2015) NCT02602756	RCT*	Large choroidal melanomas; adults, PS <=2 **Excluded**: iris damage, conjunctival damage, first melanoma surgery, enucleation planned post-proton-therapy, life expectancy <2 years, scleral exteriorisation >2 mm, metastases other than hepatic (endoresection authorized)	32	Different doses of PBT	severe complications (2 years); Enucleation rate (60 months); months without metastases (60 months); Specific global survival (60 months); Complications and toxicity (60 months)	60 months	2021	Active, not recruiting	* Proton Beam Therapy in both arms

*RCT comparing two hadrontherapies, thus not providing comparative data vs other treatments.

Table A7. HTA Reports - PRIMARY LUNG MALIGNANCIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed	a review of the evidence on lung cancer was considered premature given the fact that there are a number or ongoing studies in this indication.	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed	since the quality of the existing data is inadequate, it is presently not relevant to propose treatment with PrT for: • Non-small-cell lung cancer; ……	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	The authors identified two SRs including two unique primary studies (n=313) assessing benefits and included three unique primary studies (n=965) assessing harms. The studies were 1 cohort with historical controls and two retrospective cohorts, none of which showed any difference in outcomes between PBT, ions and Photontherapy (from pdf p 53). The 3 SR reported significantly lower risk of esophagitis or pneunominitis with PBT compared to IMRT but the reverse for dermatitis. There was no difference in any of the other outcomes. Most patients were adults with locally advanced NSCLC	No dominance of PBT compared to 3DCRT or IMRT	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	From pdf page 137 of the appendix file the authors present summary tables of 9 high RoB non comparative studies (case series, tot n=642). From pdf page 154 the authors present data on comparative studies as follows: 1 NCI-backed RCT of PBT vs. IMRT in 149 people N=57 vs. 92 Male: 22% vs. 32%. Median Age (range): 67 with a follow up of around 2 years. Randomisation was Bayesian adaptive based on probability of failure at year 1 so ITT n=177. 5-year OS: 19% vs. 37% Toxicity: radiation pneumonitis not significantly different. 4 retrospective comparative cohorts (one data linked from database of 243.822 claims) total n=469 of PBT vs. IMRT. Although very variable results by year of follow up, treatment with PBT seems to afford better survival than the alternatives, which toxicity results are mixed. All studies are assessed at high RoB 1 prospective comparative cohort n=82 of PBT vs 3DCRT reports symptom modelling and does not report toxicity.	In one fair-quality RCT, no statistically significant differences were seen between PBT versus IMRT in the probability of OS at any timepoint up to 5 years or in the cumulative incidence of local failure in patients with non-small cell lung cancer being treated with curative intent (Moderate SOE). Findings from four retrospective comparative cohort studies were consistent with those of the RCT. For safety, no statistical differences were seen between PBT and IMRT in the frequency of grade ≥3 radiation pneumonitis at any timepoint up to 5 years in the fair-quality RCT (Moderate SOE). There was insufficient evidence from two retrospective cohort studies regarding grade ≥3 toxicities (radiation pneumonitis, radiation esophagitis, and radiation dermatitis) which did not differ statistically between PBT and IMRT; clinical importance of differences in unknown. The case series illustrate the principle problems with the literature: different ages, stages, types of disease, concurrent pathologies and treatments and lack of comparable non exposed controls The RCT is underway but shows the need to flexible design in cancer different types such as NSCLC, adeno carcinoma etc Any potential benefits or harms from the comparative studies are made difficult to interpret because of low design quality of all studies.	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A7i. Ongoing studies - PRIMARY LUNG MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
212 (2013) **NCT 01993810**	RCT	Adults, Inoperable Stage II-IIIB NSCLC, Zubrod performance status 0-1, non-malignant pleural effusion. **Excluded**: prior invasive malignancy, other cancers and prior history of either small cell lung cancer or NSCLC, systemic chemotherapy for the study cancer, radiotherapy to the region of the study cancer, Severe, active co-morbidity	330	photon beam radiation therapy and chemotherapy	Overall Survival [7 years]; Progression-free survival (Analysis occurs after 390 deaths have been reported); Adverse events (end of follow-up); Progression-free survival (7 years); quality of life, cost-effectiveness	7 years	2020	Recruiting	
161 (2016) **NCT02731001**	RCT	**Included**: adults with NSCLC staged UICC IIIA or IIIB or UICC II **Excluded**: distant metastases, T1 or T2 N0 tumours that are candidates for stereotactic radiotherapy	98	Photon	Acute and late toxicity	6 months	2024	Recruiting	
173 (2012) **NCT01511081**	RCT	**Included**: adults with non-small cell lung cancer; Zubrod performance Status 0-2	21	Stereotactic Body Radiotherapy	Late toxicity	2 years	2017	Terminated	Low Accrual. Results posted: 1 out of 9 (11%) metastatic squamous cell carcinoma of the lung in PBT arm vs 0/9 in the radiotherapy arm
175 (2012) **NCT01629498**	RCT	**Included**: adults with unresected stage II-IIIB, or recurrent after surgical resection non-small cell lung cancer; suitability for concurrent chemoradiation; KPS score >/=70 **Excluded**: prior radiotherapy; T4 tumor	60	Intensity-modulated photon therapy	Maximum Tolerated Dose (MTD) of Image-Guided Intensity-Modulated Photon (IMRT) and Proton Therapy (IMPT); PFS; local progression	3 months-1 year	2019	Recruiting	
NON COMPARATIVE STUDIES									
133 (2013) **NCT01808677**	Registry	**Included**: non-small cell lung cancer (NSCLC); adults **Excluded**: life expectancy<3 months	49		High Grade Toxicity	5 years	2016	Completed	No results posted
136 (2017) **NCT03132532**	RCT*	**Included**: unresectable stage 2/3 non-small cell lung cancer; adults; ECOG 0-1; comorbidity; previous chemo, radio	120	Different doses	Progression-free survival at 3 years	3 years	2023	Recruiting	*Two arms comparing different regimens of PBT
157 (2010) **NCT01165658**	Single arm	**Included**: adults with NSCLC, SCLC, thymic tumors, or carcinoid tumors **Excluded**: concurrent chemotherapy (biologics accepted), prior radiotherapy, life expectancy <6 months	30		Maximum Tolerated Dose (MTD) of Hypofractionated Proton Therapy	1 month	2019	Active, not recruiting	
172 (2014) **NCT02172846**	Single arm	**Included**: adults with non-small cell lung cancer; plans to be treated with concurrent chemoradiotherapy; Zubrod performance Status 0-2 **Excluded**: prior radiotherapy to the thorax	23		Maximum tolerated dose (MTD) of hypofractionated proton beam therapy (PBT) with chemotherapy; acute and late toxicity	6 months-1 year	2017	Completed	No results posted
184 (2012) **NCT01565772**	Single arm	**Included**: adults with non-small cell lung cancer with a clinical stage of IIIA; candidate for chemoradiation and surgical resection; life expectancy >6 months **Excluded**: prior chemotherapy, prior chest radiation	4		Maximum tolerated dose; OS	1.5-5 years	2015	Terminated	Low accrual; proton beam radiation, plus chemotherapy with cisplatin and etoposide, followed by surgery
193 (2013) **NCT01770418**	Single arm	adults; pathologically confirmed invasive non-small cell lung cancer clinical stage II-III; ECOG 0-1 **Excluded**: evidence of distant metastasis (M1) involvement. Prior radiotherapy to thoracic area	32		maximum tolerated dose of radiotherapy in terms of Gy; acute and late adverse events (every 3 months for 5 years); overall survival (3, 5 years); percentage of patients that survive (5 years)	5 years	2019	Active, not recruiting	
211 (2010) **NCT01076231**	Single arm	Adults, Stage IIIA non-small cell lung cancer, Karnofsky performance Status of >=60 **Excluded**: prior or simultaneous malignancies within the past two years	34		Feasibility, Dose-limiting toxicity, Pathologic CR rate is defined as the fraction of patients who undergo surgery and have no evidence of disease based, Late toxicity (90 days)	3 months	2018	Active, not recruiting	

*RCT comparing different doses, thus not providing comparative data vs other treatments.

Table A8. HTA Reports - BREAST MALIGNANCIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Reports data from the same studies as CADTH 2017	The benefits of PBT were the same as other types of radiotherapy but skin toxicity was greater.	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed	since the quality of the existing data is inadequate, it is presently not relevant to propose treatment with PrT for: .....• breast cancer;.....	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	One SR including one prospective study in 98 adults with stage I breast cancer, a fair-quality study but low-strength evidence indicated no statistically significant differences in 7-year cumulative local recurrences between PBT and 3DCRT. The same study reports a significantly higher risk of skin toxicity at 7 years (atrophy, depigmentation, teleangectasia).	Very small evidence base for such a frequent cancer	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Identifies and cites three retrospective case series (n=163) all at high RoB (Appendix D pdf p 39 of appendices and one retrospective comparative database ((N=724,492)	There is low strength of evidence from one retrospective comparative database study that there is no statistical difference in the probability of OS at 5 years between PBT versus photon with or without electron boost therapy for treatment of breast cancer.	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A8i. Ongoing studies - BREAST MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
156 (2012) NCT01365845	Comparative non randomised	**Included**: stage I-III (TX, T0-4) **Excluded**: distant metastases, previous radiotherapy	18	Photon	Volume of Heart Receiving ≥5 Gray (Gy)/ Cobalt Gray Equivalent (CGE). Acute and late troxicity	2 weeks (primary outcome); 7 weeks (acute toxicity); 5 years (late toxicity)	2014	Completed	After an induction phase to assess the preferred treatment based on CGE, all patients were treated with proton
231 (2016) NCT02725840	Comparative, non randomised,	**Included**: adults, Stage II or higher primary breast cancer **Excluded**: previous radiation treatment bilateral breast cancer or metastatic disease	55	X-ray radiation therapy of the affected breast and chest wall as part of their standard of care	overall survival; treatment related death; patterns of metastatic presentation eearly severe pulmonary toxicity;long-term clinical grade 2 and higher radiation toxicity to the lung	1 year - 8 years	2021	Recruiting	
NON COMPARATIVE STUDIES									
170 (2011) NCT01340495	Single arm	**Included**: breast cancer confined to the breast and regional lymphatics; completed mastectomy **Excluded**: life expectancy <12 months; previous radiotherapy	70		Acute and late toxicity; PFS	3 months, up to 5 years	2017	Active, not recruiting	
176 (2011) NCT01310530	Single arm	**Included**: age >40 **Excluded**: distant metastasis; prior radiation or chemotherapy	150		Rate of recurrence; acute and late toxicity; PFS	5 years	2023	Active, not recruiting	
185 (2013) NCT01766297	Single arm	**Included**: >50 years old; Stage 0, I, II; life expectancy >5 years **Excluded**: any previously treated breast carcinoma in ipsilateral breast; prior radiation to the ipsilateral breast or thorax	132		Freedom from failure; acute and late toxicity; QoL; OS	3 years	2033	Recruiting	
222 (2013) NCT01839838	Single arm	adults, female, invasive or non-invasive breast cancer, T1 or T2; N0 or N1mic; Stage IA-IIA, estrogen and/or progesterone receptor positive, ECOG 0, 1 or 2, breast-conserving surgery, excised with a minimum margin width of ≥2 mm, age ≥50 **Excluded**: T2 (>3cm), T3, T4, node positive (other than N1mi), or M1 disease, lobular or mixed ductal and lobular histology, multifocal, neoadjuvant chemotherapy,	57		Number of Adverse Events [5 years]	5 years	2024	Recruiting	
225 (2014) NCT02199366	Single arm	adults, left-sided breast cancer stage I-III, Indications for adjuvant regional nodal and breast or chest wall radiation therapy. **Excluded**: prior history of cardiovascular disease, Stage 0 and IV, prior radiation therapy to chest, concurrent trastuzumab	26		changes in cardiac function. [1 year y]; serious cardiac side effects. [1 year]; Mean quality of life score [1 year]	1 year	2021	Recruiting	
254 (2015) UMIN000017579	Single arm	**Included**: adults (40 to 70 yo); UICC-TNM classification stage I; mammographicaly visible tumor without calcification; pathologically invasive ductal carcinoma; no massive lymphovascular invasion; estrogen receptor positive, favor of HER2 negative; negative lymph node no distant metastasis; performance status 0-1 **Excluded**: previous radiotherapy to the breast; previous surgery/ chemotherapy to the breast; DCIS/ LCIS; massive intra-ductal spread; comorbidities	24		location of local recurrence, duration of extra-breast recurrence, survival duration: Adverse events of normal tissue; QoL: cosmesis	Not reported	Not reported	Recruiting	
201 (2019) NCT03940248	Single arm	Adults, stage Tis, T1, or T2 and N0; ER positive **Excluded**: <50 years, tumor >3 cm, positive margins, multicentric disease, oncoplastic reconstruction, prior neoadjuvant chemotherapy or hormonal therapy ER negative, high grade ductal carcinoma in situ, BRCA1 or BRCA2 mutation, prior radio			Cosmetic outcome (2 years); Rates of acute (3 months) toxicity; Rates of late (>3 months) toxicity; ipsilateral breast tumor recurrence; regional recurrence (2 years)	2 years	2024	Recruiting	

Table A9. HTA Reports - PRIMARY THYROID

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: Low grade glioma (LGG) Primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed – Disease only mentioned as secondary tumour post photon therapy with consequent hypothyroidism (pdf p 41)		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Not assessed – Disease mentioned as secondary from uveal cancer or as a harm from radiation together hypothyroidis		10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A10. HTA Reports - PANCREAS MALIGNANCIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed	Mentions 16 studies underway on ca pancreas (pdf p 38)	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	One retrospective case series with concomitant chemotherapy n=19, one prospective case series with other concomitant treatments n=13, one prospective case series with other concomitant treatments n=2, one retrospective cohort study n=25. In this the probability of overall survival did not differ statistically between the PBT and hyper-fractionated acceleration radiotherapy (HART) arms up to 3 years' folllo up Two case-series (n=37 and 48) the probability of 1-year overall survival following PBT was 65% and 76%; at 2, 3 and 4 years probabilities were 42%, 23% and 23%, respectively, in one study. The probability of 1-year progression-free survival was 45% and 65% across both studies and 24%, 18% and 10% at 2, 3, and 4 years, respectively. Harms from concomitant treatment and radiotherapy were not distinguished; any differences are reported as non significant. The studies are classified as at high risk of bias	Low quality of evidence reporting not statistically significance differences	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A10i. Ongoing studies - PANCREAS MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
Nil									
NON COMPARATIVE STUDIES									
158 (2019) NCT03885284	Non randomised comparative*	**Included**: adults, ECOG 0-1, undergone pancreaticoduodenectomy with curative intent, completed 2 cycles of adjuvant chemotherapy **Excluded**: metastatic disease, prior radiotherapy	12	Different doses of PBT	Recommended phase II dose and schedule (RP2D) of short-course PRT; acute and late toxicity; OS; recurrence free survival	6 months	2021	Not yet recruiting	*two arms comparing different timing of proton administration in addition to adjuvant chemotherapy
206 (2018) NCT03652428	Single arm	adults; adenocarcinoma of the pancreas, M0, ecog 0-1 **Excluded**: resectable tumour, No prior radiation therapy, no prior chemotherapy except for FOLFIRINOX, Gem-Abrax, or Gem-Cap, Any grade 4 toxicity prior to start of chemoradiotherapy, HIV-positivity	24		Maximum tolerated Dose of gemcitabine and nab-paclitaxel in LAPC patients receiving proton therapy (12 months); primary tumor response (12 months); disease-free-survival and overall survival (12 months); adverse effects (12months)	12 months	2022	recruiting	

Doese not compare PBT vs other treatments.

Table A11. HTA Reports - COLON AND RECTUM MALIGNANCIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	The authors identified 2 case series with a total combined denominator of 4 patients with colonic ca and one retrospective case series of n=60 colorectal cases with liver metastases. Some may have had concomitant therapy. 2 year OS is 28% for those with liver metastases (pdf p 122 of appendix). One other retrospective case series N=34 with unclear treatment and miscellaneous cases (pdf p 178 of appendix). All studies are assessed as at high RoB	Insufficient evidence of benefit	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A11i. Ongoing studies - COLON AND RECTUM MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
Nil									
NON COMPARATIVE STUDIES									
122 (2018) **NCT03566355**	Single arm	**Included**: patients with lung metastasis of colorectal cancer; less than 2 lung metastatic lesions adults **Excluded**: other cancer/metastasis; no primary lesion resection; refuse or usuitable for surgery	36		3-year local control ratio of the treated lung area (expected 80% or more); 3 -year survival rate of treated patients; 3-year disease-free survival rate of treated patients	3 years	2025	Recruiting	
123 (2018) **NCT03577665**	Single arm	**Included**: patients with Liver metastasis of colorectal cancer; less than 2 metastatic liver lesions; adults **Excluded**: other cancer/metastasis; no primary lesion resection; refuse or usuitable for surgery	30		2-year local control ratio of the treated liver area (expected 80% or more); 5-year survival rate; 5-year disease-free survival rate	5 years	2025	Recruiting	
164 (2017) **NCT03018418**	Single arm	**Included**: adults with histologically documented squamous or basaloid carcinoma of the anal canal; Karnofsky performance Status >70%; stage T2-4 **Excluded**: life expectancy <3 months	20		Acute and late toxicity, OS, local progression free survival, complete response rate, QoL	3 months, up to 5 years	2023	Recruiting	
226 (2018) **NCT03690921**	Single arm	**Included**: adults; non-metastatic invasive primary squamous cell carcinoma of the anal canal (stages I - III), Zubrod performance status of 0-1 **Excluded**: prior invasive malignancy in the last 3 years, distant metastasis, prior systemic chemotherapy, prior radiotherapy, severe active co-morbidity	48	-	Effectiveness: Complete response; Local progression-free survival; Distant metastatic failure; Disease-free survival; Overall survival; Safety: acute grade 3 or greater gastrointestinal, genitourinary and hematologic toxicities;	3 months - 4 years	2022	Recruiting	

Table A12. HTA Report - PROSTATE CANCER

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: Low grade glioma (LGG) Primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed	Comments in general on poor quality evidence	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Mentions studies already in the CADTH report and also mentions RCT underway on low grade prostate cancer patients (NCT01617161)	"In conclusion, since the quality of the existing data is inadequate, it is presently not relevant to propose treatment with PrT for: ■ Non-small-cell lung cancer; ■ Hepatocellular carcinoma; ■ Prostate cancer; ■ Esophageal cancer; ■ Breast cancer; ■ Re-irradiation cases."	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	1 SR comparing PBT with 3DCRT for QoI and toxicity 2 SRs comparing PBT with IMRT for QoI and toxicity 1 SR comparing PBT with photon RT for QoI and toxicity 2 SRs comparing PBT with photon RT vs and toxicity brachytherapy for OS, DFS, tumour control and toxicity 3 SRs comparing PBT with photon RT vs photon RT for OS, DFS, TFS, tumour control and toxicity (pdf p 26) Quallity of SR is in Appendix 10 Dataset for benefits in 4347 people for harms 58523 Universal quality of included studies was low and most reported no differences in outcomes except two SRs reported subanalysis at 8 year with significantly better local control rates in PBT+photon RT vs RT (Table 18) PBT appears to be more gastrotoxic than the alternatives but the data are from poor quality studies (Table 19).	When interpreting the results of the SRs the universal low quality and heterogeneous nature of the data needs taking into consideration. Many of the studies included in the SRs overlapped The authors conclude that "Clinical effectiveness of PBT, alone or in combination with photon RT, was similar to other types of RT in…….. most prostate cancer (i.e., five- or eight-year tumour or cancer control, overall survival, or disease-free survival or 1.5- to four-year QoL)."	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Only cites Verma 2016: systematic review of cost-effectiveness studies. ", it has not been demonstrated that [PBRT] is cost-effective for prostate cancer."		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	From pdf p 311: 7 prospective case series n=1243 all at high RoB; 4 retrospective case series n=2963 all at high RoB; 1 RCT n=272 of fair quality 2 Retrospective cohorts n=4346 at moderate RoB In case series 5 year OS around 95% Toxicity (mainly genitourinary and GI up to 50%) ("Quasi") RCT comparing PBT + photon RT (with PBT boost) with RT alone (reported no difference in survival at 5-10 years but significantly lower gastrotoxicity in PBT group). Retrospective cohorts compared PBT with IMRT or RT alone (case matched). Reported similar gastrointestinal toxicity but higher bowel toxicity with PBT		10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A12i. Ongoing studies - PROSTATE CANCER

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
179 (2012) **NCT01617161**	RCT	**Included**: T1c-T2c **Excluded**: distant metastases or lymph node involvement, no prior surgery, chemo, radio or androgen deprivation therapy	400	IMRT	EPIC bowel scores, Quality of LIfe	2 years	2019	Recruiting	
NON COMPARATIVE STUDIES									
131 (2013) NCT01950351	Single arm	**Included**: Stage T1-2b **Excluded**: distant metastases or lymph node involvement, no prior surgery, radio or chemo	228		Gastrointestinal toxicity, acute and late toxicity, Quality of Life	2 years	2020	Recruiting	
202 (2018) NCT03564275	Single arm	**Included**: stage T1-2a **Excluded**: lymph node involvement or androgen deprivation therapy	50		Hematuria, urinary incontinence, dysuria, IPSS, rectal bleeding, erectile dysfunction	10 years	2033	Recruiting	
138 (2016) NCT02874014	Single arm	**Included**: Stage T1-2 **Excluded**: distant metastases or lymph node involvement, no prior surgery, radio, chemo or androgen deprivation therapy	51		Gastrointestinal and genitourinary toxicity, acute and late toxicity, disease free survival	2 years	2023	Suspended	
181 (2010) NCT01072513	Single arm	Low and intermediate risk	31		Sperm count	1 year	2015	Completed	No results posted
188 (2011) NCT01368055	Single arm	**Included**: low and intermediate risk **Excluded**: prior surgery, radio, chemo	360		Rectal bleeding, Quality of Life disease control	2 years	2019	Active, not recruiting	
208 (2018) NCT03624660	Single arm	**Included**: high-risk prostate cancer who are at the highest risk for recurrence **Excluded**: T4, prior prostate cancer or hypertrophy local treatment, distant metastases, with posterior or posterolateral extracapsular extension	88		Biochemical failure, Overall Survival, acute and late toxicity, disease specific survival, Quality of Life	5 years	2028	Recruiting	
186 (2018) NCT03740191	Single arm	**Included**: Low and intermediate risks (stage T1 - T2 b) **Excluded**: prior prostate cancer therapy (chemio, surgery, etc), distant metastases, regional lymph node involvement	297		Freedom from biochemical failure, acute and late toxicity, Overall Survival, disease-specific survival, Quality of Life	5 years	2027	Recruiting	
177 (2014) NCT02315989	Single arm	**Included**: solid cancer (including prostate cancer) or brain tumour **Excluded**: previous radiotherapy	6		Adverse reactions	3 months	2015	Completed	Results posted, no serious adverse event
250 (2017) UMIN000025453	Single arm	**Included**: intermediate-risk **Excluded**: previous prostate cancer treatment, distant metastases, androgen deprivation therapy <6 months	200		Biochemical relapse free; safety	5 years	Not reported	Not reported	
150 (2014) NCT02040610	Single arm	**Included**: low-intermediate risk (T1-2c) **Excluded**: previous prostate cancer treatment, distant metastases	235		Biochemical failure, toxicity, Quality of Life	5 years	2025	Recruiting	
207 (2013) NCT02110849	Registry	Prostate cancer patients who received proton radiation therapy	100		Toxicity	1 year	2016	Withdrawn	No data collected. Closure of IU Health Proton Facility
227 (2010) NCT01230866	Single arm	**Included**: Stage T1-2a **Excluded**: distant metastases or limph node involvement, no prior surgery, chemo, radio or androgen deprivation therapy	150		Failure measured by recurrence, metastasis, PSA or start of salvage therapy; toxicity	2 years	2020	Recruiting	Randomised trial to assess different fractionation strategies
174 (2016) NCT03285815	Single arm	**Included**: T1-T2c **Excluded**: distant metastases radio or androgen deprivation therapy	156		Biochemical failure, acute and late toxicity, disease free survival	5 years	2024	Recruiting	Randomised trial to assess different doses
39 (2012) NCT01641185	RCT*	Carcinoma of the prostate with Gleason score risk of lymphe node involvement of <15%; Karnofsky-Index ≥70%, age 40-80 years **Excluded**: Stadium IV (distant metastases) lymphogenous metastases hip replacement former irradiation of the pelvis	92	Carbon-ion	proctitis and cystitis via incidence grade 3-4 toxicity; PSA (3 months); overall survival; quality of life	3 years	2015	completed	No publication available

*RCT comparing two hadrontherapies, thus not providing comparative data vs other treatments.

Table A13. HTA Reports - PRIMARY BLADDER MALIGNANCIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: Low grade glioma (LGG) Primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	1 retrospective case series n=70 at high risk of bias in invasive disease. 10 years overall survival after resection, photon therapy and chemotherapy followed by PBT was 78%. Toxicity (especially haematological) up to 26% but not attributed.	There is insufficient evidence from one case series to evaluate the effectiveness or safety of PBT for bladder cancer in adults.	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A13i. Ongoing studies - PRIMARY BLADDER MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
180 (2012) NCT01520038	Comparative non randomised	Included: urothelial carcinoma Excluded: prior radiotherapy	30	IMRT	Acute and late toxicity	14-90 days	2013	Active, not recruiting	
NON COMPARATIVE STUDIES									

Table A14. HTA Reports - ESOPHAGUS MALIGNACIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Five retrospective comparative cohort studies that evaluated the effectiveness and safety of PBT compared with photon RT for curative intent in adult patients with esophageal cancer that met inclusion criteria were identified. With the exception of OS at 1 year which was similar between groups, probabilities of OS and PFS/DFS were greater following PBT versus IMRT or 3D-CRT over 1 to 5 years follow-up in two studies; however, statistical significance was achieved in only the largest study (Low SOE). Mortality (as opposed to OS) was reported by two studies with no statistically significant differences seen between the PBT and the photon groups (IMRT, 3D-CRT, XRT) (Low SOE for the large, higher quality study; Insufficient SOE for the small, poorer-quality study). For the comparison of PBT versus IMRT, with the exception of grade 4 radiation-induced lymphopenia (2 studies) and any would event (1 study) which were less common with PBT, all other RT-related and treatment-related toxicities did not differ statistically between groups. For PBT versus 3DCRT or XRT, with the exception of GI events, PBT was associated with a statistically less treatment-related toxicity (i.e., pulmonary, cardiac, and wound events; grades ≥2 or not specified) across three studies (Low SOE for all). See also gastric malignancies Table. The WHA documents presents evidence of esophageal and gastric tumours combined. Some reports of early and late middle grade toxicity (pdf p 43-44 abstraction appendices) – mostly from irradiation	Limited information from case series does not provide sufficient information to evaluate radiation safety or effectiveness of PBT.	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A14i. Ongoing studies - ESOPHAGUS MALIGNACIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
127 (2012) **NCT01512589**	RCT	**Included**: adenocarcinoma or squamous cell carcinoma of the cervical or thoracic esophagus or gastroesophageal junction or cardia of stomach; adults; ECOG=0, 1, or 2 or KPS >/=60 **Excluded**: second malignancies; metastasis; comorbidity; prior radio, chemoterapy	180	IMRT	Progression-Free Survival; Toxicity	5 years	2020	Active, not recruiting	
141 (2019) **NCT03801876**	RCT	**Included**: stage I to IVA esophageal cancer; adults **Excluded**: metastasis; comorbidities	300	IMRT	Overall Survival; grade 3+ cardiopulmonary adverse effects at 8 years; Progression Free Survival; Quality of Life	8 years	2032	Recruiting	
247 (2017) **NCT03234842**	Comparative non randomized trial	**Included**: pathologically confirmed esophageal adenocarcinoma or squamous cell carcinoma of the thoracic esophagus or esophagogastric junction; adults; stage cT1b-T4, N0-N3 **Excluded**: cervical esophageal carcinoma; prior radiotherapy with fields overlapping the current esophageal cancer; patients with cT1a disease; distant metastatic disease	0	Photon therapy	Rate of a clinically significant reduction of diffusion lung capacity of carbon monoxide; local control; progression-free survival; overall survival rates quality of life	1 year	2018	Withdrawn (non-accrual)	
NON COMPARATIVE STUDIES									
129 (2013) **NCT02023541**	Single arm	**Included**: esophageal cancer (adenocarcinoma or squamous cell carcinoma of the cervical or thoracic esophagus or gastroesophageal junction or cardia; adults; ECOG ≤ 2 (Karnofsky >60%) **Excluded**: previous or concurrent cancer; comorbidity	3		2/5-years Progression free survival; 2/5 years overall survival; physician reported toxicity Quality of life	5years	2015		
209 (2012) **NCT01684904**	Single arm	**Included**: pathologically confirmed primary squamous cell or adenocarcinoma of the esophagus,adults; stage T1N102, T2-3N0-2; Zubrod performance status 0-2 **Excluded**: cervical esophageal carcinoma, T1N0 disease and T4 disease, prior radiation for esophageal cancer or prior chest radiotherapy, prior chemotherapy for esophageal cancer, prior invasive malignancy (except non-melanomatous skin cancer), severe, active co-morbidity	38		overall survival (minimum 3 months); adverse events (minimum 3 months)	3 months	2026	recruiting	
246 (2018) **NCT03482791**	Single arm	**Included**: histologically or cytologically documented adenocarcinoma or squamous cell carcinoma of the cervical or thoracic esophagus or gastroesophageal junction or cardia of stomac; adults, stage II or III; prior endoscopic mucosal resection is eligible; Induction chemotherapy prior to concurrent chemoradiation is allowed; prior thoracic radiation is allowable if degree of overlap with the esophageal radiotherapy treatment is deemed to be safe by the treating radiation oncologist; ECOG <2 **Excluded**: planned treatment with radiation therapy alone without concurrent chemotherapy or chemotherapy alone; previous or concomitant cancers within the past 3 years; comorbidities	40		Progression-free survival and Overall Survival of proton beam therapy for patients with resectable versus unresectable esophageal cancer; Physician-reported toxicity Quality of life	6 months - 5 years	2022	Recruiting	

Table A15. HTA Reports - URINARY TRACT MALIGNANCIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Not assessed		10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A16. HTA Reports - GASTRIC MALIGNACIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	The authors identified 1 prospective case series at high risk of RoB on 89 people with different cancers, 12 of which had esophagogastric adenocarcinomas (Annex pdf p 14). 1 year OS was 35,9% overall with liver secondaries. Tx was mixed	No conclusions can be drawn	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A17. HTA Reports - UTERINE CERVICAL

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	Not assessed		8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Not assessed		11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Mentions PBT on cervical cancer only as an experimental treatment (pdf p 16 draft report)		10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A17i. Ongoing studies - UTERINE CERVICAL MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
Nil									
NON COMPARATIVE STUDIES									
146 (2017) NCT03184350	Single arm	**Included**: histologically confirmed cervical or endometrial cancer; adults; KPS ≥70 **Excluded**: prior radio	25		3 months acute ≥grade 3 toxicity; Quality of Life; 2 years progression free survival	2 years	2021	Recruiting	

Table A18. HTA Reports - LIVER MALIGNANCIES

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies	The authors identify two SRs of PBT vs. carbon ion RT (outcomes tumour or cancer control (i.e., local control), Overall survival, Progression-free survival.. and two SRs comparing PBT with photon RT (outcomes tumour or cancer control (i.e., tumour recurrences) and mortality n=471 total. The studies were low quality and there was no difference in any of the outcomes at 5 years. One study each looked at toxicity n=371 total exposed. There were no differences in toxicity either (from pdf p 49)	No obvious clinical difference between treatment, but studies were of low quality	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies	Not assessed		7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Authors identify 1 SR with unknown funding of 343 adults with liver cancer comparing PBT vs. 3DCRT; carbon ion RT; IMRT; or photon RT, with or without chemotherapy and 1 US Govt funded of 351 adults with primary or recurrent liver cancer with follow up at 31 months	Comparable effectiveness (pdf p 10)	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed		5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	From pdf p 113 of the appendices abstraction files the authors identify one high RoB prospective case series (n=129) with 5 year OS at stage C 25% and dermatoxicity; one retrospective case series (n=92) with 5 year OS 37 to 61%. Intestinal bleeding in 1.2% of patients; one high RoB retrospective case series (n=250) with 51%OS at 5 year, toxicity not reported; one high RoB retrospective case series (n=40) with 2 OS 76& and toxicity bleeding, ascites and rib fracture at 2.5%; one high RoB prospective case series (n=40) toxicity not reported and 2 year OS 56% to 34% depending on tumour (HCC and ICC respectively. Some patients had received some intercurrent treatment; one high RoB prospective case series (n=83) of unresectable HCC or ICC. 2 year OS was HCC: 63.2% and ICC: 46.5%. Toxicity episode experienced by at least 85.5% of patients; one high RoB retrospective case series (n=37). Benefits not reported, toxicity: chest wall pain requiring narcotics up to 19% of participants; 4 other observational studies on metastatic or recurrent disease; one high RoB prospective case series (n=101). Tumor response at 3-months follow-up were complete response: 53.8% (42/78), partial response: 10.3% (8/78), stable disease: 5.1% (4/78), progressive disease: 30.8% (24/78). Toxicity varied between 56% and 1%. One RCT at moderate RoB (pdf p 133) comparing PBT vs TACE (n=33 vs 36) has some serious reporting bias, e,g, raw data for OS at 2 years are not provided but text reports no substantial difference between treatment.	No statistical differences were seen between PBT and transarterial chemoembolization (TACE) for the probabilities of 2-year OS, PFS, and local control in one small RCT of adult patients with unresectable hepatocellular carcinoma (HCC) treated with curative intent, though PFS and local control tended to be greater following PBT (Moderate SOE). OS was statistically higher following PBT versus intensity-modulated radiation therapy (IMRT) in one retrospective cohort study of adult patients with unresectable HCC but there was no difference in local and regional control between groups (Low SOE). Acute toxicity and serious complications were not well described in the RCT. Fewer patients who received PBT compared with TACE were hospitalized for a complications within 30 days of treatment, translating into fewer total days hospitalized for complications (Moderate SOE). In the retrospective cohort study, compared with IMRT, PBT was associated with a lower risk of nonclassic radiation-induced liver disease (RILD) (Low SOE) and death due to liver failure (Insufficient SOE).	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A18i. Ongoing studies - LIVER MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
ID 500 (2009) **NCT00857805**	RCT	**Included**: unresectable hepatocellular cancer; adults, candidates to receive both proton beam and TACE; no evidence of metastasis or macrovascular invasion; umor burden that meets San Francisco criteria **Excluded**: treated previously for HCC by any locoregional treatment; prior liver transplant; Child class C; MELD score of >25; other comorbid diseases that may impact survival	200	Transarterial Chemoembolization (TACE)	Overall survival; Time to progression; Downstaging	Not reported	Jan 2018	Unknown	Interim analysis published in 2016, available at https://www.ncbi.nlm.nih.gov/pubmed/27084661
232 (2016) **NCT02640924**	RCT	**Included**: hepatocellular cancer; unsuitable to surgery; adults; ECOG of 0 or 1; Child-Pugh score ≤8 **Excluded**: any previous treatment for HCC; extrahepatic metastasis; extrahepatic invasion; portal or hepatic vein tumor invasion /thrombosis	166	Ablation with multiple-electrode radiofrequency	Local control rate; Overall survival; Distant metastasis free survival; Treatment-related adverse events; Quality of life	3 days - 5 years	Dec 2018	Recruiting	Many papers already published. The most important, non comparative, on proton beam: 10.1016/j.ijrobp.2010.07.015
234 (2017) **NCT03186898**	RCT	**Included**: unresectable or locally recurrent hepatocellular cancer; adults; Zubrod performance status 0-1 **Excluded**: extrahepatic tumor, uncontrolled prior invasive malignancy, prior radiotherapy; prior liver transplant	186	Photon Therapy	Overall survival; progression-free survival; local progression; incidence of adverse events. Quality of Life	5 years	2022	Recruiting	
240 (2017) **JCOG1315C** **UMIN000027811**	Prospective, non randomised, comparative	**Included**: new-onset single nodular hepatocellular carcinoma; cN0M0; adults; no previous treatment for HCC; no ascites or hepatic encephalopathy; ECOG of 0 or 1; Adequate organ functions **Excluded**: synchronous or metachronous malignancy	290	hepatectomy	Overall survival; progression-free survival, patterns of failure. Adverse events, acute and late toxicities; serious adverse events, Child-Pugh score Quality of life	1 - 5 years	2029	Recruiting	
NON COMPARATIVE STUDIES									
124 (2015) **NCT02571946**	Single arm	**Included**: hepatocellular carcinoma (HCC); adults **Excluded**: previous radiotherapy, less than 12 weeks months expected survival	53		One-year overall survival; 1/3 months objective response rate; 1 year progression free survival; adverse events; quality of life	1 year	2019	Recruiting	
140 (2015) **NCT02632864**	Single arm	**Included**: unresectable primary hepatocellular carcinoma (HCC); adults; ECOG 0-2 **Excluded**: previous upper abdominal radiotherapy; comorbidities	66		2 years overall survival; 1 year progression free survival; 6 months/1 year adverse events; Quality of Life	2 years	2022	Recruiting	
166 (2012) **NCT01697371**	Single arm	**Included**: non-lymphoma liver metastases; adults; ECOG 0-1 **Excluded**: prior radiotherapy to the liver; life expectancy <6 months	35		Acute and late toxicity; local control	3 months; 2 years	2026	Recruiting	Included only liver metastases and not hepatocellular carcinoma
252 (2016) **UMIN000020596**	Single arm	**Included**: solitary hepatocellular carcinoma without extrahepatic lesions; adults; no prior treatment for HCC; unsuitable for resection or liver transplantation or difficult to undergo local ablative therapies; ECOG Performance Status is 0, 1 or 2; Liver function of Child-Pugh class A; vital organ functions preserved **Excluded**: other malignancies,	180	-	overall survival rate; progression free survival rate; incidence of adverse events; Incidence of radiation induced liver disease	3 years	2024	Recruiting	

Table A19. HTA Reports - RECURRENT TUMOURS REQUIRING REPEAT TREATMENT IN AREAS ALREADY EXPOSED TO RADIOTHERAPY

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
KCE (Vlayen 2019)	HTA report to define indications for reimbursement of proton therapy in adults in Belgium and those for carbon ion therapy for treatment abroad. Also evidence synthesis for possible reimbursement of treatment of the following cancers: low grade glioma (LGG); primary site nasal sinuses and recurrence of head and neck, colon, breast, women, pancreas and hepatomas	4 databases to July 2018	11 systematic reviews and HTA reports, 6 comparative studies and 24 non comparative studies		Same reports conclusion of CADTH and INESS documents	8/9
INESS 2017 (in French)	Overview to update indications for proton therapy in Quebec. Proton therapy is not available in Canada, apart from a facility in Vancouver treating ocular cancers	2 databases and 10 websites to 19 July 2016	28 synthesis documents, professional association reports with 10 primary studies		In conclusion, since the quality of the existing data is inadequate, it is presently not relevant to propose treatment with PrT for r**e-irradiation cases** (among various indications)	7/9
CADTH 2017	Overview of evidence synthesis from 2007 on proton therapy on various cancers	6 databases to march 2017	11 synthesis documents with 9 meta-analyses (34 primary studies with 65,574 patients)	Excludes paper "High-dose re-irradiation following radical radiotherapy for non-small-cell lung cancer" because not a SR.	Concludes that there evidence is insufficient for **re-irradiation cases** (among various indications)	11/11
ECRI 2019	Update of previous report on the effects of proton therapy on cranial-spinal cancers in minors	6 databases to January 2019	6 systematic reviews, 8 observational studies and 6 guidelines	Not assessed	No specific studies found	5/11
Washington State Health Care Authority 2019	Update of previous report on the effects of PT, now PBT	From November 2013 to December 2018	215 single studies the bulk of which (n=115) were case series	Appendices G from pdf p 96 1 retrospective case series at high RoB of "re-irradiation" of mixed histology head and neck cancer cases reports 2 year reports Distant Metastasis-Free Survival 1-year: 74.9%; 2-year: 63.7%. 1 retrospective case series at high RoB of "re-irradiation" of mixed histology head and neck cancer cases reports Distant Metastasis-Free Survival 1-year: 84% 1 retrospective case series at high RoB of 11 reirradiation cases of Pediatric Non-metastatic Rhabdomyosarcoma reports 2 year disease related mortality of 9.1% (6/66)	All studies report varying degrees of toxicity	10/11

Key: RoB = risk of bias; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton beam therapy; QoL = quality of life; RT = radiotherapy; SRT = stereotactic radiotherapy; vs. = versus; OS = overall survival; TFS = tumor free survival; DFS = disease free survival; NR = not reported.

Table A19i. Ongoing studies - RECURRENT TUMOURS REQUIRING REPEAT TREATMENT IN AREAS ALREADY EXPOSED TO RADIOTHERAPY

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
Nil									
NON COMPARATIVE STUDIES									
133 (2013) NCT01808677	Registry	**Included**: eligible to receive thoracic reirradiation for non-small cell lung cancer (NSCLC); adults **Excluded**: life expectancy<3 months	49		High Grade Toxicity	5 years	2016	Completed	No results posted
216 (2010) NCT01126476	RCT*	Adults, histologically confirmed, non-CNS solid malignancies who have been previously radiated and have a tumor recurrence in or near prior radiation fields, Karnofsky Performance Status of 60. Life expectancy of 3 months **Excluded**: prior radiation treatment less than 3 months from planned start of re-irradiation of any part of the intended treatment volume	24	Different treatment volumes	Feasibility (90 days), Acute Toxicity (90 days), Late toxicity is defined as any grade 3 or higher toxicity observed later than 90 days from start of therapy	90 days	2017	Unknown	* Two types of PBT

*does not compare PBT vs other treatments.

Table A20. Ongoing studies - ALL MALIGNANCIES - OTHER NON CLASSIFIED MALIGNANCIES

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
COMPARATIVE STUDIES									
Nil									
NON COMPARATIVE STUDIES									
125 (2018) NCT03764787	Single arm	**Included**: pathologically confirmed unspecified adult solid tumor; adults; KPS≥70.	30		Adverse events at 1 year; 2 years progression free survival; 2 years overall survival	2 years	2021	Not yet recruiting	PB combined with immunotherapy (PD-1 antibodyfor 1 year)
126 (2018) NCT03765190	Single arm	**Included**: pathologically confirmed unspecified solid tumor with multiple metastases; adults; KPS≥70.	30		Adverse events at 1 year; 2 years progression free survival; 2 years overall survival	2 years	2022	Not yet recruiting	PB combined with immunotherapy
134 (2016) NCT02722109	Single arm	Tumor referred to curative intended external beam radiotherapy; adults	14		Stopping power ratio differences at 2 months	2 months	2017	Terminated	Not enough patients signed up
144 /2014) NCT02070328	Registry	**Included**: cancer patients who have received proton therapy; adult and children	300		6 months follow up	25 years	2022	Recruiting	
149 (2014) NCT02040467	Registry	**Included**: all patients receiving proton beam radiation therapy; adults and children	3200		None	10 years	2024	Recruiting	Only collects Treatment-specific data
121 (2016) NCT02986048	Registry	**Included**: all patients treated with proton beam at the UH Proton Therapy Center. Adults + children	999		Number of patients treated at UH Proton Therapy Center by proton beam therapy	10 years	2027	Recruiting	
168 (2011) NCT02070393	Single arm	**Included**: females between 10 and 30 years old with Hodgkins disease **Excluded**: previous radiotherapy	3		Acute and late toxicity; local control	3-5 years	2015	Terminated	Closure of Indiana University Health Proton Center
220 (2012) NCT01557790	Single arm	Adults, male, Stage I, IIA, and IIB Seminoma histologically confirmed, classical or anaplastic, candidate for definitive external beam radiotherapy, ECOG 0-1. **Excluded**: prior radiotherapy, chemotherapy, Incomplete definitive surgical orchiectomy, including diagnostic biopsy alone, known severe, active co-morbidity, pelvic lymph node dissection	5		Number of Serious Adverse Events [5 years]	5 years	2017	Terminated (Did not meet accrual)	

Table A21. HTA Reports - Carbon Ion Therapy (CIRT)

Reference	Objective	Searches	Included studies	Results (data presented)	Conclusions	AMSTAR
LBI 2018	Evidence synthesis of clinical effectiveness and safety of CIRT for 12 tumour regions (and 54 sub-indications). CRT vs PBT or all other forms of RTX	4 databases 5-7 September 2017	1 CIRT feasibility "RCT" (high RoB) 26 observational studies with moderate RoB (3 case-control studies, 3 before-after studies on QoL, 20 case series studies	No evidence for 41/54 indications Insufficient evidence for 13/54) indications in 7 regions: skull base (chordoma and chondrosarcoma), brain (glioma grade II, glioma grade III, glioblastoma), ear-nose-throat (ENT; sarcomas in the head and neck, tumours in the nasal cavity and paranasal sinus, adenoid cystic salivary gland carcinoma), bone and soft tissue (soft-tissue sarcoma), lung (non-small cell lung carcinoma), prostate (prostate carcinoma), and gastrointestinal tumours (oesophageal carcinoma, rectal carcinoma).	"CIRT is undoubtedly, theoretically, a promising cancer treatment. To date, however, it lacks randomised controlled trials assessing the long-term effectiveness and harms associated with the use of CIRT. CIRT must be considered as an experimental treatment due to the lack of high-quality clinical research". Well conducted study with credible conclusins	11/11
CADTH 2018	Comparison of pre and post op CIRT vs all types of RTX including PBT, MRI Linac, sham, chemotherapy and surgery for chordoma and chordosarcoma at any stage and any age	5 databases as at 5 October, 2018	One systematic review and meta-analysis of 25 case series (n=996, aged 5 to 155) in China; two single-centre retrospective non-randomized controlled studies, and two cost-effectiveness studies from a single centre ith overlapping authors. Methodologically these are a strange mixture of case series data and modelling. Three of the studies in the meta-analysis were from the German centre	361 patients treated with CIRT had significantly higher rates of survival vs 635 patients treated with CRT at 3, 5 and 10 years following RT but no vs SRT. CIRT had a significantly lower survival rate 10 years after treatment vs PBT but not at 3,5, and 10 years. In 79 patients treated with CIRT vs 22 patients treated with PBT, there were no differences in OS at 1, 2 and 4-years. Toxicity Sacral fractures in 35 patients treated with surgical resection plus CIRT (with or without IMRT) and 21 patients treated with CIRT alone was not significant. At 1-2-5-year fracture-free survival probability values were reported without reference to statistical significance of the differences between the two groups. The fracture-free survival probability was higher in the post-operative CIRT group at the 1-year but not at 2 and 5 years Data from pdf p 24 (Tables)	"The findings from this review suggest that there is insufficient evidence to make firm, comprehensive conclusions about the clinical effectiveness and cost-effectiveness of CIRT relative to other forms of therapy for chordoma. Caution must be taken in interpreting the evidence due to the limited quantity of studies available and their respective limitations". These are small badly designed and badly reported studies with unclear methods (how can you meta-analyse case series?) Economic evaluations are not evidence (neither are guidelines)	10/11
CADTH 2009	Environmental scan	October 2009	Nil	**Nil**	Dated environmental scan (exploration) of the situation in 2009 with useful baseline development data	NA
HeaLth PACT 2017 (Australia)	Introductory description of nature and use of CIRT from pdf p 18	January 2017	Nil	No methods chapter and no data presented but it is a useful overview with information on distribution of centres, costs, resources and list of ongoing studies	Despite promising results CIRT is considered an experimental therapy	NA
AETNA 2019	Based entirely on LBI 2018 (chapter from pdf p 11)	-	-	-	"Aetna considers carbon ion therapy experimental and investigational for all indications because its effectiveness has not been established."	NA

Key: RoB=risk of bias; 3DCRT=three-dimensional conformal radiotherapy; IMRT=intensity-modulated radiotherapy; PBT=proton beam therapy; QoL=quality of life; RT=radiotherapy; SRT=stereotactic radiotherapy; vs.=versus; OS=overall survival; TFS=tumor free survival; DFS=disease free survival; NR=not reported; NA=not applicable; RTX=radiotherapy.

Table A21i. Ongoing studies - CARBON ION HADROTHERAPY

ID (YEAR) – Ref.	Study design	Population	N.	Comparison	Outcomes	Follow-up	End date	Status	Notes
PROSTATE CANCER									
21 (2016) **NCT02935023**	Single arm	**Included:** adenocarcinoma of the prostate; stage T1-4,N0-1,M1a/b with a combined maximum of 3 synchronous lesions; adults; ECOG PS 0 or 1; Life-expectancy ≥1 year **Excluded:** visceral metastasis; previous pelvic radiotherapy or prostatectomy; severe systemic disorders	47	N/A	Time to PSA relapse; progression free survival; Overall survival; QoL	2 years	Sep 2019	Unknown	Last update: October 17, 2016
28 (2016) **NCT02739659**	Single arm	**Included:** adenocarcinoma of the prostate; no lymph node and distant metastasis (N0, M0); adults; Karnofsky Performance Score ≥70 **Excluded**: Previous pelvic radiotherapy; previous prostatectomy; previous invasive cancer (within 5 years before the prostate cancer diagnosis); urinary obstructive symptoms (IPSS >20); severe systemic disorders	61	N/A	N° of participants with treatment-related adverse events; overall survival; biochemical failure-free survival; progression-free survival	2 years	2021	Recruiting	Preliminary results published **here**
36 (2015) **NCT02672449**	Single arm	**Included:** adenocarcinoma of the prostate, high-risk category according to NCCN version 2013 (T3a and/or PSA >20 ng/ml and/or Gleason score of 8-10); cN0 and cM0; adults; ECOG ps <2; Good urinary flow (peak flow >10 ml/s) **Excluded**: previous pelvic radiotherapy or prostatectomy; pelvic lymph node metastasis (N1) distant metastasis (M1); urinary obstructive symptoms (IPSS >20); previous malignancies; severe systemic disorders	65	N/A	Grade 3 or Grade 4 adverse events related to radiotherapy treatment at 1 month; late toxicity with Grade 3 or Grade 4; biochemical progression free survival; local or distance recurrence of disease; Overall survival	2 years	2020	Active, not recruiting	Last update: September 20, 2018
39 (2012) **NCT01641185**	Comparative*	Carcinoma of the prostate with Gleason score risk of lymphe node involvement of <15%; Karnofsky-Index ≥70%, age 40-80 years **Exclusion**: Stadium IV (distant metastases) lymphogenous metastases hip replacement former irradiation of the pelvis	92	PBT	proctitis and cystitis via incidence grade 3-4 toxicity; PSA (3 months) months			Completed	No results available
51 (2016) **UMIN000020848**	Single arm	**Included:** untreated primary prostate adenocarcinoma excluding Neoadjuvant endocrine therapy; cT1c, T2a, T2b, T2c, T3a, T3b, N0M0, according to UICC 7th (2009); adults; ECOG Performance status 0, 1 or 2; patient for prostate cancer **Excluded**: previous radiotherapy for the targeted lesion; castration-resistant prostate cancer; active double cancer; active and intractable infection in the targeted lesion; metal devices in the lesion	145	N/A	Biochemical progression-free survival; Overall survival; Disease-specific survival; Event-free survival; Early and late-phase adverse event rate	5 years	2027	No longer recruiting	Last update: April 13, 2018
52 (2016) **UMIN000021517**	Single arm	**Included:** Untreated primary prostate adenocarcinoma excluding neoadjuvant endocrine therapy; clinical stage of T1b, T1c, T2a, T2b, T2c, T3a or T3b and N0 M0, according to UICC 7th (2009); adults; ECOG Performance status is 0, 1 or 2 **Excluded**: previous radiotherapy for the targeted lesion; hormone-resistant prostate cancer; active double cancer; active and intractable infection in the targeted lesion; metal devices in the lesion	145		Biochemical progression-free survival; Overall survival; Disease-specific survival; Local recurrence-free survival; Early and late-phase adverse event rate	5 years		No longer recruiting	Last update: April 13, 2018
54 (2017) **UMIN000027640**	Single arm	**Included**: untreated primary prostate adenocarcinoma excluding neoadjuvant endocrine therapy; clinical stage of T1c, T2a, T2b, T2c, T3a, or T3b and N0M0 according to UICC 7th (2009); adults; ECOG Performance status is 0, 1 or 2 **Excluded:** previous radiotherapy for the targeted lesion; castration-resistant prostate cancer; active double cancer; active and intractable infection in the targeted lesion; metal devices in the lesion; Patient eligible for Advanced Medicine Program B (Sen-shin Iryo B)	689		Biochemical progression-free survival; Overall survival; Disease-specific survival; Event-free survival; Early and late-phase adverse event rate	5 years		No longer recruiting	Last update: April 13, 2018
LIVER MALIGNANCIES									
19 (2015) **NCT 02802124**	Single arm	**Included**: hepatocellular carcinoma (HCC); adults (age: 18-80), Karnofsky ≥70 **Excluded**: previous radiotherapy, distant metastasis (M1); tumor size >12 cm; tumor invading adjacent gastrointestine (T4); Child push score B or C		N/A	Treatment-related adverse events, overall survival, PFS, tumor response	3 months-2 years	2021	Recruiting	Phase I. No comparison vs other strategies (different doses assessed)
20 (2016) **NCT 02946138**	Single arm	**Included**: hepatocellular carcinoma, Child Push score A, unresectable or medically inoperable; tumor size ≤10 cm; age ≥18 and <80; Karnofsky ≥70; **Excluded**: distant metastasis (M1); tumor invading adjacent gastrointestine (T4);	0	N/A	PFS, overall survival, adverse events, objective response rate	2 years	2019	Withdrawn	Enrollment was too slow
22 (2011) **NCT 01167374**	Single arm	**Included**: hepatocellular carcinoma (HCC); adults (age: ≥18), Karnofsky ≥60. **Excluded:** previous radiotherapy of the hepatobiliary system margin of <1cm between tumor edge and intestines	22	N/A	Maximum tolerated dose, PFS	3 months-1 year	2020	Recruiting	Phase I
46 (2013) **JPRN-UMIN000020344**	Single arm	**Included**: hepatocellular carcinoma, age 20-80, tumor size 3-10 cm, Child-Pugh score 5 to 9 points, Perfomance status 0 to 2 **Excluded:** history of radiation therapy to the lesion of interest. The alimentary tract, major branch of portal vein or major bile duct adjacent to the target lesion	3	N/A	Dose-limiting toxicity, acute and late toxicity	6 months, >6 months	?	Completed	No results available
47 (2013) **JPRN-UMIN000020436**	Single arm	**Included**: hepatocellular carcinoma, age >20, distance between target lesion and digestive tract ≤1 cm, tumor size ≤10 cm, Child-Pugh score 5 to 9 points, Perfomance status 0 to 2, expected survival >6 months **Excluded:** history of radiation therapy	6	N/A	Dose-limiting toxicity, acute and late toxicity, response rate	Not available	2017	Completed	No results available
49 (2015) **JPRN-UMIN000020444**	Single arm (restrospective)	**Included:** hepatocellular carcinoma, age >20, Child-Pugh score 5 to 9 points, Perfomance status 0 to 2 **Excluded:** history of radiation therapy	250	N/A	Overall survival, local control rate, acute and late toxicity	3 months, >3 months	2016	Completed	No results available
50 (2011) **JPRN-UMIN000020571**	Single arm	**Included:** hepatocellular carcinoma, age >20, satellite nodules and/or tumor thrombus adjacent to the main tumor, tumor size ≤10 cm, Child-Pugh score 5 to 9 points, Perfomance status 0 to 2 **Excluded:** history of radiation th	35	N/A	Local control rate, overall survival, PFS, response rate, acute toxicity (within 6 months), late toxicity	3 years, 6 months	?	No longer recruiting	No results available
55 (2018) **JPRN-UMIN000032991**	Single arm	**Included:** hepatocellular carcinoma, age ≥20, unfit for resection or liver transplantation, unfit for percutaneous tumor ablation, Child-Pugh score 5 to 9 points, ECOG 0-1 **Excluded** previous chemotherapy, extrahepatic metastases	21	N/A	Overall survival, adverse event, response rate, disease control rate, time-to-local progression, PFS	Not available	?	Preinitiation	
PANCREATIC CANCER									
11 (2019) **NCT03822936**	single arm	**Included:** histologic/cytologic diagnosis of exocrine pancreas tumour; resectable or borderline resectable exocrine pancreatic tumour; no metastasis from US, CT, PET, MRI or laparotomy; Karnofsky index >=70 **Excluded:** non resectable, locally advanced tumours; insular cells tumour; comorbidities excluding abdominal surgery and/or chemo- radiation therapy; known metastasis; past radiation therapy on abdomen	30	N/A	progression free survival at 1-year; overall survival at 2 years;resectability rate R0 stratified (4-6 weeks);Incidence of acute, medium term and late toxicity (90-180 days);. intra and perioperatory complications (30 days)	2 years	February 2021	Recruiting	
26 (2013) **NCT01795274**	single arm	**Included:** histologically confirmed locally advanced pancreatic cancer or imaging defined pancreatic cancer combined with elevated CA-19-9; macroscopic tumor after biopsy; age ≥18 years of age; Karnofsky Performance Score >=60 **Excluded:** distant metastases; previous radiotherapy of the abdomen; Patients who have not yet recovered from acute toxicities of prior therapies; Known carcinoma <5 years ago	0	N/A	1Acute toxicity of carbon ion radiotherapy observed within 3 months; Overall survival (2 years); Progression-free survival (2 years)	2 years	2018	Withdrawn (Administrative barriers)	
27 (2015) **NCT03949933**	single arm	**Included:** histologically or cytologically confirmed disease based on evidences of (1). typical symptoms of abdominal and/or back pain; (2). CA19-9 increased over the normal up limit; (3). a pancreatic mass shown on CT or MRI; and (4). SUV of PET-CT in mass increased compared to that in normal pancreas; unresectable LAPC defined by the criteria of (NCCN) guidelines (Version 1. 2013), or refusal to surgery; gastrointestinal tract (GI) not invaded; ECOG Performance Status 0-1 within 30 days prior to registration; age of ≥18 years old; enough hematological function (white blood cell count ≥3.0×109/L; platelets ≥50×109/L; hemoglobin ≥90 g/L); enough liver and kidney functions (creatinine <110gmol/L; urea nitrogen <7.1mmol/L; bilirubin <1.5 x ULN, ALT and AST ≤ 2.5 x ULN) **Exlcuded:** ECOG>=2 liver, kidney and bone marrow function are poor and not adequate for treatment; Side effect of previous treatment is not covered yet; prior radiation therapy to the abdomen or radioactive particle implantation; Dose constrain of normal liver, digested system and other OAR could not reach the expecting safe dose	10	N/A	treatment-related adverse events as assessed by CTCAE v4.0 (3 months); progression-free survival after re-irradiation at 12 months	12 months	May 2016	Completed	No results available
32 (2019) **NCT04082455**	single arm	**Included:** unresectable LAPC defined by the criteria of (NCCN) guidelines (Version 1. 2013), or refusal to surgery; gastrointestinal tract (GI) not invaded; ECOG Performance Status 0-1 within 30 days prior to registration; age of ≥18 years old; enough hematological function (white blood cell count ≥3.0×109/L; platelets ≥50×109/L; hemoglobin ≥90 g/L); enough liver and kidney functions (creatinine <110gmol/L; urea nitrogen <7.1mmol/L; bilirubin <1.5 x ULN, ALT and AST ≤ 2.5 x ULN); no evidence of distant metastases, based upon PET, CT, or MRI images of the chest, abdomen and pelvis within 30 days prior to registration **Exlcuded:** ECOG>=2Liver, kidney and bone marrow function are poor and not adequate for treatment; Side effect of previous treatment is not covered yet; interval between TACE and other anti-tumor therapy is less than one month; prior radiation therapy to the abdomen or radioactive particle implantation	49	N/A	treatment-related adverse events (4 months); Overall survival (2 years); Progression-free survival (2 years)	2 years	April 2021	recruiting	
45 (2013) **UMIN000012296**	single arm	**Included:** age 20-80; pathologically diagnosed pancreatic invasive ductal carcinoma; Locally advanced (unresectable) disease; no distant metastasis except for paraaortic lymphnode; no invasion to mucosal membrane of stomach or intestine; PS0-2 **Excluded:** past history of irradiation to the target region; Infection around the target; pleural effusions or ascites; past history of chemotherapy within 4 weeks before start of this treatment; uncontrolled severe complication; active double cancers	20	N/A	overall survival rate; Response rate; Local control rate at two year; progression free survival rate; acute and late toxicity	Not described	2018	No longer recruiting	
53 (2016) **UMIN000023602**	single arm	**Included:** age 20-80; histlogical diagnosed invasive pancreatic cancer; without gastric ulcer; T4 (UICC 7th); without direct invasion to GI tract; performance status is 0-2; no history of surgery or irradiation for pancreatic cancer **Exlcuded:** direct invasion to GI truct; visivle ascites; use of flucytosine, phenytoin or warfarin; active scar or infection within the irradiation area; severe co-occurring disorders; co-occurring malignancies; chemotherapy history over 3 month; history of irradiation to the irradiating area	20	N/A	Overall survival (2 years)	2 years	April 2021	unknown	
56 (2016) **NCT03403049**	single arm	**Included:** age ≥18; cytologically or histologically proven diagnosis of adenocarcinoma of the pancreas; unresectable adenocarcinoma of the pancreas; no evidence of distant metastases based on imaging evaluation; maximum tumor and positive lymph node diameter ≤ 6 cm; ECOG Performance Status 0-1; life expectancy ≥12 weeks; prior receipt of 2-4 cycles of gemcitabine-based systemic chemotherapy **Excluded:** ECOG Performance Status >=2; poor liver, kidney and bone marrow function that do not meet the requirements for treatment; Persistent grade ≥2 toxicity due to previous cancer treatment; Patient has previously received abdominal radiation therapy or abdominal radioactive seed implantation	20	N/A	Dose-limiting toxicity (90 days); treatment-related toxicity, scored using CTCAE (1 year); Radiographic changes following completion of study therapy (1 year) Overall survival (1 year); Progression free survival rate (1 year); QoL	1 year	July 2019	Completed	
58 (2019) **NCT03536182**	RCT	**Included:** unresectable by radiographic or exploration within 30 days of registration; age ≥18 years. Distance from the pancreas tumor edge to the bowel and stomach >3 mm (in both the prone and supine positions); Tumor does not exceed 15 cm in greatest dimension no evidence for metastatic disease; zubrod performance status of 0-1, within 30 days prior to registration **Exlcuded:** subjects receiving other investigational agents; history of allergic reactions attributed to compounds of similar chemical or biologic composition to gemcitabine or nab-paclitaxel or other agents used in study; Subjects who are pregnant or nursing; prior radiation to the upper abdomen; body weight >100 kg; active inflammatory bowel disease or active gastric/duodenal ulcer	110	x-ray-based chemoradiotherapy	Overall survival (2 years) Progression-free survival (2 years) Patterns-of-failure (2 years) Toxicity using CTCAE 5.0 (2 years) QoL	2 years	July 2023	Recruiting	
NASOPHARINGEAL CANCER									
15 (2015) **NCT02569788**	single arm	**Included:** pathologically confirmed NPC; completed a definitive course of intensity-modulated photon radiation therapy (IMXT) to a total dose of ≥66 Gy; recurrence diagnosed more than 12 months after the initial course of IMXT; Age ≥14 and <70 years of age; Karnofsky Performance Score ≥70 **Exlcuded:** local recurrence of NPC diagnosed within 12 months from the completion of previous course of radiation therapy; presence of distant metastasis; technology used other than IMXT (including brachytherapy following IMXT) for the treatment of initial diagnosis of NPC; pregnant or lactating women; patients who have not yet recovered from acute toxicities of prior therapies; a diagnosis of malignancy other than CIS of the cervix, BCC and SCC of the skin within the past 5 years	62	N/A	treatment-related adverse events (4 months) Overall survival (2 years) Progression-free survival (2 years)	2 years	March 2019	recruiting	
16 (2016) **NCT02795195**	single arm	**Included:** completed a definitive course of intensity-modulated photon radiation therapy (IMXT) to a total dose of ≥66 Gy; recurrence diagnosed more than 12 months after the initial course of IMXT; age ≥18 and <70 years of age; Karnofsky Performance Score ≥70 **Excluded:** local recurrence of NPC diagnosed within 12 months from the completion of previous course of radiation therapy; Presence of distant metastasis; Technology used other than IMXT (including brachytherapy following IMXT) for the treatment of initial diagnosis of NPC; pregnant or lactating women; patients who have not yet recovered from acute toxicities of prior therapies; a diagnosis of malignancy other than CIS of the cervix, BCC and SCC of the skin within the past 5 years	58	N/A	treatment-related adverse events (4 months) Overall survival (2 years) Progression-free survival (2 years)	2 years	July 2022	Recruiting	
17 (2018) **NCT03689556**	Single arm	**Included:** pathologically confirmed as primary nasopharyngeal carcinoma; with recurrence at nasopharynx and/or recurrent retropharyngeal lymph node, recurrence was diagnosed by imaging or pathology studies; already received one course of definitive radiation therapy, at least 6 months ago; able to receive contrast MRI scan and PET/CT scan; ECOG: 0-2; anticipated survival time >=12 months; With sufficient major organ functions **Exlcuded:** metal implants that might significantly influence the radiation dose distribution; dose constrains for organs-at-risk are beyond acceptable limit; with comorbidities/conditions that might influence the effectiveness of carbon-ion therapy; pregnant or within lactation period; Drug/alcohol addiction	40	N/A	sensitivity and specificity of FLT uptake reduction in predicting the treatment response evaluated by MRI scan at 3 months Overall survival (3 years) Progression-free survival (3 years)	3 years	August 2021	Not yet recruiting	
18 (2016) **NCT02801487**	single arm	**Included:** Pathologically confirmed NPC; completed a definitive course of intensity-modulated photon radiation therapy (IMXT) to a total dose of ≥66 Gy; recurrence diagnosed more than 12 months after the initial course of IMXT; age ≥18 and <70 years of age; Karnofsky Performance Score ≥70 **Excluded:** local recurrence of NPC diagnosed within 12 months from the completion of previous course of radiation therapy; presence of distant metastasis; technology used other than IMXT (including brachytherapy following IMXT) for the treatment of initial diagnosis of NPC; pregnant or lactating women; patients who have not yet recovered from acute toxicities of prior therapies; a diagnosis of malignancy other than CIS of the cervix, BCC and SCC of the skin within the past 5 years	62	N/A	treatment-related adverse events (4 months) Overall survival (2 years) Progression-free survival (2 years)	2 years	March 2021	Recruiting	
34 (2010) **NCT01220752**	Single arm	**Included:** histologically confirmed or surgically removed adenocarcinoma or squamous cell carcinoma of the nasal cavity or paranasal sinuses; Inoperable tumour or refusal to undergo surgical resection; macroscopic or microscopic residual tumour (R2/ R1) or ≥T3/T4; adults **Excluded:** prior radio- or chemotherapy for tumours of the head and neck; Other previous malignancy within the past 5 years; neurological or psychiatric disorders	30	N/A	mucositis CTC grade 3 at 6-8 weeks; acute toxicity CTC grade 1/2 within 90 days; late toxicity; local control; disease-free survival; overall survival	2 years	Nov 2016	Unknown	Last update: April 24, 2013
RECTAL CANCER									
24 (2012) **NCT01528683**	single arm	**Included:** locally recurrent rectal cancer; Inoperable lesion; Macroscopic tumor up to 1000ml volume-prior photon radiation of 20-60 Gy; time between initial radiotherapy and re-irradiation of at least 12 months; age ≥18 years of age; Karnofsky Performance Score >60 **Exlcuded:** advanced metastatic disease; Patients who have not yet recovered from acute toxicities of prior therapies; Previous carcinoma <5 years ago	14	N/A	toxicity measured by any Grade IV toxicity (at least 3 months) progression-free survival after re-irradiation at 12 months	12 months	May 2018	completed	
CHORDOMA, CHONDROSARCOMA, ADENOID CYSTIC CARCINOMA AND SARCOMA									
30 (2017) **NCT02838602**	RCT	**Included:** age ≥18 years; no severe comorbidity, life expectancy above 10 years; Unresectable or inoperable or R2 resection of the tumor; radioresistant tumor according to the limitative list as following: adenoid cystic carcinoma of head and neck (larynx and trachea excluded); soft tissue sarcoma; rhabdomyosarcoma; retroperitoneal sarcoma; osteosarcoma (Ewing excluded); chondrosarcoma (except of skull base); axial skeleton chordoma (except of skull base); angiosarcoma; no skin involvement; ECOG performance status ≤2 or Karnovsky index ≥60 **Excluded:** previous irradiation in of the same tumor site; active metastatic disease; any contra-indication to undergo a radiation therapy by Xray or particle therapy; planned surgery or chemotherapy to take place after completion of radiotherapy; removable metallic material in the planning target volume; any history of another cancer in remission since less than 5 years	250	Radical radiotherapy by Xrays and/or protontherapy	progression free survival at 5 year Tolerance: Grades of the CTCAE-V4.02 classification (5 years) Overall survival (5 years) QoL EQ-5D questionnaire	5 years	November 2023	Recruiting	
35 (2013) **NCT01811394**	RCT*	**Included:** histological confirmation of sacrococcygeal chordoma; Macroscopic tumour (MRI); adults; Karnofsky performance status ≥70% **Excluded:** prior radiotherapy of the pelvic region; Tumor extension in craniocaudal direction >16cm; Active medical implants or metal implants at the level of the tumor; inability of the patient to lie quiet for at least 20 minutes (eg due to pain)	100	Carbon Ion vs Proton therapy	Proportion of treatments without Grade 3-5 toxicity (NCI-CTC-AE) and/or discontinuation of the treatment for any reason; local progression free survival; overall survival; QoL	1 year	2023	Recruiting	
43 (2010) **NCT01182753**	RCT*	**Included**: low/intermediate grade chondrosarcoma with infiltration of the skull base; adults; Karnofsky Performance Score ≥60% **Excluded:** prior radiotherapy of skull base region; simultaneous chemotherapy or Immunotherapy; other malignancies with disease-free interval <5 years	154	Carbon ion vs Proton therapy	Local-Progression Free Survival; overall survival, progression free; metastasis free survival; Acute and late toxicity according to CTCAE V4.0 for acute side effects and RTOG/EORTC for late reaction; Patterns of recurrence and local control rate	5 years	2022	Recruiting	
44 (2010) **NCT01182779**	RCT*	**Included**: chordoma with infiltration of the skull base; adults; Karnofsky Performance Score ≥60% **Excluded:** prior radiotherapy of skull base region; simultaneous chemotherapy or immunotherapy; other malignancies with disease-free interval <5 years	319	Carbon ion vs Proton therapy	local-progression free survival; overall survival, progression free and metastasis free survival; Local control and patterns of recurrence; Acute and late toxicity due to CTCAE V4.0 for acute reaction and RTOG/EORTC for late effects.	8 years	2023	Recruiting	
GLIOMA – GLIOBLASTOMA – MENINGIOMA									
23 (2010) **NCT 01166308**	RCT	**Included** unifocal, supratentorial recurrent glioma; indication re-irradiation; age ≥18; Karnofsky Performance Score ≥60 **Excluded:** multifocal glioma or gliomatosis cerebri; previous re-irradiation or prior radiosurgery or prior treatment with interstitial radioactive seeds; time interval of <6 months after primary radiotherapy	56	Fractionated Stereotacitc Radiotherapy	Overall survival, PFS	1 year	2016	Completed	Phase I/II, no results posted
41 (2011) **ISRCTN 01460925**	RCT	**Included** unifocal, supratentorial recurrent glioma; indication re-irradiation; age ≥18 years; Karnofsky Performance Score ≥60 **Excluded:** multifocal glioma or gliomatosis cerebri; previous re-irradiation or prior radiosurgery or prior treatment with interstitial radioactive seeds; time interval of <6 months after primary radiotherapy	436	Fractionated stereotactic radiotherapy	Overall survival, PFS, toxicity, safety	1 year	2014	Completed	No results posted
31 (2010) **NCT 01165671**	RCT*	**Included**: unifocal, supratentorial primary glioblastoma; macroscopic tumor, prior photon irradiation, age >18, Karnofsky Performance Score ≥60 **Excluded**: previous radiotherapy of the brain or chemotherapy with DTIC or TMZ	150	Proton radiotherapy	Overall survival, PFS, toxicity	1 year	2014	Unknown	No results posted
25 (2019) **NCT 01795300**	RCT	**Included**: skull base meningioma, age ≥18, macroscopic tumor, Karnofsky Performance Score ≥60 **Excluded**: previous radiotherapy of the brain; atypical or anaplastic meningioma; optic nerve sheath meningioma	80	Proton Therapy; Hypofractionated Photon Therapy; Conventional Photon Radiotherapy	Toxicity, Overall survival, PFS, QoL	1-3 years	2022	Not yet recruiting	
29 (2012) **NCT 01166321**	Single arm	**Included**: atypical meningioma; prior photon radiotherapy to the clinical target volume; age ≥18; Karnofsky Performance Score ≥60 **Excluded:** previous radiotherapy of the brain; optic nerve sheath meningioma	40	N/A	PFS, overall survival	3 years	2020	Recruiting	
HEAD & NECK									
38 (2012) **NCT01192087**	Single arm	**Included:** histologically proven or surgically resected adenoid-cystic carcinoma of the head and neck and macroscopic or microscopic residual tumor (R1/ R2) or tumor stage >T3/T4 or perineural invasion and M0 stage; adults; Karnofsky Index ≥70% **Excluded**: prior radiotherapy or chemotherapy for tumors of the head and neck; prior immunotherapy; R0 resection; M1, serious illnesses; previous malignancy within the past 5 years	49	N/A	Acute (within 6 weeks) or late (3 years) mucositis or any other toxicity of severity grade 3 or 4 according to NCI CTCAE V. 4; local relapse-free survival; distant relapse-free survival; overall disease-free survival; overall survival	3 years	Jul 2017	Unknown	Last update: April 24, 2013
40 (2010) **NCT01245985**	Single arm	**Included:** locally advanced (stage III or IV), non-metastatic squamous cell carcinoma of oro-, hypopharynx and larynx (T2-4, any N, M0), oral cavity or oro-, ypopharynx or laynx as the primary tumor site, adults; at least one uni-measurable lesion according to the RECIST criteria; Karnofsky Performances Status >70% **Excluded:** previous systemic chemotherapy, radiotherapy or surgery for carcinoma of the head, neck and larynx; prior exposure to EGFR pathway targeting therapy; nasopharyngeal carcinoma; evidence of distant metastases; other serious illness or medical conditions	8 (originally 50)		Local-Regional Control; disease-free survival; progression-free survival; overall survival; acute radiation effects (within 6 weeks); late radiation effects; adverse events; proteomic and genomic analyses at week 6	1 year	Nov 2013	Terminated (slow recruitment only 8 patients recruited and treated until 12/2012	Last update: April 24, 2013