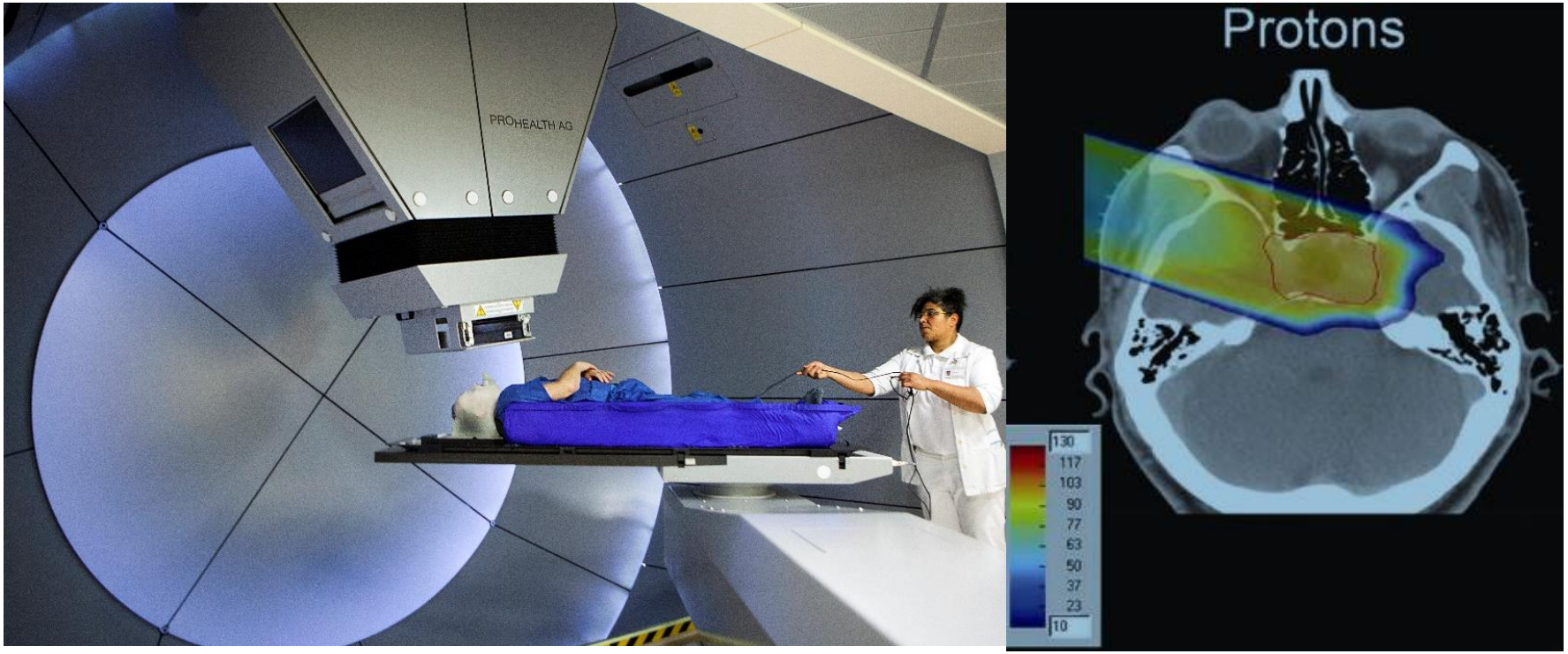
KCE REPORT 307S

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

HADRON THERAPY IN ADULTS

SUPPLEMENT



KCE REPORT 307S
HEALTH TECHNOLOGY ASSESSMENT

Federaal Kenniscentrum voor de Gezondheidszorg
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HADRON THERAPY IN ADULTS

SUPPLEMENT

JOAN VLAYEN, LLENALIA GARCÍA FERNÁNDEZ, TOM BOTERBERG, LORENA SAN MIGUEL

COLOPHON

Title:	**Hadron therapy in adults**
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Layout:	Ine Verhulst

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1.1. Electronic databases

Date	26-07-2018
Database	**Medline (OVID)**
Search strategy	1 heavy ions/ae, tu (389) 2 elementary particles/ae, tu (59) 3 protons/ae, tu and (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*).ti,ab,kf,kw,hw. (1492) 4 alpha particles/ae, tu (468) 5 exp Proton Therapy/ or Radiotherapy, High-Energy/ae, ct, ec, sn, ut (3022) 6 particletherap*.mp. or hadrontherap*.tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (112) 7 proton therap*.mp. or protontherap*.tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2549) 8 proton? beam?.tw. (2499) 9 ion? gantry.tw. (6) 10 (hadron? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (126) 11 (heavy-ion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (645) 12 (proton? adj3 (beam* or minibeam* or therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (6813) 13 (particle? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (3263) 14 (ion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (3317) 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 (14947) 16 heavy ions/ or elementary particles/ or protons/ or alpha particles/ or Radiotherapy, High-Energy/ (42906) 17 (therapy or therapies or therapeut* or treatment?).tw. (4701515) 18 th.xs. (6483169) 19 (radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*).tw. (477352) 20 17 or 18 or 19 (8531826)

21	16 and 20 (16921)
22	(proton* and therap*).ti,kf,kw. (2488)
23	(proton* adj3 therap*).ab. (3226)
24	(PBT or PBRT).ti,ab,kf,kw. (1060)
25	22 or 23 or 24 (5238)
26	exp Neoplasms/ (3063172)
27	(cancer* or neoplasm* or tumor* or tumour* or oncolog* or malignanc* or metastatic* or metastasis or metastases or cyst*).ti,ab,kf,kw,hw,jw. (3708376)
28	(adenocarcinoma* or adenoma* or angiosarcoma* or astrocytoma* or carcinoma* or cholangiocarcinoma* or chondrosarcoma* or chordoma* or choriocarcinoma* or craniopharyngioma* or cytoma* or ependymoblastoma* or esthesioneuroblastoma* or fibrosarcoma* or germinoma* or glioblastoma* or glioma* or hemangioma* or hemangiosarcoma* or histiocytoma* or hypernephroma* or incidentaloma* or leiomyosarcoma* or leukaemia* or leukemia* or lipoma* or liposarcoma* or lymphangiosarcoma* or lymphoma* or medulloblastoma* or melanoma* or meningioma* or mesothelioma* or myeloma* or myxosarcoma* or neuroblastoma* or neurofibrosarcoma* or oligoastrocytoma* or oligodendroglioma* or osteosarcoma* or paraganglioma* or pheochromocytoma* or plasmacytoma* or pineoblastoma* or pleomorphic xanthoastrocytoma* or rhabdomyosarcoma* or sarcoma* or schwannoma* or seminoma*).ti,ab,kf,kw,hw. (1782094)
29	(radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*).ti,ab,kf,kw,hw,jw. (636627)
30	26 or 27 or 28 or 29 (4358762)
31	25 and 30 (3319)
32	15 or 21 or 31 (26456)
33	(proton? adj3 pump).tw. (13218)
34	ion? channel?.mp. (70376)
35	exp ion pumps/ (169620)
36	exp ion channels/ (225649)
37	exp Hydrogen-Ion Concentration/ (291442)
38	protonation.tw. (8780)
39	33 or 34 or 35 or 36 or 37 or 38 (680332)
40	32 not 39 (23565)
41	exp animals/ not humans.sh. (4477680)
42	40 not 41 (20879)
43	exp Glioma/ (74737)
44	glioma*.mp. (51914)
45	astrocytoma*.mp. (19829)
46	oligodendroglioma*.mp. (4949)
47	ganglioglioma*.mp. (1400)
48	oligoastrocytoma*.mp. (799)

49	xanthoastrocytoma*.mp. (426)
50	astroblastoma*.mp. (128)
51	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (85955)
52	breast/ or breast diseases/ (44851)
53	Neoplasms/ (386641)
54	52 and 53 (1993)
55	(breast$ adj5 neoplas$).tw. (3233)
56	(breast$ adj5 cancer$).tw. (226494)
57	(breast$ adj5 carcin$).tw. (41447)
58	(breast$ adj5 tumo$).tw. (37854)
59	(breast$ adj5 metasta$).tw. (27830)
60	(breast$ adj5 malig$).tw. (10778)
61	exp Carcinoma, Ductal, Breast/ (14635)
62	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (264032)
63	exp Liver Neoplasms/ (151053)
64	exp Carcinoma, Hepatocellular/ (75209)
65	((liver or hepat$) and (neoplas$ or cancer$ or $carcin$ or tumo$ or metasta$ or malig$)).mp. (303679)
66	63 or 65 (303683)
67	primary.mp. (1247239)
68	66 and 67 (40669)
69	(hepatocellular carcinoma* or HCC* or hepatoma*).mp. (92061)
70	64 or 68 or 69 (135228)
71	Pancreatic Neoplasms/ (65918)
72	(pancrea$ adj5 neoplas$).tw. (5845)
73	(pancrea$ adj5 cancer$).tw. (33458)
74	(pancrea$ adj5 carcin$).tw. (13822)
75	(pancrea$ adj5 tumo$).tw. (19338)
76	(pancrea$ adj5 metasta$).tw. (5621)
77	(pancrea$ adj5 malig$).tw. (4911)
78	71 or 72 or 73 or 74 or 75 or 76 or 77 (80385)
79	(rect$ adj5 neoplas$).tw. (790)
80	(rect$ adj5 cancer$).tw. (22632)
81	(rect$ adj5 carcin$).tw. (7218)

82	(rect$ adj5 tumo$).tw. (5581)
83	(rect$ adj5 metasta$).tw. (2124)
84	(rect$ adj5 malig$).tw. (1056)
85	exp Rectal Neoplasms/ (43894)
86	79 or 80 or 81 or 82 or 83 or 84 or 85 (52882)
87	recurrence/ (170758)
88	Neoplasm Recurrence, Local/ (104943)
89	recur$.ti,ab. (455892)
90	87 or 88 or 89 (576148)
91	86 and 90 (10721)
92	"head and neck neoplasms"/ or exp mouth neoplasms/ or exp otorhinolaryngologic neoplasms/ or tracheal neoplasms/ (186936)
93	((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. (25820)
94	92 or 93 (189840)
95	90 and 94 (27137)
96	exp Paranasal Sinus Neoplasms/ (8838)
97	(sinonas* adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. (1425)
98	96 or 97 (9315)
99	51 or 62 or 70 or 78 or 91 or 95 or 98 (596763)
100	42 and 99 (2469)

Date	**26-07-2018**
Database	**PreMedline (OVID)**
Search strategy	1 heavy ions/ae, tu (0) 2 elementary particles/ae, tu (0) 3 protons/ae, tu and (beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*).ti,ab,kf,kw,hw. (2) 4 alpha particles/ae, tu (4) 5 exp Proton Therapy/ or Radiotherapy, High-Energy/ae, ct, ec, sn, ut (11) 6 particletherap*.mp. or hadrontherap*.tw. (22) 7 proton therap*.mp. or protontherap*.tw. (549) 8 proton? beam?.tw. (728)

9 ion? gantry.tw. (2)

10 (hadron? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (32)

11 (heavy-ion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (162)

12 (proton? adj3 (beam* or minibeam* or therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (1659)

13 (particle? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (717)

14 (ion? adj3 (therapy or therapeut* or therapies or treatment? or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)).tw. (1124)

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 (3385)

16 heavy ions/ or elementary particles/ or protons/ or alpha particles/ or Radiotherapy, High-Energy/ (24)

17 (therapy or therapies or therapeut* or treatment?).tw. (619568)

18 th.xs. (3831)

19 (radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*).tw. (81699)

20 17 or 18 or 19 (671510)

21 16 and 20 (17)

22 (proton* and therap*).ti,kf,kw. (751)

23 (proton* adj3 therap*).ab. (698)

24 (PBT or PBRT).ti,ab,kf,kw. (249)

25 22 or 23 or 24 (1220)

26 exp Neoplasms/ (2042)

27 (cancer* or neoplasm* or tumor* or tumour* or oncolog* or malignanc* or metastatic* or metastasis or metastases or cyst*).ti,ab,kf,kw,hw,jw. (356231)

28 (adenocarcinoma* or adenoma* or angiosarcoma* or astrocytoma* or carcinoma* or cholangiocarcinoma* or chondrosarcoma* or chordoma* or choriocarcinoma* or craniopharyngioma* or cytoma* or ependymoblastoma* or esthesioneuroblastoma* or fibrosarcoma* or germinoma* or glioblastoma* or glioma* or hemangioma* or hemangiosarcoma* or histiocytoma* or hypernephroma* or incidentaloma* or leiomyosarcoma* or leukaemia* or leukemia* or lipoma* or liposarcoma* or lymphangiosarcoma* or lymphoma* or medulloblastoma* or melanoma* or meningioma* or mesothelioma* or myeloma* or myxosarcoma* or neuroblastoma* or neurofibrosarcoma* or oligoastrocytoma* or oligodendroglioma* or osteosarcoma* or paraganglioma* or pheochromocytoma* or plasmacytoma* or pineoblastoma* or pleomorphic xanthoastrocytoma* or rhabdomyosarcoma* or sarcoma* or schwannoma* or seminoma*).ti,ab,kf,kw,hw. (151397)

29 (radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*).ti,ab,kf,kw,hw,jw. (88651)

30 26 or 27 or 28 or 29 (449828)

31 25 and 30 (750)

32	15 or 21 or 31 (3448)
33	(proton? adj3 pump).tw. (2061)
34	ion? channel?.mp. (3851)
35	exp ion pumps/ (101)
36	exp ion channels/ (137)
37	exp Hydrogen-Ion Concentration/ (137)
38	protonation.tw. (3479)
39	33 or 34 or 35 or 36 or 37 or 38 (9686)
40	32 not 39 (3127)
41	exp animals/ not humans.sh. (1973)
42	40 not 41 (3121)
43	exp Glioma/ (74)
44	glioma*.mp. (5942)
45	astrocytoma*.mp. (1123)
46	oligodendroglioma*.mp. (322)
47	gangliоglioma*.mp. (115)
48	oligoastrocytoma*.mp. (65)
49	xanthoastrocytoma*.mp. (54)
50	astroblastoma*.mp. (24)
51	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (6775)
52	breast/ or breast diseases/ (36)
53	Neoplasms/ (231)
54	52 and 53 (1)
55	(breast$ adj5 neoplas$).tw. (336)
56	(breast$ adj5 cancer$).tw. (32094)
57	(breast$ adj5 carcin$).tw. (4032)
58	(breast$ adj5 tumo$).tw. (5045)
59	(breast$ adj5 metasta$).tw. (4391)
60	(breast$ adj5 malig$).tw. (1597)
61	exp Carcinoma, Ductal, Breast/ (10)
62	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (35415)
63	exp Liver Neoplasms/ (105)
64	exp Carcinoma, Hepatocellular/ (65)

65 ((liver or hepat$) and (neoplas$ or cancer$ or $carcin$ or tumo$ or metasta$ or malig$)).mp. (29853)
66 63 or 65 (29853)
67 primary.mp. (161451)
68 66 and 67 (4525)
69 (hepatocellular carcinoma* or HCC* or hepatoma*).mp. (14049)
70 64 or 68 or 69 (17068)
71 Pancreatic Neoplasms/ (65)
72 (pancrea$ adj5 neoplas$).tw. (891)
73 (pancrea$ adj5 cancer$).tw. (5403)
74 (pancrea$ adj5 carcin$).tw. (1188)
75 (pancrea$ adj5 tumo$).tw. (2494)
76 (pancrea$ adj5 metasta$).tw. (980)
77 (pancrea$ adj5 malig$).tw. (768)
78 71 or 72 or 73 or 74 or 75 or 76 or 77 (8300)
79 (rect$ adj5 neoplas$).tw. (69)
80 (rect$ adj5 cancer$).tw. (2889)
81 (rect$ adj5 carcin$).tw. (561)
82 (rect$ adj5 tumo$).tw. (645)
83 (rect$ adj5 metasta$).tw. (346)
84 (rect$ adj5 malig$).tw. (121)
85 exp Rectal Neoplasms/ (22)
86 79 or 80 or 81 or 82 or 83 or 84 or 85 (3769)
87 recurrence/ (79)
88 Neoplasm Recurrence, Local/ (100)
89 recur$.ti,ab. (63728)
90 87 or 88 or 89 (63778)
91 86 and 90 (745)
92 "head and neck neoplasms"/ or exp mouth neoplasms/ or exp otorhinolaryngologic neoplasms/ or tracheal neoplasms/ (103)
93 ((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. (2460)
94 92 or 93 (2548)
95 90 and 94 (366)
96 exp Paranasal Sinus Neoplasms/ (1)
97 (sinonas* adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. (302)

	98	96 or 97 (302)
	99	51 or 62 or 70 or 78 or 91 or 95 or 98 (67083)
	100	42 and 99 (154)

Date		**26-07-2018**	
Database		**EMBASE**	
Search strategy	#1	'heavy ion'/exp	1221
	#2	'elementary particle'/exp	999
	#3	'proton'/exp	36642
	#4	beam*:ti,ab OR minibeam*:ti,ab OR radiation*:ti,ab OR irradiation*:ti,ab OR radiotherap*:ti,ab OR 'radio therap*':ti,ab OR chemoradiation*:ti,ab OR chemoradiotherap*:ti,ab	798969
	#5	(#1 OR #2 OR #3) AND #4	6390
	#6	'alpha radiation'/exp	4523
	#7	'proton therapy'/exp	6333
	#8	'megavoltage radiotherapy'/exp	5766
	#9	(particletherap*:ti,ab OR hadrontherap*:ti,ab OR proton:ti,ab) AND therap*:ti,ab OR protontherap*:ti,ab OR ((proton* NEAR/1 beam*):ti,ab) OR ((ion* NEAR/1 gantry):ti,ab)	22764
	#10	(hadron* NEAR/3 (therapy OR therapeut* OR therapies OR treatment* OR radiotherap* OR radiation* OR irradiation* OR 'radio therap*' OR chemoradiation* OR chemoradiotherap*)):ti,ab	324
	#11	('heavy ion*' NEAR/3 (therapy OR therapeut* OR therapies OR treatment* OR radiotherap* OR radiation* OR irradiation* OR 'radio therap*' OR chemoradiation* OR chemoradiotherap*)):ti,ab	926
	#12	(proton* NEAR/3 (beam* OR minibeam* OR therapy OR therapeut* OR therapies OR treatment* OR radiotherap* OR radiation* OR irradiation* OR 'radio therap*' OR chemoradiation* OR chemoradiotherap*)):ti,ab	13376
	#13	(particle* NEAR/3 (therapy OR therapeut* OR therapies OR treatment* OR radiotherap* OR radiation* OR irradiation* OR 'radio therap*' OR chemoradiation* OR chemoradiotherap*)):ti,ab	5053
	#14	(ion* NEAR/3 (therapy OR therapeut* OR therapies OR treatment* OR radiotherap* OR radiation* OR irradiation* OR 'radio therap*' OR chemoradiation* OR chemoradiotherap*)):ti,ab	46209
	#15	'proton radiation'/exp	3790
	#16	'hadron'/exp	356

#17	proton*:ti,ab AND therap*:ti,ab	22557
#18	(proton* NEAR/3 therap*):ab	6921
#19	pbt:ti,ab OR pbrt:ti,ab	1879
#20	#17 OR #18 OR #19	23941
#21	'neoplasm'/exp	4399664
#22	cancer*:ti,ab OR neoplasm*:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR oncolog*:ti,ab OR malignanc*:ti,ab OR metastatic*:ti,ab OR metastasis:ti,ab OR metastases:ti,ab OR cyst*:ti,ab	3982539
#23	(adenocarcinoma*:ti,ab OR adenoma*:ti,ab OR angiosarcoma*:ti,ab OR astrocytoma*:ti,ab OR carcinoma*:ti,ab OR cholangiocarcinoma*:ti,ab OR chondrosarcoma*:ti,ab OR chordoma*:ti,ab OR choriocarcinoma*:ti,ab OR craniopharyngioma*:ti,ab OR cytoma*:ti,ab OR ependymoblastoma*:ti,ab OR esthesioneuroblastoma*:ti,ab OR fibrosarcoma*:ti,ab OR germinoma*:ti,ab OR glioblastoma*:ti,ab OR glioma*:ti,ab OR hemangioma*:ti,ab OR hemangiosarcoma*:ti,ab OR histiocytoma*:ti,ab OR hypernephroma*:ti,ab OR incidentaloma*:ti,ab OR leiomyosarcoma*:ti,ab OR leukaemia*:ti,ab OR leukemia*:ti,ab OR lipoma*:ti,ab OR liposarcoma*:ti,ab OR lymphangiosarcoma*:ti,ab OR lymphoma*:ti,ab OR medulloblastoma*:ti,ab OR melanoma*:ti,ab OR meningioma*:ti,ab OR mesothelioma*:ti,ab OR myeloma*:ti,ab OR myxosarcoma*:ti,ab OR neuroblastoma*:ti,ab OR neurofibrosarcoma*:ti,ab OR oligoastrocytoma*:ti,ab OR oligodendroglioma*:ti,ab OR osteosarcoma*:ti,ab OR paraganglioma*:ti,ab OR pheochromocytoma*:ti,ab OR plasmacytoma*:ti,ab OR pineoblastoma*:ti,ab OR pleomorphic:ti,ab) AND xanthoastrocytoma*:ti,ab OR rhabdomyosarcoma*:ti,ab OR sarcoma*:ti,ab OR schwannoma*:ti,ab OR seminoma*:ti,ab	142499
#24	radiation*:ti,ab OR irradiation*:ti,ab OR radiotherap*:ti,ab OR 'radio therap*':ti,ab OR chemoradiation*:ti,ab OR chemoradiotherap*:ti,ab	741784
#25	#21 OR #22 OR #23 OR #24	5727356
#26	#20 AND #25	11266
#27	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #26	88035
#28	proton* NEAR/3 pump	43662
#29	ion* NEAR/3 channel*	74466
#30	'proton pump'/exp	3781
#31	'proton pump inhibitor'/exp	69194
#32	'proton ionophore'/exp	52
#33	'ion channel'/exp	221687
#34	'ion transport'/exp	232180

#35	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	448808
#36	#27 NOT #35	75191
#37	'glioma'/exp	118127
#38	glioma*	84772
#39	astrocytoma*	30383
#40	oligodendroglioma*	8831
#41	gangliоglioma*	2017
#42	oligoastrocytoma*	1583
#43	xanthoastrocytoma*	910
#44	astroblastoma*	236
#45	#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	137593
#46	'breast cancer'/exp	411866
#47	breast* NEAR/5 (neoplas* OR cancer* OR carcin* OR tumo* OR metasta* OR malig*)	559531
#48	#46 OR #47	563604
#49	'liver cell carcinoma'/exp	138978
#50	(liver OR hepat*) NEAR/5 (neoplas* OR cancer* OR carcin* OR tumo* OR metasta* OR malig*)	340083
#51	'liver cancer'/exp	217505
#52	#50 OR #51	342208
#53	primary	1982996
#54	#52 AND #53	56067
#55	(hepatocellular NEAR/1 carcinoma*) OR hcc* OR hepatoma*	154062
#56	#49 OR #54 OR #55	220278
#57	pancrea* NEAR/5 (neoplas* OR cancer* OR carcin* OR tumo* OR metasta* OR malig*)	147541
#58	'pancreas cancer'/exp	87626
#59	#57 OR #58	151238
#60	rect* NEAR/5 (neoplas* OR cancer* OR carcin* OR tumo* OR metasta* OR malig*)	79704
#61	'rectum cancer'/exp	184910

#62	#60 OR #61	217397
#63	'recurrent disease'/exp OR 'cancer recurrence'/exp OR recur*	923960
#64	#62 AND #63	30033
#65	'head and neck cancer'/de OR 'head and neck carcinoma'/de OR 'head and neck squamous cell carcinoma'/exp OR 'lip carcinoma'/exp OR 'maxilla sinus carcinoma'/exp OR 'mouth carcinoma'/exp OR 'nose carcinoma'/exp OR 'paranasal sinus carcinoma'/exp OR 'lip cancer'/exp OR 'mouth cancer'/exp OR 'neck cancer'/exp OR 'nose cancer'/exp OR 'paranasal sinus cancer'/exp OR 'pharynx cancer'/exp OR 'salivary gland cancer'/exp OR 'tongue cancer'/exp OR 'tonsil cancer'/exp	127296
#66	(laryn* OR hypopharyn* OR oropharyn* OR glotti* OR supraglotti* OR epiglotti* OR subglotti*) NEAR/5 (cancer* OR tumour* OR tumor* OR neoplas* OR malignan* OR carcinoma* OR metatasta*)	57604
#67	#65 OR #66	161698
#68	#63 AND #67	26949
#69	'paranasal sinus cancer'/exp	3632
#70	sinonas* NEAR/5 (cancer* OR tumour* OR tumor* OR neoplas* OR malignan* OR carcinoma* OR metatasta*)	2503
#71	#69 OR #70	5644
#72	#45 OR #48 OR #56 OR #59 OR #64 OR #68 OR #71	1077002
#73	#36 AND #72	7571
#74	#36 AND #72 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND ([embase]/lim OR [medline]/lim)	4322

Date	**26-07-2018**	
Database	**Cochrane Library**	
Search strategy	#1	MeSH descriptor: [Heavy Ions] explode all trees
	#2	MeSH descriptor: [Elementary Particles] explode all trees
	#3	MeSH descriptor: [Protons] explode all trees
	#4	(beam* or minibeam* or radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*):ti,ab
	#5	#3 and #4
	#6	MeSH descriptor: [Alpha Particles] explode all trees
	#7	MeSH descriptor: [Proton Therapy] explode all trees
	#8	MeSH descriptor: [Radiotherapy, High-Energy] explode all trees

#9	(particletherap* or hadrontherap* or proton therap* or protontherap* or "proton beam" or "protons beam" or "proton beams" or "protons beams" or "ion gantry" or "ions gantry"):ti,ab
#10	((hadron or hadrons) near/3 (therapy or therapeut* or therapies or treatment or treatments or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)):ti,ab
#11	((heavy-ion or heavy-ions) near/3 (therapy or therapeut* or therapies or treatment or treatments or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)):ti,ab
#12	((proton or protons) near/3 (beam or minibeam or therapy or therapeut* or therapies or treatment or treatments or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)):ti,ab
#13	((particle or particles) near/3 (therapy or therapeut* or therapies or treatment or treatments or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)):ti,ab
#14	((ion or ions) near/3 (therapy or therapeut* or therapies or treatment or treatments or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*)):ti,ab
#15	#1 or #2 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	#1 or #2 or #3 or #6 or #8
#17	(therapy or therapies or therapeut* or treatment* or radiotherap* or radiation* or irradiation* or radio-therap* or chemoradiation* or chemoradiotherap*):ti,ab
#18	#16 and #17
#19	(proton* and therap*):ti,ab
#20	(proton* near/3 therap*):ti,ab
#21	(PBT or PBRT):ti,ab
#22	#19 or #20 or #21
#23	MeSH descriptor: [Neoplasms] explode all trees
#24	(cancer* or neoplasm* or tumor* or tumour* or oncolog* or malignanc* or metastatic* or metastasis or metastases or cyst*):ti,ab
#25	(adenocarcinoma* or adenoma* or angiosarcoma* or astrocytoma* or carcinoma* or cholangiocarcinoma* or chondrosarcoma* or chordoma* or choriocarcinoma* or craniopharyngioma* or cytoma* or ependymoblastoma* or esthesioneuroblastoma* or fibrosarcoma* or germinoma* or glioblastoma* or glioma* or hemangioma* or hemangiosarcoma* or histiocytoma* or hypernephroma* or incidentaloma* or leiomyosarcoma* or leukaemia* or leukemia* or lipoma* or liposarcoma* or lymphangiosarcoma* or lymphoma* or medulloblastoma* or melanoma* or meningioma* or mesothelioma* or myeloma* or myxosarcoma* or neuroblastoma* or neurofibrosarcoma* or oligoastrocytoma* or oligodendroglioma* or osteosarcoma* or paraganglioma* or pheochromocytoma* or plasmacytoma* or pineoblastoma* or pleomorphic xanthoastrocytoma* or rhabdomyosarcoma* or sarcoma* or schwannoma* or seminoma*):ti,ab
#26	(radiation* or irradiation* or radiotherap* or radio-therap* or chemoradiation* or chemoradiotherap*):ti,ab
#27	#23 or #24 or #25 or #26
#28	#22 and #27
#29	#15 or #18 or #28
#30	((proton or protons) near/3 (pump or pumps)):ti,ab

#31	("ion channel" or "ions channel" or "ions channels" or "ion channels"):ti,ab
#32	MeSH descriptor: [Ion Pumps] explode all trees
#33	MeSH descriptor: [Ion Channels] explode all trees
#34	MeSH descriptor: [Hydrogen-Ion Concentration] explode all trees
#35	protonation:ti,ab
#36	#30 or #31 or #32 or #33 or #34 or #35
#37	#29 not #36
#38	MeSH descriptor: [Glioma] explode all trees
#39	(glioma* or astrocytoma* or oligodendroglioma* or ganglioglioma* or oligoastrocytoma* or xanthoastrocytoma* or astroblastoma*):ti,ab
#40	MeSH descriptor: [Breast] explode all trees
#41	MeSH descriptor: [Breast Diseases] explode all trees
#42	MeSH descriptor: [Neoplasms] explode all trees
#43	(#40 or #41) and #42
#44	MeSH descriptor: [Carcinoma, Ductal, Breast] explode all trees
#45	(breast* near/5 (neoplas* or cancer* or carcin* or tumo* or metasta* or malig*)):ti,ab
#46	((liver* or hepat*) near/5 (neoplas* or cancer* or carcin* or tumo* or metasta* or malig*)):ti,ab
#47	MeSH descriptor: [Liver Neoplasms] explode all trees
#48	primary:ti,ab
#49	(#46 or #47) and #48
#50	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees
#51	(hepatocellular carcinoma* or HCC* or hepatoma*):ti,ab
#52	(pancrea* near/5 (neoplas* or cancer* or carcin* or tumo* or metasta* or malig*)):ti,ab
#53	MeSH descriptor: [Pancreatic Neoplasms] explode all trees
#54	(rect* near/5 (neoplas* or cancer* or carcin* or tumo* or metasta* or malig*)):ti,ab
#55	MeSH descriptor: [Rectal Neoplasms] explode all trees
#56	recur*:ti,ab
#57	MeSH descriptor: [Recurrence] explode all trees
#58	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#59	(#54 or #55) and (#56 or #57 or #58)
#60	MeSH descriptor: [Head and Neck Neoplasms] this term only
#61	MeSH descriptor: [Mouth Neoplasms] explode all trees
#62	MeSH descriptor: [Otorhinolaryngologic Neoplasms] explode all trees
#63	MeSH descriptor: [Tracheal Neoplasms] this term only

	#64	((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) near/5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)):ti,ab
	#65	(#60 or #61 or #62 or #63 or #64) and (#56 or #57 or #58)
	#66	MeSH descriptor: [Paranasal Sinus Neoplasms] explode all trees
	#67	(sinonas* near/5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)):ti,ab
	#68	#38 or #39 or #43 or #44 or #45 or #49 or #50 or #51 or #52 or #53 or #59 or #65 or #66 or #67
	#69	#37 and #68

2. SELECTION RESULTS

On July 26, 2018 a search was performed to identify publications regarding the clinical effectiveness of proton beam therapy for selected indications. MEDLINE (including PreMedline), Embase and the Cochrane Library were searched.

7111 potentially relevant references were identified (Figure 1). After de-duplication (N=1243) and removing references published in an excluded language (other than English, German, French and Dutch; N=330) 5538 references remained. Based on title and abstract 5281 references were excluded. Of the remaining 257 references, 33 references were included based on full-text evaluation and 224 references were excluded with reason (Table 1).

HTA websites were also searched, and ten additional HTA reports were identified. Of these, six were included and four were excluded (Table 2).

Finally, screening of the reference lists identified 20 additional potentially relevant references. Of these, 18 were excluded (Table 3) and two were included.

In total, 11 systematic reviews / HTA reports were included. Six studies compared proton beam therapy with photon therapy, while two studies had the wrong comparator but sufficient patients in the proton beam therapy group. Finally, 22 single-arm studies included at least 50 patients and reported on the relevant outcomes.

Figure 1 – Study flow of selection (electronic databases)

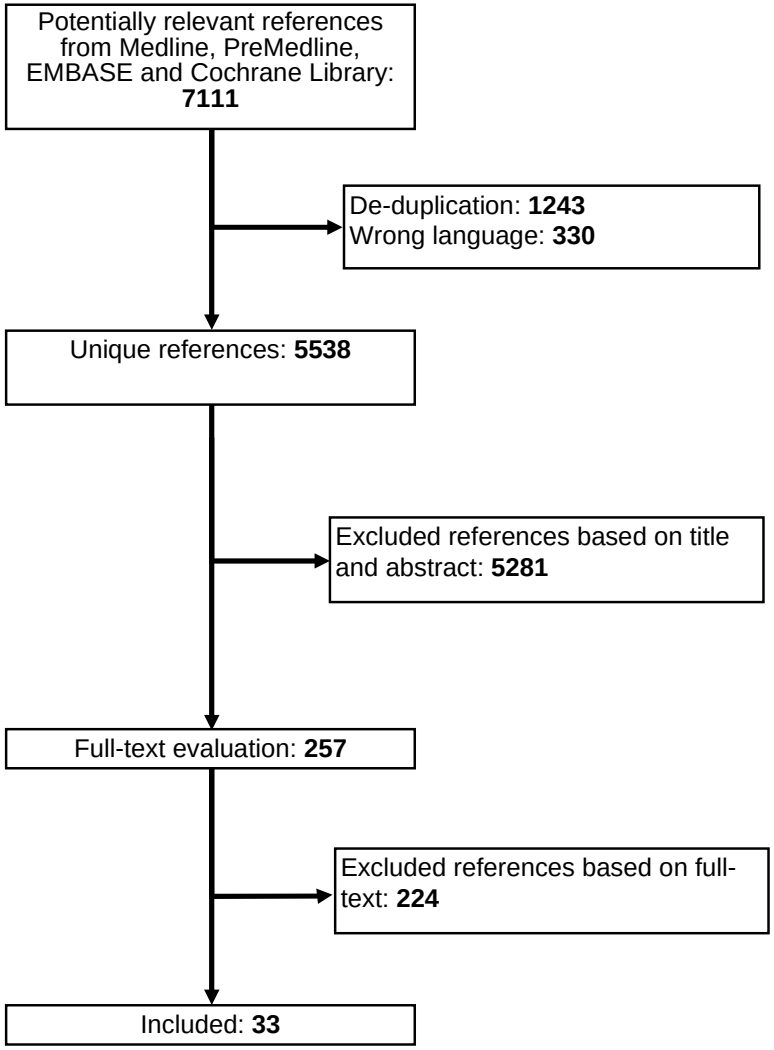

Table 1 – Overview of excluded papers based on full-text evaluation.

Author	Reference	Title	Reason for exclusion
Abei M	Radiation Oncology 2013 8(239):16	A phase I study on combined therapy with proton-beam radiotherapy and in situ tumor vaccination for locally advanced recurrent hepatocellular carcinoma	Sample size <50
Adeberg S	Radiat 2017 12(1):193	Treatment of meningioma and glioma with protons and carbon ions	Narrative review
Adeberg S	Radiother Oncol 2017 125(2):266-272	Sequential proton boost after standard chemoradiation for high-grade glioma	High-grade glioma
Adeberg S	Strahlenther Onkol 2016 192(11):770-779	Intensity-modulated proton therapy, volumetric-modulated arc therapy, and 3D conformal radiotherapy in anaplastic astrocytoma and glioblastoma : A dosimetric comparison	High-grade glioma
Ahmadi T	J Comput Assist Tomogr 1999 23(5):655-63	CT evaluation of hepatic injury following proton beam irradiation: appearance, enhancement, and 3D size reduction pattern	Sample size <50
Ahmadi T	Clin Radiol 1999 54(4):253-6	Preservation of hypervascularity in hepatocellular carcinoma after effective proton-beam radiotherapy—CT observation	No clinical results
Ahmed S.K	Semin. Radiat. Oncol. 2018 28(2):97-107	Protons vs Photons for Brain and Skull Base Tumors	Narrative review
Ahn PH	Cancer J 2014 20(6):421-6	The use of proton therapy in the treatment of head and neck cancers	Narrative review
Allen AM	Radiother Oncol 2012 103(1):8-11	An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee	Search not reported
Ask A	Acta Oncol. 2005 44(8):896-903	The potential of proton beam radiation therapy in gastrointestinal cancer	Narrative review
Barney CL	Neuro-oncol 2014 16(2):303-309	Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation	Sample size <50 for relevant histologies
Batista V	Radiat. Oncol. 2018 13(1):	Significance of intra-fractional motion for pancreatic patients treated with charged particles	Dosimetric study
Bjork-Eriksson T	Acta Oncologica 2005 44(8):884-9	The potential of proton beam radiation therapy in breast cancer	Narrative review

Blanchard P	Semin. Radiat. Oncol. 2018 28(1):53-63	Proton Therapy for Head and Neck Cancers	Only PubMed search
Blanchard P	Cancer Radiother 2017 21(6-7):515-520	Proton therapy for head and neck cancers	Narrative review
Blomquist E	Acta Oncologica 2005 44(8):862-70	The potential of proton beam radiation therapy in intracranial and ocular tumours	Narrative review
Boimel PJ	J 2017 8(4):665-674	Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma	Sample size <50
Brada M	J. Clin. Oncol. 2007 25(8):965-970	Proton therapy in clinical practice: Current clinical evidence	No quality appraisal
Bradley JA	Int J Radiat Oncol Biol Phys 2016 95(1):411-21	Initial Report of a Prospective Dosimetric and Clinical Feasibility Trial Demonstrates the Potential of Protons to Increase the Therapeutic Ratio in Breast Cancer Compared With Photons	All patients received PBT; sample size <50
Braunstein LZ	Semin Radiat Oncol 2018 28(2):138-149	Potential Morbidity Reduction With Proton Radiation Therapy for Breast Cancer	Narrative review
Brown AP	Int J Radiat Oncol Biol Phys 2013 86(2):277-84	Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma	No low-grade glioma
Bush D.A	Cancer J. 2007 13(2):114-118	A technique of partial breast irradiation utilizing proton beam radiotherapy: Comparison with conformal X-ray therapy	Planning study
Bush DA	Gastroenterology 2004 127(5 Suppl 1):S189-93	High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial	Sample size <50
Bush DA	Clin Breast Cancer 2011 11(4):241-5	Partial breast irradiation delivered with proton beam: results of a phase II trial	Same study as Bush 2014, fewer inclusions (earlier report)
Bush DA	Int J Radiat Oncol Biol Phys 2016 95(1):477-82	Randomized Clinical Trial Comparing Proton Beam Radiation Therapy with Transarterial Chemoembolization for Hepatocellular Carcinoma: Results of an Interim Analysis	RCT with wrong comparison, but <50 patients in proton group
Castro JR	Int J Radiat Oncol Biol Phys 1994 29(4):647-55	Experience in charged particle irradiation of tumors of the skull base: 1977-1992	No separate results for low-grade glioma or HNSCC
Chadha AS	International journal of radiation oncology. 2016 96(2 Supplement 1): E181-E182	Proton therapy outcomes for localized, unresectable hepatocellular carcinoma	Abstract

Chang JH	Radiother Oncol 2013 108(2):209-14	Phase II trial of proton beam accelerated partial breast irradiation in breast cancer	Sample size <50
Combs S.E	Curr. Treat. Options Neurol. 2017 19(3):	Does Proton Therapy Have a Future in CNS Tumors?	Narrative review
Combs SE	Acta Oncol 2010 49(7):1132-40	Heidelberg Ion Therapy Center (HIT): Initial clinical experience in the first 80 patients	No clinical results
Combs SE	Acta Oncol 2013 52(7):1504-9	Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base	No separate results for low-grade glioma
Combs SE	Radiother Oncol 2013 108(1):132-5	Comparison of carbon ion radiotherapy to photon radiation alone or in combination with temozolomide in patients with high-grade gliomas: explorative hypothesis-generating retrospective analysis	High-grade glioma
Combs SE	Progress in Neurological Surgery 2018 32(57-65	Proton and Carbon Ion Therapy of Intracranial Gliomas	Narrative review
Cuaron JJ	Int J Radiat Oncol Biol Phys 2015 92(2):284-91	Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer	Sample size <50
Dasu A	Phys. Med. 2018 52(81-85	Normal tissue sparing potential of scanned proton beams with and without respiratory gating for the treatment of internal mammary nodes in breast cancer radiotherapy	Dosimetric study
Davydova I.G	Med Radiol (Mosk) 1979 24(5):26-34	Brain bioelectrical activity during proton irradiation of the hypophysis at high doses	Russian
Dawson LA	Int J Radiat Oncol Biol Phys 2009 74(3):661-3	Protons or photons for hepatocellular carcinoma? Let's move forward together	Editorial
Douglas JG	Head Neck 2001 23(12):1037-42	Neutron radiotherapy for recurrent pleomorphic adenomas of major salivary glands	No proton therapy
Doyen J	Cancer Radiother 2016 20(6-7):513-8	Indications and results for protontherapy in cancer treatments	Only PubMed search
Doyen J	Cancer Treat. Rev. 2016 43(104-112	Proton beams in cancer treatments: Clinical outcomes and dosimetric comparisons with photon therapy	Only PubMed search
Drost L	Clin. Breast Cancer 2018	A Systematic Review of Heart Dose in Breast Radiotherapy	Review on dosimetric studies
Durante M	Nat. Rev. Clin. Oncol. 2017 14(8):483-495	Charged-particle therapy in cancer: Clinical uses and future perspectives	Narrative review

Eekers DBP	Radiother Oncol 2016 121(3):387-394	Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric in silico ROCOCO trial	Dosimetric study
English M	Lancet Oncol 2016 17(5):e174	Proton beam therapy for medulloblastoma	No low-grade glioma; letter
Feehan PE	International Journal of Radiation Oncology, Biology, Physics 1992 23(4):881-4	Recurrent locally advanced nasopharyngeal carcinoma treated with heavy charged particle irradiation	No proton therapy
Fitzek MM	J Neurosurg 1999 91(2):251-60	Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial	No low-grade glioma
Fitzek MM	Int J Radiat Oncol Biol Phys 2001 51(1):131-7	Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial	Sample size <50
Fitzek MM	Cancer 2002 94(10):2623-34	Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy	Sample size <50
Fuji H	Radiation Oncology 2013 8(255):01	Assessment of organ dose reduction and secondary cancer risk associated with the use of proton beam therapy and intensity modulated radiation therapy in treatment of neuroblastomas	Wrong histology
Fukumitsu N	Jpn J Radiol 2018 36(7):456-461	Simulation study of dosimetric effect in proton beam therapy using concomitant boost technique for unresectable pancreatic cancers	Dosimetric study
Fukumitsu N	Int J Radiat Oncol Biol Phys 2012 83(2):704-11	Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or recurrent nasal cavity and paranasal sinus carcinoma treated with proton beam	Sample size <50
Fukumitsu N	Mol 2017 7(1):56-60	Follow-up study of liver metastasis from breast cancer treated by proton beam therapy	Wrong indication
Giantsoudi D	Int J Radiat Oncol Biol Phys 2016 95(1):287-96	Incidence of CNS Injury for a Cohort of 111 Patients Treated With Proton Therapy for Medulloblastoma: LET and RBE Associations for Areas of Injury	Wrong histology
Granovetter M	Lancet Oncol 2016 17(2):e49	Proton radiotherapy for primary liver cancers	Commentary
Gridley D.S	Expert Rev. Neurother. 2010 10(2):319-330	Proton-beam therapy for tumors of the CNS	Narrative review

Grosshans DR	Neuro-oncol 2017 19(suppl_2):ii30-ii37	The role of image-guided intensity modulated proton therapy in glioma	Narrative review
Guenzi M	Frontiers in Oncology 2018 8(207):	Comparison of Local Recurrence Among Early Breast Cancer Patients Treated With Electron Intraoperative Radiotherapy vs Hypofractionated Photon Radiotherapy an Observational Study	No proton therapy
Gunn GB	Int J Radiat Oncol Biol Phys 2016 95(1):360-7	Clinical Outcomes and Patterns of Disease Recurrence After Intensity Modulated Proton Therapy for Oropharyngeal Squamous Carcinoma	Not recurrent H&N cancer
Habrand J.L	Cancer Radiother. 1999 3(6):480-488	Radiation therapy in locally aggressive intracranial tumours with photons and protons. Preliminary results of protocol 94-C1	Double
Habrand JL	Cancer Radiother 1999 3(6):480-8	Radiotherapy using a combination of photons and protons for locally aggressive intracranial tumors. Preliminary results of protocol CPO 94-C1	Sample size <50
Hashimoto T	Int J Radiat Oncol Biol Phys 2006 65(1):196-202	Repeated proton beam therapy for hepatocellular carcinoma	Sample size <50
Hata M	Cancer 2005 104(4):794-801	Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus	Sample size <50
Hata M	Strahlenther Onkol 2006 182(12):713-20	Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis	Sample size <50
Hata M	Cancer 2006 107(3):591-8	Proton beam therapy for hepatocellular carcinoma with limited treatment options	Sample size <50
Hata M	Int J Radiat Oncol Biol Phys 2007 69(3):805-12	Proton beam therapy for aged patients with hepatocellular carcinoma	Sample size <50
Hauswald H	Radiation Oncology 2012 7(189):09	First experiences in treatment of low-grade glioma grade I and II with proton therapy	Sample size <50
Hayashi Y	Head Neck 2016 38(8):1145-51	Retrograde intra-arterial chemotherapy and daily concurrent proton beam therapy for recurrent oral cavity squamous cell carcinoma: Analysis of therapeutic results in 46 cases	Sample size <50
Hayashi Y	Asia Pac J Clin Oncol 2017 13(5):e394-e401	Re-irradiation using proton beam therapy combined with weekly intra-arterial chemotherapy for recurrent oral cancer	Sample size <50

Hernandez M	Journal of Proton Therapy 2015 1(1):	A treatment planning comparison of volumetric modulated arc therapy and proton therapy for a sample of breast cancer patients treated with post-mastectomy radiotherapy	Dosimetric study
Hitchcock KE	World J Gastrointest Surg 2017 9(4):103-108	Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer	Sample size <50
Holliday EB	Int J Radiat Oncol Biol Phys 2014 89(2):292-302	Proton radiation therapy for head and neck cancer: a review of the clinical experience to date	Narrative review
Holm AIS	Acta Oncol 2017 56(6):826-831	Functional image-guided dose escalation in gliomas using of state-of-the-art photon vs. proton therapy	No clinical results
Hong TS	J Clin Oncol 2016 34(5):460-8	Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma	Sample size <50
Hong TS	Pract Radiat Oncol 2014 4(5):316-322	A prospective feasibility study of respiratory-gated proton beam therapy for liver tumors	Sample size <50
Hong TS	Int J Radiat Oncol Biol Phys 2014 89(4):830-8	A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma	Sample size <50
Hong TS	Int J Radiat Oncol Biol Phys 2011 79(1):151-7	Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head	Sample size <50
Houweling AC	Phys Med Biol 2017 62(8):3051-3064	Comparing the dosimetric impact of interfractional anatomical changes in photon, proton and carbon ion radiotherapy for pancreatic cancer patients	Dosimetric study
Hug E.B	Breast Care 2018 13(3):168-172	Proton Therapy for Primary Breast Cancer	Narrative review
Igaki H	Int J Clin Oncol 2018 23(3):423-433	A systematic review of publications on charged particle therapy for hepatocellular carcinoma	Only PubMed search
Ishikawa Y	Jpn. J. Clin. Radiol. 2013 58(10):1340-1346	Early experience of proton beam therapy combined with chemotherapy for locally advanced oropharyngeal cancer	Sample size <50, no recurrent HNSCC

Jensen AD	Int J Radiat Oncol Biol Phys 2018 101(4):761-762	Organ Preservation in Sinonasal Malignancies Through Particle Therapy	Letter
Jensen AD	Radiother Oncol 2011 101(3):383-7	Re-irradiation with scanned charged particle beams in recurrent tumours of the head and neck: acute toxicity and feasibility	Sample size <50
Jereczek-Fossa B.A	Head Neck 2006 28(8):750-760	Particle beam radiotherapy for head and neck tumors: Radiobiological basis and clinical experience	Narrative review
Jethwa K.R	Adv. Radiat. Oncol. 2018 3(3):314-321	Initial experience with intensity modulated proton therapy for intact, clinically localized pancreas cancer: Clinical implementation, dosimetric analysis, acute treatment-related adverse events, and patient-reported outcomes	Sample size <50
Kammerer E	Cancer Treatment Reviews 2018 63(19-27	Proton therapy for locally advanced breast cancer: A systematic review of the literature	Only PubMed search
Kanamoto M	Radiol Phys Technol 2016 9(2):233-9	Preliminary study of apparent diffusion coefficient assessment after ion beam therapy for hepatocellular carcinoma	Dosimetric study
Kanemoto A	Int. Cancer Conf. J. 2012 1(4):210-214	Proton beam therapy for liver metastasis from breast cancer: Five case reports and a review of the literature	Case reports
Kawashima M	J Clin Oncol 2005 23(9):1839-46	Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma	Sample size <50
Kim DY	Radiother Oncol 2017 122(1):122-129	Risk-adapted simultaneous integrated boost-proton beam therapy (SIB-PBT) for advanced hepatocellular carcinoma with tumour vascular thrombosis	Sample size <50
Kim J.K	Curr. Treat. Options Oncol. 2018 19(6):	Proton Therapy for Head and Neck Cancer	Narrative review
Kim JY	Acta Oncol 2015 54(10):1827-32	Normal liver sparing by proton beam therapy for hepatocellular carcinoma: Comparison with helical intensity modulated radiotherapy and volumetric modulated arc therapy	No clinical results
Kim T.H	Cancer Res. Treat. 2015 47(1):34-45	Phase I dose-escalation study of proton beam therapy for inoperable hepatocellular carcinoma	Sample size <50
Kim TH	Technol Cancer Res Treat 2018 17(1533033818783879):01	Effectiveness and Safety of Simultaneous Integrated Boost-Proton Beam Therapy for Localized Pancreatic Cancer	All patients received PBT; sample size <50

Kimura K	Hepatol 2017 47(13):1368-1374	Clinical results of proton beam therapy for hepatocellular carcinoma over 5 cm	Sample size <50
Kinj R	Cancer Radiother 2018 22(2):171-179	Re-irradiation of head and neck cancers: Target volumes, technical evolutions and prospects	Only PubMed search
Kjellberg RN	Neurochirurgie 1972 18(3):235-65	The Bragg Peak proton beam in stereotaxic neurosurgery	Narrative review
Komatsu S	Br J Surg 2011 98(4):558-64	Risk factors for survival and local recurrence after particle radiotherapy for single small hepatocellular carcinoma	No separate results for PBT
Komatsu S	J Gastroenterol 2011 46(7):913-20	The effectiveness of particle radiotherapy for hepatocellular carcinoma associated with inferior vena cava tumor thrombus	Sample size <50
Komatsu S	Surgery 2017 162(6):1241-1249	Particle radiotherapy, a novel external radiation therapy, versus liver resection for hepatocellular carcinoma accompanied with inferior vena cava tumor thrombus: A matched-pair analysis	Wrong comparator, sample size <50
Kozak KR	Int J Radiat Oncol Biol Phys 2006 66(3):691-8	Accelerated partial-breast irradiation using proton beams: initial clinical experience	Sample size <50
Lee SU	Strahlenther Onkol 2014 190(9):806-14	Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis	Sample size <50
Leeman JE	Lancet Oncol 2017 18(5):e254-e265	Proton therapy for head and neck cancer: expanding the therapeutic window	Narrative review
Leung HWC	Oncotarget 2017 8(43):75568-75576	Cost-utility of stereotactic radiation therapy versus proton beam therapy for inoperable advanced hepatocellular carcinoma	Used results of Kawashima 2005
Lewis G.D	Head Neck 2016 38(E1886-E1895	Intensity-modulated proton therapy for nasopharyngeal carcinoma: Decreased radiation dose to normal structures and encouraging clinical outcomes	Not recurrent H&N cancer
Li Q	J. Intervent. Radiol. 2009 18(4):278-280	Interventional chemoembolization combined with proton radiotherapy for the treatment of hepatocellular carcinoma accompanied with portal cancerous thrombus	Sample size <50

Lin LL	Acta Oncol 2015 54(7):1032-9	Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer	No clinical results
Lin R	Radiology 1999 213(2):489-94	Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy—dose-volume histogram analysis	Sample size <50
Lischalk J.W	J. Gastrointest. Oncol. 2017 8(2):279-292	Radiation therapy for hepatobiliary malignancies	Narrative review
Lukovic J	J. Radiat. Oncol. 2015 4(2):141-148	A systematic review on the role for reirradiation in locally recurrent rectal cancer	No quality appraisal
Lundkvist J	Acta Oncologica 2005 44(8):850-61	Proton therapy of cancer: potential clinical advantages and cost-effectiveness	Economic study
Lundkvist J	Radiother Oncol 2005 75(2):179-85	Economic evaluation of proton radiation therapy in the treatment of breast cancer	Economic study
MacDonald S.M	Cancer Invest. 2006 24(2):199-208	Proton beam radiation therapy	Narrative review
MacDonald SM	Cancer J 2007 13(2):84-6	Is it time to use protons for breast cancer?	Commentary
MacDonald SM	Int J Radiat Oncol Biol Phys 2013 86(3):484-90	Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial	Sample size <50
Mailhot Vega RB	Int J Radiat Oncol Biol Phys 2016 95(1):11-8	Establishing Cost-Effective Allocation of Proton Therapy for Breast Irradiation	Cost-effectiveness study
Maquilan G	Am J Clin Oncol 2014 37(5):438-43	Acute toxicity profile of patients with low-grade gliomas and meningiomas receiving proton therapy	Sample size <50
Matsumura A	Appl Radiat Isot 2009 67(7-8 Suppl):S12-4	Current practices and future directions of therapeutic strategy in glioblastoma: survival benefit and indication of BNCT	Wrong histology
Matsuzaki Y	J Gastroenterol Hepatol 1999 14(10):941-5	Powerful radiotherapy for hepatocellular carcinoma	Editorial
Matsuzaki Y	Gastroenterology 1994 106(4):1032-41	A new, effective, and safe therapeutic option using proton irradiation for hepatocellular carcinoma	Sample size <50
Matsuzaki Y	Intern Med 1995 34(4):302-4	New, effective treatment using proton irradiation for unresectable hepatocellular carcinoma	All patients received PBT; sample size <50
McDonald MW	Radiation Oncology 2016 11(32):27	Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus	No separate results for paranasal tumours

		cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy	
McKeever M.R	Chin. Clin. Oncol. 2016 5(4):	Reduced acute toxicity and improved efficacy from intensitymodulated proton therapy (IMPT) for the management of head and neck cancer	Narrative review
Mendenhall NP	Acta Oncol 2011 50(6):763-71	Proton therapy for head and neck cancer: rationale, potential indications, practical considerations, and current clinical evidence	Narrative review
Mihailidis DN	Int J Radiat Oncol Biol Phys 2014 88(3):754	Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. In regard to MacDonald et al	Letter
Milenic DE	Dalton trans. 2017 46(42):14591-14601	Comparative studies on the therapeutic benefit of targeted alpha-particle radiation therapy for the treatment of disseminated intraperitoneal disease	No proton therapy
Mishra M.V	Int. J. Radiat. Oncol. Biol. Phys. 2017 97(2):228-235	Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials	Search for ongoing trials
Miyawaki D	Int J Radiat Oncol Biol Phys 2009 75(2):378-84	Brain injury after proton therapy or carbon ion therapy for head-and-neck cancer and skull base tumors	Primary HNSCC
Mizuhata M	Cancers 2018 10(2):21	Respiratory-gated Proton Beam Therapy for Hepatocellular Carcinoma Adjacent to the Gastrointestinal Tract without Fiducial Markers	Sample size <50
Mizumoto M	Pract Radiat Oncol 2015 5(1):e9-16	Long-term survival after treatment of glioblastoma multiforme with hyperfractionated concomitant boost proton beam therapy	Wrong histology
Mizumoto M	J Neurooncol 2016 130(1):165-170	Proton beam therapy with concurrent chemotherapy for glioblastoma multiforme: comparison of nimustine hydrochloride and temozolomide	Wrong histology
Mizumoto M	Strahlenther Onkol 2013 189(8):656-63	Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy. Technical considerations based on experience at a single institution	Sample size <50
Monzul G.D	VOPR. ONKOL. 1990 36(4):427-433	Combined treatment of disseminated breast cancer with proton irradiation of the pituitary and zone gamma-ray teletherapy of the skeleton	Wrong indication

Morimoto K	Jpn. J. Clin. Oncol. 2014 44(5):428-434	Particle radiotherapy using protons or carbon ions for unresectable locally advanced head and neck cancers with skull base invasion	Not recurrent H&N cancer, no separate results for sinonasal tumours
Murray EM	Strahlentherapie und Onkologie 2005 181(2):77-81	Neutron versus photon radiotherapy for local control in inoperable breast cancer	No proton therapy
Mutter R.W	Pract. Radiat. Oncol. 2017 7(4):e243-e252	Initial clinical experience of postmastectomy intensity modulated proton therapy in patients with breast expanders with metallic ports	Sample size <50
Mutter RW	Pract Radiat Oncol 2017 7(4):e243-e252	Initial clinical experience of postmastectomy intensity modulated proton therapy in patients with breast expanders with metallic ports	Double
Mutter RW	Cancer research. Conference: 39th annual CTRC-AACR san 29ntonio breast cancer symposium. United states 2017 77(4 Supplement 1) (no pagination):	A randomized trial of 15 fraction vs 25 fraction pencil beam scanning proton radiotherapy after mastectomy in patients requiring regional nodal irradiation	Ongoing trial
Nakamura T	Jpn J Clin Oncol 2016 46(1):46-50	Preliminary results of proton beam therapy combined with weekly cisplatin intra-arterial infusion via a superficial temporal artery for treatment of maxillary sinus carcinoma	Sample size <50
Nakayama H	Int J Radiat Oncol Biol Phys 2011 80(4):992-5	Proton beam therapy for hepatocellular carcinoma located adjacent to the alimentary tract	Sample size <50
Nemoto K	J. JASTRO 2004 16(3):177-182	Proton beam therapy for large hepatocellular carcinoma	Japanese
Ng SP	Cancers 2018 10(3):16	Stereotactic Radiotherapy and Particle Therapy for Pancreatic Cancer	Narrative review
Nichols RC, Jr.	Acta Oncol 2013 52(3):498-505	Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity	Sample size <50
Niizawa G	J Gastroenterol 2005 40(3):283-90	Monitoring of hepatocellular carcinoma, following proton radiotherapy, with contrast-enhanced color Doppler ultrasonography	No clinical results
Nishimura H	Int J Radiat Oncol Biol Phys 2007 68(3):758-62	Proton-beam therapy for olfactory neuroblastoma	Wrong histology

Nishioka K	J Radiat Res (Tokyo) 2018 59(suppl_1):i63-i71	Prospective study to evaluate the safety of the world-first spot-scanning dedicated, small 360-degree gantry, synchrotron-based proton beam therapy system	Relevant tumour sites: sample size <50
Oden J	Acta Oncol 2017 56(11):1428-1436	The influence of breathing motion and a variable relative biological effectiveness in proton therapy of left-sided breast cancer	Treatment planning
Ohkubo J-I	Eur Arch Otorhinolaryngol 2016 273(12):4397-4402	Treatment outcome of ion beam therapy in eight patients with head and neck cancers	Primary HNSCC
Okano S	Jpn J Clin Oncol 2012 42(8):691-6	Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin in patients with T4b nasal and sinonasal malignancies	Sample size <50
Okubo H	Oto-Rhino-Laryngol. Tokyo 2013 56(SUPPL.1):118-122	Treatment of head and neck cancer by proton beam radiotherapy during the last 10 years at Tsukuba	Japanese
Okumura T	Jpn. J. Clin. Radiol. 1999 44(6):685-689	Treatment of hepatocellular carcinoma with proton radiotherapy	No full-text
Orlandi E	Oral Oncology 2016 60(146-56	Salivary Gland. Photon beam and particle radiotherapy: Present and future	Narrative review
Ovalle V	Cancers 2018 10(4): 111	Proton partial breast irradiation: Detailed description of acute clinico-radiologic effects	Less than 50 patients included in analysis
Patel SA	Semin Radiat Oncol 2016 26(3):220-5	Advancing Techniques of Radiation Therapy for Rectal Cancer	Narrative review
Rajan SS	J. Cancer Res. Ther. 2014 10(4):889-895	Clinical and cosmetic results of breast boost radiotherapy in early breast cancer: a randomized study between electron and photon	No proton therapy
Raldow A.C	Semin. Radiat. Oncol. 2018 28(2):125-130	Will There Be a Clinically Significant Role for Protons in Patients With Gastrointestinal Malignancies?	Narrative review
Ramaekers BLT	Cancer Treat Rev 2011 37(3):185-201	Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons	Only PubMed search
Ramaswamy V	Lancet Oncol 2016 17(5):e173-4	Proton beam therapy for medulloblastoma	No low-grade glioma; letter

Reiazi R	Internat. Jour. of Canc. Managt. 2015 8(6):	A literature survey on cost-effectiveness of proton beam therapy in the management of breast cancer patients	Review on cost-effectiveness
Rieken S	Radiation Oncology 2012 7(41):21	Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts	Sample size <50
Rieken S	Int J Radiat Oncol Biol Phys 2011 81(5):e793-801	Assessment of early toxicity and response in patients treated with proton and carbon ion therapy at the Heidelberg ion therapy center using the raster scanning technique	Only 4 patients treated with proton
Royce TJ	Int J Radiat Oncol Biol Phys 2016 96(2 Supplement 1):E70	Neuroendocrine function following proton therapy for low-grade gliomas: results from a prospective trial	Abstract
Rutz HP	Int J Radiat Oncol Biol Phys 2008 71(1):220-5	Postoperative spot-scanning proton radiation therapy for chordoma and chondrosarcoma in children and adolescents: initial experience at paul scherrer institute	Wrong histology
Saito Y	Hepatol. Res. 2014 44(4):403-409	Post-therapeutic needle biopsy in patients with hepatocellular carcinoma is a useful tool to evaluate response to proton irradiation	Wrong outcomes
Sakurai H	Journal of hepato-biliary-pancreatic sciences. Conference: joint congress of the 6th biennial congress of the 31apan-pacific hepato-pancreato-biliary association and the 29th meeting of 31apanese society of hepato-biliary-pancreatic surgery. Japan 2017 24(A15	Proton radiotherapy for liver cancer	Abstract
Santoni R	Int J Radiat Oncol Biol Phys 1998 41(1):59-68	Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull	Wrong histology
Sas-Korczynska B	Nowotwory 2017 67(3):157-161	The tolerance of proton radiotherapy – Preliminary results	Sample size <50
Sas-Korczyńska B	Nowotwory 2016 66(5):396-402	Proton radiotherapy for treating the most common carcinomas	Narrative review
Schaffer M	J. Photochem. Photobiol. B Biol. 2000 59(1-3):1-8	Preliminary results	Wrong intervention

Schwab FJ	Int J Radiat Oncol Biol Phys 2004 58(5):1641-2	A commentary on IMRT with photons and protons of breast cancer	Letter
Sethi RV	Int J Radiat Oncol Biol Phys 2014 88(3):655-63	Patterns of failure after proton therapy in medulloblastoma; linear energy transfer distributions and relative biological effectiveness associations for relapses	Wrong histology
Sherman JC	J Neurooncol 2016 126(1):157-64	Neurocognitive effects of proton radiation therapy in adults with low-grade glioma	Sample size <50
Shibata S	Cancers 2018 10(3):14	Proton Beam Therapy without Fiducial Markers Using Four-Dimensional CT Planning for Large Hepatocellular Carcinomas	Sample size <50
Shih HA	Cancer 2015 121(10):1712-9	Proton therapy for low-grade gliomas: Results from a prospective trial	Sample size <50
Shinoto M	Curr Oncol Rep 2016 18(3):17	Particle Radiation Therapy for Gastrointestinal Cancers	Narrative review
Sio TT	Phys Med 2016 32(2):331-42	Spot-scanned pancreatic stereotactic body proton therapy: A dosimetric feasibility and robustness study	Planning study
Skołyszewski J	Nowotwory 2007 57(4):370-375	Hadron and light ion radiotherapy: Results and perspectives	Narrative review
Slater JM	International Journal of Radiation Oncology, Biology, Physics 1992 22(2):311-9	Carcinoma of the tonsillar region: potential for use of proton beam therapy	Only PubMed search
Sorin Y	Liver Cancer 2018	Effectiveness of Particle Radiotherapy in Various Stages of Hepatocellular Carcinoma: A Pilot Study	No separate results for PBT
Stick LB	Int J Radiat Oncol Biol Phys 2017 97(4):754-761	Joint Estimation of Cardiac Toxicity and Recurrence Risks After Comprehensive Nodal Photon Versus Proton Therapy for Breast Cancer	No clinical study
Strom EA	Int J Radiat Oncol Biol Phys 2014 90(3):506-8	Initial clinical experience using protons for accelerated partial-breast irradiation: longer-term results	Editorial
Sugahara S	Int J Radiat Oncol Biol Phys 2010 76(2):460-6	Proton beam therapy for large hepatocellular carcinoma	Sample size <50
Sugahara S	Strahlenther Onkol 2009 185(12):782-8	Proton-beam therapy for hepatocellular carcinoma associated with portal vein tumor thrombosis	Sample size <50

Taddei PJ	Phys Med Biol 2010 55(23):7055-65	Risk of second malignant neoplasm following proton versus intensity-modulated photon radiotherapies for hepatocellular carcinoma	No clinical study
Takayama K	Jpn. J. Head Neck Cancer 2011 37(1):36-41	Initial experience of proton therapy combined with selective intra-arterial infusion chemotherapy for locally advanced tongue cancer	sample size <50
Tanaka N	Lancet 1992 340(8831):1358	Proton irradiation for hepatocellular carcinoma	Letter
Taunk NK	Expert Review of Anticancer Therapy 2016 16(3):347-58	External beam re-irradiation, combination chemoradiotherapy, and particle therapy for the treatment of recurrent glioblastoma	Narrative review
Terasawa T	Ann. Intern. Med. 2009 151(8):556-565	Systematic review: Charged-particle radiation therapy for cancer	Only PubMed search
Terashima K	Annals of oncology. Conference: 14th annual meeting of the japanese society of medical oncology. Japan 2016 27(vii42	Proton radiotherapy with concurrent chemotherapy for unresectable locally advanced pancreatic cancer	Abstract
Tian X	Mol. Clin. Oncol. 2018 8(1):15-21	The evolution of proton beam therapy: Current and future status (review)	Narrative review
Tommasino F	Physica Medica 2018 50(7-12	Impact of dose engine algorithm in pencil beam scanning proton therapy for breast cancer	Dosimetric study
Toyomasu Y	Int J Radiat Oncol Biol Phys 2018 101(5):1096-1103	Outcomes of Patients With Sinonasal Squamous Cell Carcinoma Treated With Particle Therapy Using Protons or Carbon Ions	Sample size <50
Truong MT	Head Neck 2009 31(10):1297-308	Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors	Sample size <50
Tsujii H	Int J Radiat Oncol Biol Phys 1993 25(1):49-60	Clinical results of fractionated proton therapy	Relevant tumour sites: sample size <50
van de Water T.A	Oncologist 2011 16(3):366-377	The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: A systematic review of literature	Review on dosimetric studies
Verma V	J. Gastrointest. Oncol. 2016 7(4):644-664	Clinical outcomes and toxicities of proton radiotherapy for gastrointestinal neoplasms: A systematic review	No quality appraisal

Verma V	Cancer 2016 122(10):1483-501	A systematic review of the cost and cost-effectiveness studies of proton radiotherapy	SR of cost studies
Verma V	Radiother Oncol 2017 125(1):21-30	Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation	Only PubMed search
Verma V	Journal of the National Cancer Institute 2018 110(4):01	Quality of Life and Patient-Reported Outcomes Following Proton Radiation Therapy: A Systematic Review	Only PubMed search
Verma V	Clin Breast Cancer 2016 16(3):145-54	Clinical Outcomes and Toxicity of Proton Radiotherapy for Breast Cancer	No quality appraisal
Vítek P	Onkol. 2015 9(4):175-177	Proton radiotherapy of colorectal cancer-options and expectations	Wrong language
Wang D	Med. Devices Evid. Res. 2015 8(439-446	A critical appraisal of the clinical utility of proton therapy in oncology	Narrative review
Wilkinson B	Int J Radiat Oncol Biol Phys 2016 96(2S):E135	Low Levels of Acute Toxicity Associated With Proton Therapy for Low-Grade Glioma: A Proton Collaborative Group Study	Abstract
Wolden SL	Int J Radiat Oncol Biol Phys 2013 87(2):231-2	Protons for craniospinal radiation: are clinical data important?	Commentary
Woodhouse KD	Int J Radiat Oncol Biol 2016 96(2 Supplement 1):E208-E209	Acute toxicity of proton versus photon adjuvant chemoradiation in the treatment of pancreatic cancer: a cohort study	Abstract
Yamazaki H	Radiother Oncol 2016 118(2):420	Superiority of charged particle therapy in treatment of hepatocellular carcinoma (Regarding Qi W.X. et al. charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis)	Letter
Yamazaki H	Strahlenther Onkol 2017 193(7):525-533	Reirradiation for recurrent head and neck cancers using charged particle or photon radiotherapy	No separate results for PBT
Yamazaki H	Anticancer Res 2016 36(10):5507-5514	Comparison of Re-irradiation Outcomes for Charged Particle Radiotherapy and Robotic Stereotactic Radiotherapy Using CyberKnife for Recurrent Head and Neck Cancers: A Multi-institutional Matched-cohort Analysis	Unclear how many patients received proton therapy; no separate results for proton therapy

Yeung R	Pract Radiat Oncol 2018 8(4):287-293	Chest wall toxicity after hypofractionated proton beam therapy for liver malignancies	Sample size <50
Yeung RH	Expert Rev Anticancer Ther 2017 17(10):911-924	Proton beam therapy for hepatocellular carcinoma	Narrative review
Zacharatou Jarlskog C	Int J Radiat Oncol Biol Phys 2008 72(1):228-35	Risk of developing second cancer from neutron dose in proton therapy as function of field characteristics, organ, and patient age	No clinical study
Zenda S	Int J Radiat Oncol Biol Phys 2011 81(1):135-9	Proton beam therapy as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study	Wrong histology
Zenda S	Int J Radiat Oncol Biol Phys 2011 81(5):1473-8	Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses	Sample size <50
Zenda S	Jpn. J. Head Neck Cancer 2013 39(4):402-404	Proton beam therapy for nasal cavity and/or paranasal malignancies	Japanese
	Https://clinicaltrials.gov/show/nct01854554 2013	Glioblastoma Multiforme (GBM) Proton vs. Intensity Modulated Radiotherapy (IMRT)	Wrong histology
	Https://clinicaltrials.gov/show/nct02179086 2014	Dose-Escalated Photon IMRT or Proton Beam Radiation Therapy Versus Standard-Dose Radiation Therapy and Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma	Wrong histology
	Oncology 2015 29(4 Suppl 1):21	(P034) Proton Therapy (PT) Large-Volume Re-Irradiation for Recurrent Glioma: Overall Survival (OS) and Toxicity Outcomes	Abstract
	Oncology 2015 29(4 Suppl 1):21	(P022) proton therapy on an incline beam line: acute toxicity outcomes in locally advanced breast cancer patients	Abstract
	Https://clinicaltrials.gov/show/nct02603341 2015	Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: a Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial	Ongoing trial
	Https://clinicaltrials.gov/show/nct03270072 2017	The Differential Impact of Proton Beam Irradiation Versus Conventional Radiation on Organs-at-risk in Stage II-III Breast Cancer Patients	Ongoing trial

	Https://clinicaltrials.gov/show/nct00857805 2009	Transarterial Chemoembolization Versus Proton Beam Radiotherapy for the Treatment of Hepatocellular Carcinoma	Ongoing trial
	Https://clinicaltrials.gov/show/nct01141478 2010	Proton Beam Radiotherapy Plus Sorafenib Versus Sorafenib for Patients With Hepatocellular Carcinoma Exceeding San Francisco Criteria	Ongoing trial
	Https://clinicaltrials.gov/show/nct02640924 2015	Proton Radiotherapy Versus Radiofrequency Ablation for Patients With Medium or Large Hepatocellular Carcinoma	Ongoing trial
	Https://clinicaltrials.gov/show/nct03186898 2017	Radiation Therapy With Protons or Photons in Treating Patients With Liver Cancer	Ongoing trial
	Https://clinicaltrials.gov/show/nct03180502 2017	Proton Beam or Intensity-Modulated Radiation Therapy in Preserving Brain Function in Patients With IDH Mutant Grade II or III Glioma	Ongoing trial

Table 2 – Overview of excluded HTA reports based on full-text evaluation.

Organisation	Title	Reason for exclusion
KCE report 235	Hadron therapy in children: an update of the scientific evidence for 15 paediatric cancers	Focus on children
HealthPACT	Proton and heavy ion therapy: an overview	No explicit search strategy
China National Health Development Research Centre 2017	Rapid health technology assessment on proton and heavy ion therapy in China	PowerPoint presentation
UnitedHealthcare 2018	Proton Beam Radiation Therapy	No explicit search strategy

Table 3 – Overview of excluded references based on full-text evaluation.

Author	Reference	Title	Reason for exclusion
AHRQ 2009	Technical Brief No. 1. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA-290-07-10055.) Rockville, MD: Agency for Healthcare Research and Quality	Particle Beam Radiation Therapies for Cancer	Medline search only
ASERNIP-S 2007		Horizon Scanning Report. Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures	No formal quality appraisal
Berman AT	Int J Particle Ther 2014;1:2–13	Proton reirradiation of recurrent rectal cancer: dosimetric comparison, toxicities, and preliminary outcomes	Sample size <50
Buckner JC	N Engl J Med. 2016;374(14):1344–55	Radiation plus Procarbazine, CCNU, and Vincristine in low-grade Glioma	No proton therapy
Demizu Y	Int J Radiat Oncol Biol Phys 2009;75:1487–92	Analysis of vision loss caused by radiation-induced optic neuropathy after particle therapy for head- and-neck and skull-base tumors adjacent to optic nerves	Not recurrent HNSCC
Frank S	Med Phys 2015;42:3457	SU-E- T-529: Is MFO-IMPT robust enough for the treatment of head and neck tumors? A 2-year outcome analysis following proton therapy on the first 50 Oropharynx patients at the MD Anderson Cancer Center	Abstract
Frank S	Int J Radiat Oncol Biol Phys 2014;89:846–53	Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice	Not recurrent HNSCC
Hong TS	Int J Radiat Oncol Biol Phys 2009;75:S166	Pilot study of respiratory gated proton beam therapy for liver tumors	Abstract
Iftekaruddin Z	Presented at the Particle Therapy Co-Operative Group North America 2nd Annual Meeting, 22 May 2015, San Diego, California. Available at: http://www.grupio.com/events_2/index.php?event_id1⁄411080	Acute toxicity out- comes in breast cancer patients treated with adjuvant proton therapy	Abstract

Kim T	Presented at PTCOG 51, available at http://ptcog.web.psi.ch/archive_talks.html	Clinical applications and preliminary results of proton beam therapy (PBT) for hapatocellular carcinoma in NCC	Abstract
Laack NN	Int J Radiat Oncol Biol Phys. 2005;63(4): 1175–83	Cognitive function after radiotherapy for supratentorial low-grade glioma: a north central cancer treatment group prospective study	No proton therapy
Lee J	Presented at PTCOG 46, WPTC, China, avalaible at http://ptcog.web.psi.ch/ptcog46_talks.html	Proton therapy for hepatocellular carcinoma	Abstract
Sachsman S	Int. J. Part. Ther. 2014, 1, 692–701	Proton Therapy and Concomitant Capecitabine for Non-Metastatic Unresectable Pancreatic Adenocarcinoma	Sample size <50
Sckolnik S	Presented at the Particle Therapy Co-Operative Group North America 2nd Annual Meeting, 22 May 2015, San Diego, California. Available at: http://www.grupio.com/events_2/index.php?event_id1⁄41 1080	Intensity modulated proton therapy for accelerated partial breast irradiation	Abstract
Slater JD	Int J Radiat Oncol Biol Phys 2005;62:494-500	Proton radiation for treatment of cancer of the oropharynx: Early experience at Loma Linda University Medical Center using a concomitant boost technique	Not recurrent HNSCC
Takagi M	Radiother Oncol 113:364-370, 2014	Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck	Sample size <50 for proton treatment
Tokuuye K	Strahlenther Onkol 2004;180:96-101	Proton therapy for head and neck malignancies at Tsukuba	Only 1 patient with recurrent HNSCC
Tokuuye K	Int J Radiat Oncol Biol Phys 2003; 383	Clinical results of proton radiotherapy for hepatocellular carcinoma	Abstract

3. QUALITY APPRAISAL

3.1. HTA reports and systematic reviews

3.1.1. CADTH 2017

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☒ Yes ☐ NO
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☒ review question(s) ☒ a search strategy ☒ inclusion/exclusion criteria ☒ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☒ a meta-analysis/synthesis plan, if appropriate, and ☒ a plan for investigating causes of heterogeneity ☒ justification for any deviations from the protocol	☒ Yes ☐ Partial Yes ☐ No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ Explanation for including only RCTs ☐ OR Explanation for including only NRSI ☒ OR Explanation for including both RCTs and NRSI		☒ Yes, but only HTA and SRs included ☐ No
4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key word and/or search strategy ☒ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☒ searched trial/study registries ☒ included/consulted content experts in the field	☒ Yes ☐ Partial Yes ☐ No

☒ where relevant, searched for grey literature
☒ conducted search within 24 months of completion of the review

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☒ Yes
☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☒ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes
- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

☒ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☒ described populations
- ☒ described interventions
- ☒ described comparators
- ☒ described outcomes
- ☒ described research design

For Yes, should also have ALL the following:
- ☒ described population in detail
- ☒ described intervention in detail (including doses where relevant)
- ☒ described comparator in detail (including doses where relevant)
- ☒ described study's setting
- ☒ timeframe for follow-up

☒ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, and

For Yes, must also have assessed RoB from:
- ☐ allocation sequence that was not truly random, and
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No

☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)		☒ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☒ Includes only RCTs Includes only SRs and HTAs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies	☒ Yes ☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☒ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☒ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes: ☐ included only low risk of bias RCTs	☐ Yes

☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒ Yes , contains SRs and HTAs ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒ Yes ☐ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☒ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☒ No

3.1.2. Dionisi F 2014

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☒ Yes (see supplementary appendix) ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:

The authors state that they had a written protocol or guide that included ALL the following:

- ☒ review question(s)
- ☒ a search strategy
- ☒ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:

As for partial yes, plus the protocol should be registered and should also have specified:

- ☐ a meta-analysis/synthesis plan, if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☐ Yes
- ☐ Partial Yes
- ☒ No: no formal RoB assessment

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☒ OR Explanation for including both RCTs and NRSI

- ☒ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

- ☒ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☒ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☒ No: no justified language restriction

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include

- ☒ Yes
- ☐ No

☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

☐ at least two reviewers achieved consensus on which data to extract from included studies
☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☒ No, at least not reported as such

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes

☒ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☒ Partial Yes: only justification for some papers
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

☒ described populations
☒ described interventions
☒ described comparators
☒ described outcomes
☒ described research design

For Yes, should also have ALL the following:

☒ described population in detail
☒ described intervention in detail (including doses where relevant)
☒ described comparator in detail (including doses where relevant)
☒ described study's setting
☐ timeframe for follow-up

☐ Yes
☒ Partial Yes: no timeframe for follow-up
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

☐ unconcealed allocation, and
☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)

For Yes, must also have assessed RoB from:

☐ allocation sequence that was not truly random, and
☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☒ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- ☐ from confounding, and
- ☐ from selection bias

For Yes, must also have assessed RoB:

- ☐ methods used to ascertain exposures and outcomes, and
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ☐ Yes
- ☐ Partial Yes
- ☒ No: only design assessed
- ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies

- ☐ Yes
- ☒ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
- ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- ☐ AND investigated the causes of any heterogeneity

- ☐ Yes
- ☐ No
- ☒ No meta-analysis conducted

For NRSI

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
- ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
- ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
- ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

- ☐ Yes
- ☐ No
- ☒ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒ Yes ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☒ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☒ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☒ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒ Yes ☐ No

3.1.3. ICER 2014

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☒ Population
- ☒ Intervention
- ☒ Comparator group
- ☒ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

- ☒ Yes
- ☐ NO

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:

The authors state that they had a written protocol or guide that included ALL the following:
- ☒ review question(s)
- ☒ a search strategy
- ☒ inclusion/exclusion criteria
- ☒ a risk of bias assessment

For Yes:

As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☐ Yes
- ☒ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☒ OR Explanation for including both RCTs and NRSI

- ☒ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☒ No, focus on English articles without justification

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☐ Yes
- ☒ No, not reported

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- ☐ Yes
- ☒ No, not reported

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

- ☐ Yes
- ☐ Partial Yes
- ☒ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- ☒ described populations
- ☒ described interventions
- ☒ described comparators
- ☒ described outcomes
- ☒ described research design

For Yes, should also have ALL the following:

- ☒ described population in detail
- ☒ described intervention in detail (including doses where relevant)
- ☒ described comparator in detail (including doses where relevant)
- ☒ described study's setting
- ☒ timeframe for follow-up

- ☒ Yes
- ☐ Partial Yes
- ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- ☐ unconcealed allocation, and
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)

For Yes, must also have assessed RoB from:

- ☐ allocation sequence that was not truly random, and
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ☐ Yes
- ☐ Partial Yes
- ☐ No
- ☒ Includes only NRSI: for us relevant studies

NRSI For Partial Yes, must have assessed RoB: ☒ from confounding, and ☒ from selection bias	For Yes, must also have assessed RoB: ☒ methods used to ascertain exposures and outcomes, and ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs
10. Did the review authors report on the sources of funding for the studies included in the review?		
For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies		☐ Yes ☒ No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		
RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity		☐ Yes ☐ No ☒ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review		☐ Yes ☐ No ☒ No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.		☐ Yes ☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?		

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☒ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☒ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☒ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☒ No

3.1.4. INESSS 2017

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- ☐ Population
- ☒ Intervention
- ☒ Comparator group
- ☒ Outcome

Optional (recommended)

- ☐ Timeframe for follow-up

☐ Yes
☒ NO

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:

For Yes:

The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan,if appropriate, and ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☒ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following: ☐ Explanation for including only RCTs ☐ OR Explanation for including only NRSI ☐ OR Explanation for including both RCTs and NRSI	☐ Yes ☒ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key word and/or search strategy ☐ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☐ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☐ Partial Yes ☒ No: no justification for restrictions

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☐ Yes ☒ No: not reported

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☐ Yes ☒ No: not reported

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes	For Yes, must also have:

☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☒ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research design	For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up	☒ Yes ☐ Partial Yes ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes, ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies	☐ Yes ☒ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☒ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☒ No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒ Yes ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☒ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No

☒ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☒ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒ Yes ☐ No

3.1.5. KCE 2007

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☒ Yes ☐ NO, no clear definition of P

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan,if appropriate, and ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☒ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?	
For Yes, the review should satisfy ONE of the following: ☐ Explanation for including only RCTs ☐ OR Explanation for including only NRSI ☐ OR Explanation for including both RCTs and NRSI	☒ Yes ☐ No

4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question)	For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies	☒ Yes ☐ Partial Yes

☒ provided key word and/or search strategy ☒ justified publication restrictions (e.g. language)	☒ searched trial/study registries ☒ included/consulted content experts in the field ☒ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review	☐ No
5. Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		☐ Yes ☒ No, not reported
6. Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.		☐ Yes ☒ No, not reported
7. Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☒ No
8. Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☐ described populations ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research design	For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☒ Yes ☐ Partial Yes ☐ No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and	☒ Yes

☒ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☒ from confounding, and ☒ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies

☐ Yes
☒ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

☐ The authors justified combining the data in a meta-analysis
☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☒ No meta-analysis conducted

For NRSI

For Yes:

☐ The authors justified combining the data in a meta-analysis
☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☒ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒ Yes ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☒ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☒ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☒ No

3.1.6. Lodge M 2007

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☐ Population ☒ Intervention ☐ Comparator group ☐ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☐ Yes ☒ NO

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☒ a search strategy ☒ inclusion/exclusion criteria ☒ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, and ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☒ No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ Explanation for including only RCTs ☐ OR Explanation for including only NRSI ☒ OR Explanation for including both RCTs and NRSI		☒ Yes ☐ No
4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key word and/or search strategy ☒ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☐ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☒ included/consulted content experts in the field ☒ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review	☐ Yes ☒ Partial Yes ☐ No
5. Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		☒ Yes ☐ No
6. Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☒ at least two reviewers achieved consensus on which data to extract from included studies		☒ Yes ☐ No

☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes

☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☒ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

☒ described populations
☒ described interventions
☒ described comparators
☒ described outcomes
☒ described research design

For Yes, should also have ALL the following:

☐ described population in detail
☐ described intervention in detail (including doses where relevant)
☐ described comparator in detail (including doses where relevant)
☐ described study's setting
☐ timeframe for follow-up

☐ Yes
☒ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

☐ unconcealed allocation, and
☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)

For Yes, must also have assessed RoB from:

☐ allocation sequence that was not truly random, and
☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☒ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

☒ from confounding, and
☒ from selection bias

For Yes, must also have assessed RoB:

☒ methods used to ascertain exposures and outcomes, and
☒ selection of the reported result from among multiple measurements or analyses of a specified outcome

☒ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☐ Yes

☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information also qualifies	☒ No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☒ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☒ No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒ Yes ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☒ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☒ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒ Yes ☐ No

3.1.7. Olsen DR 2007

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☒ Population ☒ Intervention ☐ Comparator group ☒ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☐ Yes ☒ NO: comparator not stated
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan,if appropriate, and ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☒ No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ Explanation for including only RCTs ☐ OR Explanation for including only NRSI		☐ Yes ☒ No

☐ OR Explanation for including both RCTs and NRSI

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☒ No: no justified restrictions (not stated)

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☒ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- ☐ Yes
- ☒ No: data extraction not mentioned explicitly

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes
- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

- ☐ Yes
- ☐ Partial Yes
- ☒ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☒ described populations
- ☒ described interventions
- ☒ described comparators
- ☒ described outcomes
- ☒ described research design

For Yes, should also have ALL the following:
- ☐ described population in detail
- ☒ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)

- ☐ Yes
- ☒ Partial Yes
- ☐ No

	☐ described study's setting ☐ timeframe for follow-up	
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☒ No: No RoB for study on HCC ☐ Includes only RCTs
10. Did the review authors report on the sources of funding for the studies included in the review?		
For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies		☐ Yes ☒ No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		
RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity		☐ Yes ☐ No ☒ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available		☐ Yes ☐ No ☒ No meta-analysis conducted

☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒ Yes ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☒ There was no significant heterogeneity in the results: *only 1 study ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒ Yes ☐ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☒ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☒ No

3.1.8. Patel SH 2014

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☒ Population
- ☒ Intervention
- ☒ Comparator group
- ☒ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

- ☒ Yes
- ☐ NO

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:

The authors state that they had a written protocol or guide that included ALL the following:
- ☒ review question(s)
- ☒ a search strategy
- ☒ inclusion/exclusion criteria
- ☒ a risk of bias assessment

For Yes:

As for partial yes, plus the protocol should be registered and should also have specified:
- ☒ a meta-analysis/synthesis plan, if appropriate, and
- ☒ a plan for investigating causes of heterogeneity
- ☒ justification for any deviations from the protocol

- ☒ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☒ OR Explanation for including both RCTs and NRSI

- ☒ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☒ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☒ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☒ Yes ☐ No
6. Did the review authors perform data extraction in duplicate?	
For Yes, either ONE of the following: ☒ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒ Yes ☐ No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	
For Partial Yes ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☒ No
8. Did the review authors describe the included studies in adequate detail?	
For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research design For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up	☒ Yes ☐ Partial Yes ☐ No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality) For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☒ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☒ from confounding, and For Yes, must also have assessed RoB: ☒ methods used to ascertain exposures and outcomes, and	☒ Yes ☐ Partial Yes

☒ from selection bias	☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☒ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information also qualifies

☒ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

☐ The authors justified combining the data in a meta-analysis
☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI

For Yes:

☒ The authors justified combining the data in a meta-analysis
☒ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
☒ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☒ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

☐ included only low risk of bias RCTs
☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☒ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

☐ included only low risk of bias RCTs
☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☒ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒ Yes ☐ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☒ Yes ☐ No ☐ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒ Yes ☐ No

3.1.9. Qi W-X 2015

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☐ Population ☐ Intervention ☐ Comparator group ☐ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☒ Yes ☐ NO
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☒ review question(s) ☒ a search strategy ☒ inclusion/exclusion criteria	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☒ a meta-analysis/synthesis plan, if appropriate, and ☒ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☒ Partial Yes ☐ No

☒ a risk of bias assessment

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☒ OR Explanation for including both RCTs and NRSI

- ☒ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☒ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

- ☒ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☒ conducted search within 24 months of completion of the review

- ☐ Yes
- ☒ Partial Yes
- ☐ No

Some of "Yes"-criteria fulfilled but not all of those mentioned explicitly

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☒ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☒ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- ☒ Yes
- ☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

- ☐ Yes
- ☐ Partial Yes
- ☒ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research design	For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up	☒ Yes ☐ Partial Yes ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☒ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☒ from confounding, and ☒ from selection bias	For Yes, must also have assessed RoB: ☒ methods used to ascertain exposures and outcomes, and ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies	☐ Yes ☒ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☐ No meta-analysis conducted
For NRSI For Yes:	

☒ The authors justified combining the data in a meta-analysis ☒ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☒ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☒ No: comparative meta-analysis without taking into account differences in baseline risk ☐ No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☒ No, There was consideration of bias but not in the detail required here ☐ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒ Yes, to a limited extent ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒ Yes ☐ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☒ Yes ☐ No ☐ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒ Yes ☐ No

3.1.10. QUERI 2015

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

- ☒ Yes
- ☐ NO

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:

The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:

As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan,if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☐ Yes
- ☐ Partial Yes
- ☒ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☐ OR Explanation for including both RCTs and NRSI

- ☐ Yes
- ☒ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☒ searched the reference lists / bibliographies of included studies
- ☒ searched trial/study registries
- ☒ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☒ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☒ No: no justification for only English studies

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☒ Yes ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒ Yes ☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☒ Yes ☐ Partial Yes ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research design	For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up	☒ Yes ☐ Partial Yes ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI

NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes, AMSTAR, RoB tool ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies	☐ Yes ☒ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☒ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☒ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☒ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:	☒ Yes

☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☒ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☒ No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☒ No

3.1.11. RIHTA

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☒ Yes ☐ NO
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:	For Yes: As for partial yes, plus the protocol should be registered and should also have specified:	

☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	☐ a meta-analysis/synthesis plan,if appropriate, and ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☒ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☒ OR Explanation for including both RCTs and NRSI

☒ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):	For Yes, should also have (all the following):	
☒ searched at least 2 databases (relevant to research question) ☒ provided key word and/or search strategy ☒ justified publication restrictions (e.g. language)	☐ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☒ Partial Yes ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☒ Yes
☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☒ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes	For Yes, must also have:	
	☐ Justified the exclusion from the review of each potentially relevant study	☒ Yes ☐ Partial Yes

☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review		☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following): ☐ described populations ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research design	For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐ Yes ☐ Partial Yes ☒ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes, AMSTAR for SR ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies	☐ Yes ☒ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☒ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☒ No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☒ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ Yes ☒ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☒ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No

☒ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

☐ The authors reported no competing interests OR

☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes

☒ No

3.2. Comparative studies

	Acharya S 2018	Bronk JK 2018	Galland-Girodet S 2014	Kahn J 2011	Maemura K 2017	Otsuka M 2003
Random sequence generation (selection bias)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Allocation concealment (selection bias)	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Blinding of participants and personnel (performance bias)	High risk of bias	High risk of bias	Unclear risk of bias	High risk of bias	Unclear risk of bias	High risk of bias
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Incomplete outcome data (attrition bias)	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias
Selective reporting (reporting bias)	Low risk of bias	Low risk of bias	High risk of bias	High risk of bias	Low risk of bias	High risk of bias
Concurrency of the intervention and comparator group	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Comparability of the intervention and comparator group	Low risk of bias	High risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias
Other bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

3.3. Single-arm studies

	Bush DA 2011	Bush DA 2014	Chiba T 2005	Dagan R 2016	Fukuda K 2017	Fukumitsu N 2009
Adequate definition of the disease	Yes	Yes	Yes	Yes	Yes	Yes
Clear description of baseline characteristics	Yes	Yes	Yes	Yes	Yes	Yes
Inclusion of a representative cohort	Unclear	Unclear	Unclear	Unclear	No	Unclear
Adequate diagnosis of the disease using a valid method	Yes	Yes	Yes	Yes	Yes	Yes
Standardised collection of the outcome data	Yes	Yes	Yes	Yes	Yes	Yes
Objective measurement of the outcomes	Yes	Unclear	Yes	Yes	Yes	Yes

	Kawashima M 2011	Kim TH 2018	Komatsu S 2011	Matsuzaki Y 1998	McDonald MW 2016	Mizumoto M 2008
Adequate definition of the disease	Yes	Yes	Yes	Yes	Yes	Yes
Clear description of baseline characteristics	Yes	Yes	Yes	No	Yes	Yes
Inclusion of a representative cohort	Yes	Unclear	Yes	Unclear	Unclear	Yes
Adequate diagnosis of the disease using a valid method	Yes	Yes	Yes	Yes	Yes	Yes
Standardised collection of the outcome data	Yes	Yes	Yes	Unclear	Yes	Yes
Objective measurement of the outcomes	Yes	Yes	Yes	Unclear	Yes	Yes

	Mizumoto M 2011	Mizumoto M 2012	Nakayama H 2009	Oshiro Y 2017	Phan J 2016	Romesser PB 2016
Adequate definition of the disease	Yes	Yes	Yes	Unclear	Yes	Yes
Clear description of baseline characteristics	Yes	Yes	Yes	Yes	Yes	Yes
Inclusion of a representative cohort	Unclear	Unclear	Yes	Yes	Yes	Yes

Adequate diagnosis of the disease using a valid method	Yes	Yes	Yes	Yes	Yes	Yes
Standardised collection of the outcome data	Unclear	Unclear	Yes	Yes	Yes	Yes
Objective measurement of the outcomes	Unclear	Unclear	Yes	Yes	Yes	Yes

	Russo AL 2016	Takatori K 2014	Terashima K 2012	Verma V 2017	Yu JI 2018	Zenda S 2015
Adequate definition of the disease	Yes	Yes	Yes	Yes	Yes	Yes
Clear description of baseline characteristics	Yes	Yes	Yes	Yes	Yes	Yes
Inclusion of a representative cohort	Unclear	Yes	Unclear	Yes	Yes	Yes
Adequate diagnosis of the disease using a valid method	Yes	Yes	Yes	Yes	Yes	Yes
Standardised collection of the outcome data	Yes	Yes	Yes	Yes	Yes	Yes
Objective measurement of the outcomes	Yes	Yes	Yes	Yes	Yes	Yes

4. EVIDENCE TABLES

4.1. HTA reports and systematic reviews

CADTH 2017	
Methods	
• **Design**	HTA report
• **Source of funding and competing interest**	CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec No conflicts to declare
• **Search date**	January 2007 - June 2017
• **Searched databases**	MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment database, PubMed
• **Included study designs**	Systematic reviews with or without meta-analyses or network meta-analyses or in HTAs, of randomized controlled studies and/or non-randomized controlled studies
• **Number of included studies**	N=9 systematic reviews, of which 3 relevant for the present review: ICER 2014, Peterson 2015, Verma 2016
• **Statistical analysis**	Qualitative analysis
Patient characteristics	
• **Eligibility criteria**	Adults and children, including infants, diagnosed with any non-skin malignancies
• **Exclusion criteria**	SRs were excluded if they did not meet all of the inclusion criteria. Reviews that were not SRs (i.e. narrative reviews or not fully systematic) or reviews that met all criteria for SRs, but did not conduct a quality assessment of the included primary studies were excluded if they had relevant outcomes or subgroups, or included primary studies that were present in any of the other SRs included in this overview. SRs that completely or partially overlapped in their included primary studies on specific cancer types and benefits or harms outcomes were not excluded based on the overlap
• **Patient & disease characteristics**	Peterson 2015: 98 adults with stage I breast cancer from a prospective nonrandomized study Peterson 2015, ICER 2014: 32 children and adults with intramedullary spinal cord glioma from a retrospective cohort study ICER 2014: 75 adults with head and neck cancer or skull-base tumours from a prospective nonrandomized study Verma 2016, ICER 2014: 343 adults with liver cancer from a retrospective study Peterson 2015, ICER 2014: 8 adults with recurrent liver cancer from a retrospective cohort study
Interventions	
• **Intervention group**	Proton beam therapy (PBT) in any form, alone or in combination with one or more concurrent or neoadjuvant non-PBT radiotherapy and/or radiation-free therapy (e.g. chemotherapy, immunotherapy, or surgery)

• **Control group**	External radiotherapy, of any type other than PBT, alone or in combination with one or more concurrent or neoadjuvant non-PBT radiotherapy and/or radiation-free therapy Internal radiotherapy in all dosimetric methods, alone or in combination with one or more concurrent or neoadjuvant non-PBT radiotherapy and/or radiation-free therapy
Results	
Narratively presented, no meta-analysis All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3) Main conclusions: "The overall evidence from the assessment of the clinical effectiveness suggests that proton beam therapy, alone or in combination with photon radiotherapy, is comparable to other types of radiotherapy in most types of cancer, and safety varies by type of cancer. The budget impact analysis suggests that installing a proton facility in Canada, if the facility is in operation for greater than nine years and assuming current patient loads and an annual growth of 3%, may demonstrate cost savings compared with sending patients out of country for treatment. The evidence from the reviews of patient perspectives and experiences, ethical issues, and implementation issues highlights several important considerations to help decide whether patients should continue to be sent out of country for proton beam treatment, or if proton beam therapy should be installed and implemented in Canada."	
Limitations and other comments	
• **Limitations**	Search of good quality Review of reviews

Dionisi F 2014	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	Source of funding not stated, no conflict of interest to declare
• **Search date**	December 2012; included period of studies 1990–2012
• **Searched databases**	Medline and Scopus databases; abstracts of meetings of the American and the European Societies of Therapeutic Radiation Oncology (ASTRO, ESTRO), the Particle Therapy Co-operative Group (PTCOG) and the American Society of Clinical Oncology (ASCO)
• **Included study designs**	Any type, except single case reports
• **Number of included studies**	N=16, of which 5 full papers reporting on clinical experience
• **Statistical analysis**	-
Patient characteristics	

• **Eligibility criteria**	HCC patients treated with proton therapy; reporting on outcome and/or toxicity
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Included studies: Chiba T 2005, Nakayama H 2009, Komatsu S 2011, Kawashima M 2011, Bush DA 2011 Sample size: N=858 (range 60-162) Heterogeneous reporting of patient characteristics (see table 3 of article): all 5 studies are reported separately in the evidence tables below (see 4.2 and 4.3)
Interventions	
• **Intervention group**	Proton therapy
• **Control group**	-
Results	
Narratively presented, no meta-analysis All 5 studies are reported separately in the evidence tables below (see 4.2 and 4.3) Main conclusions: “The low quality of the retrieved studies reduces without eliminating the interest toward the impressive clinical results that have been registered in several stages of HCC. The cost-benefit of proton versus other treatment options is worth of study given the high cost of protons. A number of proton therapy centers are currently recruiting patients in various prospective trials and are testing proton therapy alone (NCT00976898), comparing proton therapy vs. TACE (NCT00857805), or evaluating the role of proton therapy in advanced disease (NCT01141478). A positive outcome of such trials would suggest the role of proton therapy as an effective option in the local treatment of unresectable HCC. Active-scanning based proton treatment for HCC is under development, and it should be considered one of the ‘‘modern approaches’’ to be tested in the next future.”	
Limitations and other comments	
• **Limitations**	Limited search Quality appraisal very limited, although acknowledged in conclusions English literature only Unclear if duplicate data extraction

ICER 2014	
Methods	
• **Design**	HTA report
• **Source of funding and competing interest**	Not stated
• **Search date**	January 1990 – February 2014

• **Searched databases**	MEDLINE, EMBASE, The Cochrane Library
• **Included study designs**	Randomized controlled trials, comparative cohort studies (case series were abstracted and summarized)
• **Number of included studies**	N=321, of which: - LGG: 1 retrospective comparison, 6 case series - Breast cancer: no comparative studies, 4 case series - Pancreatic cancer: no comparative studies, 3 case series - Head and neck cancer: 2 retrospective comparisons (primary cancer), 27 case series - HCC: 2 prospective comparisons, 21 case series - Rectal cancer: no studies
• **Statistical analysis**	Qualitative analysis
Patient characteristics	
• **Eligibility criteria**	Children and adults treated with PBT for multiple types of cancer (bone cancer; lung cancer; brain, spinal and paraspinal tumors; lymphomas, breast cancer; ocular tumors, esophageal cancer, pediatric cancers, gastrointestinal cancers; prostate cancer; gynecologic cancers; sarcomas; head & neck cancers; seminoma; liver cancer; thymoma) as well as those with selected noncancerous conditions (arteriovenous malformations; other benign tumours; hemangiomas)
• **Exclusion criteria**	Not stated
• **Patient & disease characteristics**	All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3)
Interventions	
• **Intervention group**	Proton beam therapy as primary treatment or for recurrent disease or for failure of initial therapy
• **Control group**	All relevant comparators
Results	

All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3)

Main conclusions: “Proton beam therapy has been used for clinical purposes for over 50 years and has been delivered to tens of thousands of patients with a variety of cancers and noncancerous conditions. Despite this, evidence of proton beam therapy’s comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review. As mentioned previously, it is unlikely that significant comparative study will be forthcoming for childhood cancers despite uncertainty over long-term outcomes, as the potential benefits of proton beam therapy over alternative forms of radiation appear to be generally accepted in the clinical and payer communities. In addition, patient recruitment for potential studies may be untenable in very rare conditions (e.g., thymoma, arteriovenous malformations). In other areas, however, including common cancers such as breast and prostate, the poor evidence base and residual uncertainty around the effects of proton beam therapy is highly problematic.

We rated the net health benefit of proton beam therapy relative to alternative treatments to be “Superior” (moderate-large net health benefit) in ocular tumors and “Incremental” (small net health benefit) in adult brain/spinal cancers and pediatric cancers. We judged the net health benefit to be “Comparable” (equivalent net health benefit) in several other cancers, including liver, lung, and prostate cancer, as well as hemangiomas. It should be noted, however, that we made judgments of comparability

based on a limited evidence base that provides relatively low certainty that proton beam therapy is roughly equivalent to alternative therapies. While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that proton beam therapy is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions. It should also be noted that we examined evidence for 11 cancers and noncancerous conditions not listed above, and determined that there was insufficient evidence to obtain even a basic understanding of proton beam therapy's comparative clinical effectiveness and comparative value.

For relatively common cancers, the ideal evidence of proton beam therapy's clinical impact would come from randomized clinical trials such as those currently ongoing in liver, lung, and prostate cancer. To allay concerns regarding the expense and duration of trials designed to detect survival differences, new RCTs can focus on validated intermediate endpoints such as tumour progression or recurrence, biochemical evidence of disease, development of metastases, and near-term side effects or toxicities. In any event, overall and disease-free survival should be included as secondary measures of interest.

In addition, the availability of large, retrospective databases that integrate clinical and economic information should allow for the development of robust observational studies even as RCTs are being conceived of and designed. Advanced statistical techniques and sampling methods have been used to create observational datasets of patients treated with proton beam therapy and alternative therapies using national databases like the Medicare-SEER database and Chronic Conditions Warehouse used in some of the studies summarized in this review. These studies will never produce evidence as persuasive as randomized comparisons because of concerns regarding selection and other biases, and administrative databases lack the clinical detail necessary to create rigorously-designed observational datasets.

The continued growth of electronic health records from integrated health systems may allow for the creation of more detailed clinical and economic comparisons in large, well-matched patient groups receiving alternative radiation modalities. Use of clinical records-based registries and other observational datasets may therefore yield substantial information on proton beam therapy's benefits and harms under typical-practice conditions, as well as an indication of whether RCTs should be considered in the first place. Use of available clinical and administrative datasets also represents an opportunity for the payer and clinical communities to collaborate in setting standards for study design, identifying the outcomes of most interest, and sharing resources so that evidence can be generated in the most efficient manner possible."

Limitations and other comments	
• **Limitations**	Search of good quality, although focus on English-only articles Unclear if independent reviewers for selection and data extraction

INESSS 2017	
Methods	
• **Design**	HTA report
• **Source of funding and competing interest**	Funding not reported; Charpentier AM received funding for her participation at the congress of the Children Oncology Group
• **Search date**	2010 – Oct 2016
• **Searched databases**	PubMed, EBM Reviews, grey literature
• **Included study designs**	Guidelines, systematic reviews, primary studies
• **Number of included studies**	3 HTA reports, of which 2 were relevant (CADTH 2017, ICER 2014)

	4 SR, of which 3 were relevant (Patel 2014, Verma 2016, Qi 2015)
• **Statistical analysis**	Qualitative analysis
Patient characteristics	
• **Eligibility criteria**	Cancer patients; comparison between proton treatment and photon treatment; at least 20 patients (for primary studies)
• **Exclusion criteria**	Planning and dosimetric studies; economic studies
• **Patient & disease characteristics**	All relevant primary studies are reported separately in the evidence tables below (see 4.2 and 4.3)
Interventions	
• **Intervention group**	Proton treatment
• **Control group**	Photon treatment
Results	

Narratively presented, no meta-analysis

All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3)

Main conclusions: “Since the quality of the existing data is inadequate, it is presently not relevant to propose treatment with proton therapy for non-small-cell lung cancer, hepatocellular carcinoma, prostate cancer, esophageal cancer, breast cancer, re-irradiation cases. For the indications recognized in Québec, the following principles should be applied when evaluating treatment requests:

• Proton therapy should confer to the patient a significant benefit over the latest photon therapy techniques available in Québec, such as image-guided radiotherapy (IGRT), volumetric-modulated arc therapy (VMAT), 4-dimensional radiotherapy or radiosurgery.

• Approved proton therapy treatments should:

o be curative in intent;

o be for patients with a good performance score (0 to 2);

o be for patients with a life expectancy greater than 5 years.

• The patient's ability and willingness to travel should be taken into consideration.

• Whether proton therapy is to be used as first- or second-line treatment, all cases involving patients likely to receive proton therapy should be discussed within a committee specializing in cancer diagnosis and treatment.

• Every request for proton therapy should be submitted to the Comité provincial de protonthérapie by a radiation oncologist who has evaluated the patient concerned.

Research in the area of proton therapy is growing rapidly, which suggests that the clinical indications for this treatment modality might be broadened in the more or less long term. Within the next 3 years, the current phase III studies will provide new efficacy and safety data for better assessing the actual role of proton therapy in the treatment of several types of cancer.”

Limitations and other comments	
• **Limitations**	Search of fair quality, although limited to English and French articles

	Unclear if independent researchers for selection and data extraction Mainly review of reviews

KCE 2007	
Methods	
• **Design**	HTA report
• **Source of funding and competing interest**	Funded by government Competing interest reported in detail
• **Search date**	2000 - March 2007
• **Searched databases**	CRD database, Medline and Embase
• **Included study designs**	HTA reports, systematic reviews and clinical trials with at least 10 patients
• **Number of included studies**	N=45, of which 3 were relevant: Lodge M 2007, Brada M 2007, Olsen 2007
• **Statistical analysis**	Qualitative analysis
Patient characteristics	
• **Eligibility criteria**	Patients with cancer (or ocular diseases) treated with hadrontherapy, proton beam therapy, ion therapy
• **Exclusion criteria**	Letter, comment, narrative review, case report, patients with other conditions, other intervention or non-clinical outcomes
• **Patient & disease characteristics**	Too few details of the primary studies
Interventions	
• **Intervention group**	Hadrontherapy
• **Control group**	Not specified
Results	
Narratively presented, no meta-analysis All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3) Main conclusions: “Our research was not able to show any evidence in favour of hadrontherapy. The only RCT with neutrontherapy (vs photons) was in the treatment of salivary glands tumours. It showed a better local control without improvement of survival. There were no comparative studies with regard to the toxicity of hadrontherapy. There were no reports of patients with toxicity Grade ≥ 4 severity. Proton beam therapy can represent an indication for rare and specific tumours in selected groups of patients where conventional therapy presents a significant risk for fragile structures in the vicinity. The quality of actual evidence is nevertheless poor. Carbon ion therapy is an appealing but still experimental approach. There is currently no evidence for the use of hadrontherapy in the treatment of non-malignant diseases. ”	

Limitations and other comments	
• **Limitations**	Search of good quality Mainly review of reviews

Lodge M 2007	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	Support of the European Investment Bank Conflict of interest not reported
• **Search date**	January 2007
• **Searched databases**	MEDLINE, EMBASE, The Cochrane Library, DARE, HTA database, Biological Abstracts, CINAHL, ISI Science and Technology Proceedings, NHS EED, SIGLE
• **Included study designs**	All types
• **Number of included studies**	N=137 studies on proton therapy, of which: - Head and neck cancer: 2 retrospective studies (Slater JD 2005, Tokuuye K 2004) - Hepatocellular cancer: 3 case series (Kawashima 2005, Bush 2004, Hata 2006) - Low-grade glioma: 1 case series (Fitzek 2001)
• **Statistical analysis**	Qualitative analysis
Patient characteristics	
• **Eligibility criteria**	Children and adults treated with hadron therapy for multiple types of cancer
• **Exclusion criteria**	Not stated
• **Patient & disease characteristics**	All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3)
Interventions	
• **Intervention group**	Proton beam therapy
• **Control group**	All relevant comparators
Results	
All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3)	

Main conclusions: “The current literature shows that the introduction, or significant extension, of hadron therapy as a major treatment modality – except on a minor scale for certain rare tumours (ocular, chordomas, etc.) – into standard clinical patient care cannot be supported by the evidence base currently available. There are little reliable evidence-based data available concerning the relative cost-effectiveness of hadron therapy interventions when compared with each other, with photon therapy, or with other cancer treatments. This also represents an important area for future research.”

Limitations and other comments	
• **Limitations**	Search of good quality Few details on actual selection process Individual quality appraisal not reported Few details on included studies

Olsen DR 2007	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	Not stated
• **Search date**	March 2006
• **Searched databases**	Medline and Embase
• **Included study designs**	Randomized controlled trials, cohort and case-control studies, patient series and cross-sectional studies Except for studies in children, papers involving <50 patients were excluded
• **Number of included studies**	N=1 for hepatocellular cancer
• **Statistical analysis**	-
Patient characteristics	
• **Eligibility criteria**	Patients with malign or benign tumour, treated with proton irradiation alone or in combination with surgery or external beam irradiation
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Included study: Chiba T 2005 N=162 with hepatic tumours, mainly stage I and stage II Study is reported separately in the evidence tables below (see 4.2 and 4.3)
Interventions	

• **Intervention group**	Proton therapy
• **Control group**	-
Results	
Narratively presented, no meta-analysis Study is reported separately in the evidence tables below (see 4.2 and 4.3) Main conclusions: "The evidence on clinical efficacy of proton therapy relies to a large extent on non-controlled studies, and thus is associated with low level of evidence according to standard heath technology assessment and evidence based medicine criteria."	
Limitations and other comments	
• **Limitations**	Limited search Quality appraisal not reported for study on HCC Unclear if duplicate data extraction

Patel SH 2014	
Methods	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	Funded by Mayo Foundation for Medical Education and Research SES received a grant from the Alliance cooperative research group for travel-related expenses as vice chair of the respiratory committee. All other authors declared no competing interests
• **Search date**	April 2014
• **Searched databases**	Embase, Medline, Medline In-Process & Other Non-Indexed Citations, Scopus, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews
• **Included study designs**	Randomised controlled trial, non-randomised clinical trial, observational studies, or case series
• **Number of included studies**	41 observational studies
• **Statistical analysis**	Event rates of outcome (proportion of patients who developed outcomes of interest); 95%CIs with Jeffreys method Pooling of log-transformed event rates with DerSimonian and Laird random-effect models Heterogeneity assessed using the Mantel-Haenszel test Test of interaction proposed by Altman and Bland to compare log-transformed rates of outcomes between charged particle therapy and photon therapy. When the difference between treatments was significant, they calculated the number needed to treat (NNT) from the absolute difference of the pooled estimates between the two groups

	Ad-hoc subgroup analysis to compare primary outcomes for proton beam therapy with those for intensity-modulated radiation therapy Planned subgroup analyses of treatment history and grades of toxic effect Multivariable random-effects meta-regression models to compare outcomes between charged particle therapy and photon therapy, by adjusting for tumour stage among treatment-naive patients; p values with Monte Carlo permutation tests Publication bias: Duval and Tweedie non-parametric trim-and-fill method Overall heterogeneity across the included cohorts: I2 statistic Potential publication bias: visual inspection of the symmetry of funnel plots and Egger regression asymmetry test
Patient characteristics	
• **Eligibility criteria**	1) patients with malignant disease of either the paranasal sinuses (i.e. frontal, sphenoid, ethmoid, or maxillary) or the nasal cavity; 2) treatment with photon therapy, charged particle therapy, or combined photon therapy and charged particle therapy; 3) reported outcomes of interest (i.e. tumour control, survival, and complications)
• **Exclusion criteria**	Studies before 1990 Case reports with fewer than five patients, reviews, notes, letters, errata, commentaries, and studies published only as abstracts
• **Patient & disease characteristics**	N patients: charged particle therapy (CPT) 286, photon therapy (PT) 1186 Mean age (years): CPT 57.7 (44-73), PT 59.2 (45-73), p=0.10 Men (%): CPT 57%, PT 64%, p=0.28 Median follow-up (mo): CPT 38, PT 40, p=0.72
Interventions	
• **Intervention group**	Charged particle therapy: radiation therapy using beams of protons, carbon ions, helium ions, or other charged particles (including patients who received both photon therapy (PBT) and charged particle therapy); N=286
• **Control group**	Photon therapy: any type of photon therapy, using either two-dimensional, three-dimensional, or intensity-modulated radiation therapy (IMRT) techniques; N=1186
Results	
• **Overall survival (or mortality)**	Overall survival: CPT: 10 cohorts, N=242, pooled event rate 0.66 (95%CI 0.56-0.79); RR compared with PT: 1.27 (95%CI 1.01-1.59), p=0.037 PT: 26 cohorts, N=1120, pooled event rate 0.52 (95%CI 0.46-0.60) PBT: 8 cohorts, N=191, pooled event rate 0.63 (95%CI 0.53-0.76); RR compared with IMRT: 1.02 (95%CI 0.77-1.35), p=0.89 IMRT: 8 cohorts, N=348, pooled event rate 0.62 (95%CI 0.50-0.77)

	5-year overall survival: CPT: 6 cohorts, N=146, pooled event rate 0.72 (95%CI 0.58-0.90); RR compared with PT: 1.51 (95%CI 1.14-1.99), p=0.0038 PT: 15 cohorts, N=779, pooled event rate 0.48 (95%CI 0.40-0.57) PBT: 5 cohorts, N=124, pooled event rate 0.66 (95%CI 0.52-0.85); RR compared with IMRT: 1.39 (95%CI 0.99-1.94), p=0.057 IMRT: 4 cohorts, N=212, pooled event rate 0.48 (95%CI 0.38-0.60)
• **Recurrence-free survival**	Disease-free survival at the longest duration of complete follow-up: CPT: 3 cohorts, N=78, pooled event rate 0.67 (95%CI 0.48-0.95); RR compared with PT: 1.51 (95%CI 1.00-2.30), p=0.052 PT: 8 cohorts, N=411, pooled event rate 0.44 (95%CI 0.35-0.56) PBT: 2 cohorts, N=56, pooled event rate 0.49 (95%CI 0.21-1.16); RR compared with IMRT: 0.98 (95%CI 0.40-2.42), p=0.97 IMRT: 3 cohorts, N=187, pooled event rate 0.50 (95%CI 0.38-0.67) 5-year disease-free survival at the longest duration of complete follow-up: CPT: 2 cohorts, N=58, pooled event rate 0.80 (95%CI 0.67-0.95); RR compared with PT: 1.93 (95%CI 1.36-2.75), p=0.0003 PT: 6 cohorts, N=341, pooled event rate 0.41 (95%CI 0.30-0.56) PBT: 1 cohorts, N=36, pooled event rate 0.72 (95%CI 0.59-0.89); RR compared with IMRT: 1.44 (95%CI 1.01-2.05), p=0.045 IMRT: 3 cohorts, N=187, pooled event rate 0.50 (95%CI 0.38-0.67)
• **Progression-free survival**	Not reported
• **Quality of life**	Not reported
• **Tumour or cancer control**	Locoregional control at the longest duration of complete follow-up: CPT: 10 cohorts, N=208, pooled event rate 0.76 (95%CI 0.68-0.86); RR compared with PT: 1.18 (95%CI 1.01-1.37), p=0.031 PT: 14 cohorts, N=736, pooled event rate 0.65 (95%CI 0.59-0.71) PBT: 7 cohorts, N=147, pooled event rate 0.81 (95%CI 0.71-0.92); RR compared with IMRT: 1.26 (95%CI 1.05-1.51), p=0.011 IMRT: 4 cohorts, N=258, pooled event rate 0.64 (95%CI 0.57-0.72) 5-year locoregional control at the longest duration of complete follow-up: CPT: 3 cohorts, N=58, pooled event rate 0.66 (95%CI 0.43-1.02); RR compared with PT: 1.06 (95%CI 0.68-1.67), p=0.79 PT: 8 cohorts, N=546, pooled event rate 0.62 (95%CI 0.55-0.71)

	PBT: 2 cohorts, N=36, pooled event rate 0.43 (95%CI 0.09-2.10); RR compared with IMRT: 0.73 (95%CI 0.15-3.58), p=0.70 IMRT: 2 cohorts, N=166, pooled event rate 0.59 (95%CI 0.52-0.67)
• **Complications / side effects**	Eye: CPT: pooled event rate 0.19 (95%CI 0.08-0.45), p=0.12 vs. PT PT: pooled event rate 0.43 (95%CI 0.24-0.75) Head and neck: CPT: pooled event rate 0.54 (95%CI 0.24-1.24), p=0.30 vs. PT PT: pooled event rate 0.87 (95%CI 0.62-1.22) Nasal: CPT: pooled event rate 0.07 (95%CI 0.01-0.55), p=0.66 vs. PT PT: pooled event rate 0.12 (95%CI 0.04-0.37) Ear: CPT: pooled event rate 0.20 (95%CI 0.09-0.47), p=0.56 vs. PT PT: pooled event rate 0.14 (95%CI 0.06-0.32) Neurological: CPT: pooled event rate 0.20 (95%CI 0.13-0.31), p=0.0002 vs. PT PT: pooled event rate 0.04 (95%CI 0.02-0.08) Miscellaneous: CPT: pooled event rate 0.41 (95%CI 0.17-1.02), p=0.78 vs. PT PT: pooled event rate 0.49 (95%CI 0.24-1.00) Haematological: CPT: pooled event rate 2.31 (95%CI 1.59-3.36), p=0.40 vs. PT PT: pooled event rate 1.92 (95%CI 1.55-2.37)
• **Secondary tumours**	Not reported
Limitations and other comments	

• **Limitations**	Search of good quality Meta-analysis used correct methods when looking at the individual treatments. When comparing the treatments, baseline risk was taken into account by adjusting for tumour stage

Qi W-X 2015	
Methods	
• **Design**	Systematic review with meta-analysis
• **Source of funding and competing interest**	Stated as none
• **Search date**	August 2014
• **Searched databases**	Embase, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews
• **Included study designs**	Original study, i.e. randomized controlled trial, non-randomized clinical trial, observational studies, or case series
• **Number of included studies**	N=70
• **Statistical analysis**	Pooling of log-transformed event rates with random-effect models; heterogeneity assessment using the Mantel–Haenszel test Test of interaction proposed by Altman and Bland to compare log-transformed rates of outcomes Potential effect of publication bias accounted for using the Duval and Tweedie non-parametric trim-and-fill method Overall heterogeneity across the included cohorts measured by I-square
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma Treatment with photon therapy, charged particle therapy, or combined photon therapy and charged particle therapy Reported outcomes of interest (i.e. tumour control, survival, and complications)
• **Exclusion criteria**	Studies before 1990 Case reports with fewer than five patients, reviews, notes, letters, errata, commentaries, and studies published only as abstracts
• **Patient & disease characteristics**	N patients: charged particle therapy (CPT) 1627, stereotactic body radiation therapy (SBRT) 1473, conventional radiotherapy (CRT) 2104 Median age (years): CPT 67 (55-81), SBRT 62.4 (53-74), CRT 59.0 (51-68), p=0.002 Median N HCC patients with tumour vascular thrombosis: CPT 19, SBRT 4.5, CRT 33, p=0.064 Median tumour size (cm): CPT 4.5, SBRT 4.4, CRT 9.0, p=0.06 Men (%): CPT 72.3, SBRT 77.4, CRT 85.5, p=0.064

	Median Child-Pugh A class (%): CPT 72.5, SBRT 72.7, CRT 86.3, p=0.007 Median follow-up (mo): CPT 23, SBRT 18, CRT 18.4, p=0.064
Interventions	
• **Intervention group**	Charged particle therapy: radiation therapy using beams of protons, carbon ions, helium ions, or other charged particles (including patients who received both photon therapy and charged particle therapy); N=1627
• **Control group**	Conventional radiotherapy: N=2104; stereotactic body radiation therapy: N=1473
Results	
• **Overall survival (or mortality)**	1-year overall survival: CPT: 6 cohorts, N=704, pooled event rate 0.79 (95%CI 0.66-0.88) CRT: 10 cohorts, N=1130, pooled event rate 0.47 (95%CI 0.34-0.60); RR compared with CPT: 1.68 (95%CI 1.22-2.31), p<0.001 SBRT: 21 cohorts, N=1014, pooled event rate 0.80 (95%CI 0.71-0.87); RR compared with CPT: 0.98 (95%CI 0.83-1.18), p=0.44 3-year overall survival: CPT: 9 cohorts, N=844, pooled event rate 0.59 (95%CI 0.51-0.66) CRT: 6 cohorts, N=528, pooled event rate 0.24 (95%CI 0.17-0.33); RR compared with CPT: 2.46 (95%CI 1.72-3.51), p<0.001 SBRT: 7 cohorts, N=507, pooled event rate 0.58 (95%CI 0.40-0.74); RR compared with CPT: 1.02 (95%CI 0.73-1.42), p=0.46 5-year overall survival: CPT: 11 cohorts, N=1276, pooled event rate 0.37 (95%CI 0.31-0.43) CRT: 1 cohort, N=45, pooled event rate 0; RR compared with CPT: 25.9 (95%CI 1.64-408.5), p=0.02 SBRT: 4 cohorts, N=308, pooled event rate 0.31 (95%CI 0.17-0.48); RR compared with CPT: 1.19 (95%CI 0.69-2.06), p=0.26
• **Recurrence-free survival**	Not reported
• **Progression-free survival**	At longest duration of complete follow-up: CPT: 7 cohorts, N=284, pooled event rate 0.54 (95%CI 0.31-0.75) CRT: 6 cohorts, N=340, pooled event rate 0.29 (95%CI 0.11-0.59); RR compared with CPT: 1.86 (95%CI 1.08-3.22), p=0.013 SBRT: 7 cohorts, N=290, pooled event rate 0.36 (95%CI 0.23-0.51); RR compared with CPT: 1.34 (95%CI 0.83-2.72), p=0.09
• **Quality of life**	Not reported
• **Tumour or cancer control**	Locoregional control at longest duration of complete follow-up: CPT: 12 cohorts, N=1021, pooled event rate 0.86 (95%CI 0.83-0.88) CRT: 1 cohort, N=30, pooled event rate 0.20 (95%CI 0.09-0.38); RR compared with CPT: 4.30 (95%CI 2.09-8.84), p<0.001 SBRT: 12 cohorts, N=750, pooled event rate 0.87 (95%CI 0.83-0.92); RR compared with CPT: 0.99 (95%CI 0.93-1.05), p=0.35

• **Complications / side effects**	≥grade 3 acute and late toxic effect event rates: <u>Acute toxicity</u> Hepatic CPT: 14 studies, 21 events, pooled event rate 3.1% (95%CI 1.3-7.6%) SBRT: 19 studies, 59 events, pooled event rate 4.9% (95%CI 3.0-8.1%), p=0.19 vs. CPT CRT: 10 studies, 111 events, pooled event rate 9.9% (95%CI 6.0-16%), p=0.014 vs. CPT Bone marrow CPT: 14 studies, 40 events, pooled event rate 5.1% (95%CI 1.9-12.7%) SBRT: 11 studies, 23 events, pooled event rate 4.9% (95%CI 3.4-7.2%), p=0.47 vs. CPT CRT: 12 studies, 26 events, pooled event rate 6.1% (95%CI 4.3-8.8%), p=0.36 vs. CPT Overall CPT: 16 studies, 68 events, pooled event rate 6.1% (95%CI 2.8-12.6%) SBRT: 21 studies, 137 events, pooled event rate 9.6% (95%CI 6.0-15.1%), p=0.16 vs. CPT CRT: 13 studies, 172 events, pooled event rate 20% (95%CI 13.2-29.2%), p=0.003 vs. CPT <u>Late toxicity</u> CPT: 7 studies, 6 events, pooled event rate 2.5% (95%CI 1.3-4.9%) SBRT: 6 studies, 17 events, pooled event rate 6.4% (95%CI 4.0-10.1%), p=0.011 vs. CPT CRT: 5 studies, 11 events, pooled event rate 6.9% (95%CI 3.9-12%), p=0.011 vs. CPT
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Search of good quality Meta-analysis used correct methods when looking at the individual treatments. However, when comparing the treatments, baseline risk was not taken into account

QUERI 2015	
Methods	
• **Design**	HTA report

• **Source of funding and competing interest**	Funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative No competing interest
• **Search date**	December 2014
• **Searched databases**	MEDLINE, Cochrane Clinical Register of Controlled Trials, ClinicalTrials.gov
• **Included study designs**	Comparative studies, SRs
• **Number of included studies**	N=31, of which: - LGG: 1 retrospective comparison (Kahn 2011) - Breast cancer: 1 comparative study (Galland-Girodet 2014) - Pancreatic cancer: no comparative studies - Head and neck cancer: 1 retrospective comparison (primary cancer) (Solares CA 2005) - HCC: 1 prospective comparison (Otsuka 2003) - Rectal cancer: no comparative studies
• **Statistical analysis**	Qualitative analysis
Patient characteristics	
• **Eligibility criteria**	Adults with any cancer type (except ocular)
• **Exclusion criteria**	-
• **Patient & disease characteristics**	All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3)
Interventions	
• **Intervention group**	Proton beam therapy
• **Control group**	Conventional X-ray-based external beam treatments and state-of-the-art therapies
Results	

Narratively presented, no meta-analysis

All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3)

Main conclusions: “Despite the common claim that the advantage of proton beam therapy is self-evident, comparative studies have not demonstrated any common clinical situations in which proton beam therapy has an important clinical advantage over photon radiotherapy modalities on meaningful long-term health outcomes, but have uncovered low-strength evidence of the potential for increased late toxicity compared with IMRT and 3D-CRT for breast, … and spinal cord glioma cancers. Existing comparative studies have numerous methodological deficiencies that limited our confidence in their findings, and their findings may have limited applicability across all US proton beam facilities. Although numerous randomized controlled trials are underway that carry the promise of improved toxicity measurement, it is unclear whether they will fully address gaps in evidence on other important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall

severe late toxicity, and secondary malignancies. Because this is still a rapidly evolving field, with ongoing efforts to improve techniques and reduce costs, this review may need frequent updating to keep up-to-date with emerging research."
Limitations and other comments
• **Limitations** — Search of fair quality, focus on English-only studies

RIHTA	
Methods	
• **Design**	HTA report
• **Source of funding and competing interest**	Not reported
• **Search date**	2007 – November 2011
• **Searched databases**	Secondary literature: Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; NHS Economic Evaluation Database (NHS EED); Trip Database; INAHTA and AHRQ web sites Primary literature: Pubmed; Clinicaltrials.gov; Controlled-trials.com; Cochrane Central Register of Controlled Trials
• **Included study designs**	SR, HTAs, RCT
• **Number of included studies**	N=33 reviews, of which 5 relevant for the present review: VATAP 2010, AHRQ 2009, ANZHSN 2007, KCE 2007, Lodge 2007 No additional primary studies were included
• **Statistical analysis**	Qualitative analysis
Patient characteristics	
• **Eligibility criteria**	Cancer patients treated with hadrontherapy
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Too few details
Interventions	
• **Intervention group**	Hadrontherapy (proton, ion and neutron beam therapy)
• **Control group**	Other radiotherapy techniques (conventional radiotherapy, IMRT, stereotactic surgery, brachytherapy)
Results	
Narratively presented, no meta-analysis	

All relevant studies are reported separately in the evidence tables below (see 4.2 and 4.3) Main conclusions: "All the secondary studies included in this report state that the paucity of well conducted clinical studies (RCTs, prospective cohort studies, comparative studies) makes it impossible to draw firm conclusions about the effects of hadrontherapy for cancer treatment. In some cases, clinical studies suggested an increase of safety and effectiveness by using hadrontherapy instead of traditional radiotherapy for some type of tumours (uveal melanoma, skull and neck chordomas, and NSCLC). Nonetheless, there is uncertainty regarding these estimates, due to methodological and design biases. Given the burden of disease of pathologies for which hadrontherapy is suggested to be more promising and the high costs associated with hadrontherapy, the Italian requirements for hadrontherapy facilities should be satisfied by the 3 centres in development. In such centres, priority should be given to the treatment of those tumours for which hadrontherapy has shown any evidence of effectiveness and safety (uveal melanoma, skull base chordoma, NSCLC). Because of the lack of evidence regarding hadrontherapy, hadrontherapy facilities operating in Italy in the next years should produce high quality evidence, setting up comparative studies adequate in design and methods. It is important that high quality evidence be sought prior to planning the diffusion of this technology."	
Limitations and other comments	
• **Limitations**	Poor description of included studies

4.2. Comparative studies

Acharya S 2018	
Methods	
• **Design**	Retrospective comparative study
• **Source of funding and competing interest**	Funding not reported Conflict of interest reported in detail in article
• **Setting**	1 University radiation oncology centre, USA
• **Sample size**	N=160
• **Duration and follow-up**	Inclusion 2007 to 2015 Follow-up in months: median 28.5
• **Statistical analysis**	Frequency distributions between groups were assessed with the Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables The cumulative incidence of radiation necrosis was calculated using a competing-risk model with death and recurrence as competing risks Factors predictive of radiation necrosis were identified using a Cox proportional hazards regression model. Variables significant on Cox univariate analysis were considered for Cox multivariate analysis
Patient characteristics	

• **Eligibility criteria**	Adults (age ≥ 18 years) with newly diagnosed WHO grade 2 or 3 cranial oligodendrogliomas or astrocytomas between 2007 and 2015 treated with either proton or photon therapy
• **Exclusion criteria**	Patients were excluded if they had gliomatosis, leptomeningeal disease, or brainstem glioma; underwent prior cranial irradiation; or did not receive standard intensity modulated photon therapy or have at least 1 follow-up MRI scan
• **Patient & disease characteristics**	Median age: proton 38y vs. photon 42y Male sex: proton 65% vs. photon 61% WHO grade 2: proton 51% vs. photon 39%
Interventions	
• **Intervention group**	Proton therapy (N=37)
• **Control group**	Photon-based (N=123): intensity-modulated radiotherapy
Results	
• **Overall survival (or mortality)**	Not reported
• **Recurrence-free survival**	Not reported
• **Progression-free survival**	Not reported
• **Quality of life**	Not reported
• **Tumour or cancer control**	Not reported
• **Complications / side effects**	Radiation necrosis: - Incidence: proton N=6 vs. photon N=12 - 2-year cumulative incidence:18.7% (95%CI 7.5-33.8%) vs. 9.7% (95%CI 5.1-16%), p=0.16
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	No randomization or allocation concealment, retrospective design Probably no blinding, but evaluation of cases by board Risk adjustment used

Bronk JK 2018	
Methods	
• **Design**	Retrospective comparative study
• **Source of funding and competing interest**	Not stated
• **Setting**	University centre, USA
• **Sample size**	N=99
• **Duration and follow-up**	Patients treated between 2004 – 2015; Median follow-up: oligodendroglioma photon 46 mo vs. proton 38 mo; astrocytoma photon 46 mo vs. proton 24 mo
• **Statistical analysis**	Group-wise and multivariate analysis; Cox regression analysis
Patient characteristics	
• **Eligibility criteria**	Patients with histologically confirmed grade II or III oligodendroglioma (N=67) or astrocytoma (N=32), with age over 18 years, treated with IMRT or proton therapy, and with MRI available for at least 6 months following completion of radiation therapy
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Age: median=48, range: 24-94 Gender: 65% male Grade II: N=36; grade III: N=63 Concurrent chemotherapy: N=14 Adjuvant chemotherapy: N=54
Interventions	
• **Intervention group**	Photon therapy (N=65): IMRT
• **Control group**	Proton therapy (N=34; passive scatter N=29, scanning beam technique N=5)
Results	
• **Overall survival (or mortality)**	3-year OS: patients with pseudoprogression 100% vs. patients without pseudoprogression 82.6%; p=0.04
• **Recurrence-free survival**	Not reported
• **Progression-free survival**	3-year PFS: patients with pseudoprogression 100% vs. patients without pseudoprogression 61.6%; p=0.03 Median time to progression: patients with pseudoprogression 100 mo vs. patients without pseudoprogression 21 mo; p=0.02
• **Quality of life**	Not reported

• **Tumour or cancer control**	Not reported
• **Complications / side effects**	Pseudoprogression: • Overall: photon 13.8% vs. proton 14.7%, p=1.00 • Oligodendroglioma: photon 14.3% vs. proton 16%, p=1.00 • Astrocytoma: photon 13% vs. proton 11.1%, p=1.00
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	No random assignment or allocation concealment (retrospective design) Participants were not blinded (but radiologists were) Probably no concurrency of the treatment groups

Galland-Girodet S 2014	
Methods	
• **Design**	Multicenter, prospective clinical trial (NCT00694577)
• **Source of funding and competing interest**	Funding not reported Conflict of interest reported as none
• **Setting**	3 radiation oncology centres, USA
• **Sample size**	N=98
• **Duration and follow-up**	Inclusion October 2003 to April 2006 Follow-up in months: median 82.5, range 2-104
• **Statistical analysis**	Cumulative incidence, Kaplan-Meier, log-rank test
Patient characteristics	
• **Eligibility criteria**	Patients aged 18 years or older with pT1N0M0 invasive breast carcinoma
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age: 61y Tumour size cm: median 0.9 Tumour side: right 41% Histology: IDC no DCIS 91%, Tubular 5%, Mucinous 3%, IDC with DCIS 1%

	Grade: 1: 47%; 2: 42%, 3: 10%
Interventions: accelerated partial-breast irradiation (32 Gy in 8 fractions given twice daily)	
• **Intervention group**	Proton beam therapy (N=19)
• **Control group**	Photon-based (N=79): 60 with mixed photons and electrons, 19 with photons only
Results	
• **Overall survival (or mortality)**	Not reported
• **Recurrence-free survival**	7-year cumulative incidence of local failure rate in the entire population was 6% 7-year local failure rate: PBT 11% vs. photon 4%, p=0.22
• **Progression-free survival**	Not reported
• **Quality of life**	Physician rating overall cosmesis as good/excellent at 60 mo: PBT 62% vs. photon 94%, p=0.03 Patient rating overall cosmesis as good/excellent at 60 mo: PBT 88% vs. photon 93%, p=0.69 Overall patient satisfaction for the entire cohort at 84 mo: 93%
• **Tumour or cancer control**	Not reported
• **Complications / side effects**	Moderate skin colour change at 5y: PBT 44% vs. photon 2%, p<0.0001 Patchy atrophy in irradiation portal at 5y: PBT 50% vs. photon 5%, p<0.0001 Skin toxicities for PBT vs. photon at 7y: telangiectasia 69% vs. 16%, p=0.0013; pigmentation changes 54% vs. 22%, p=0.02; late skin toxicities 62% vs. 18%, p=0.029 No difference between treatment groups at either 5 or 7 years for breast pain, breast edema, fibrosis, fat necrosis (proton N=2 vs. photon N=10, p=0.47), skin desquamation, rib pain, rib fracture (at 60 mo: proton N=1 vs. photon N=3, p=0.072) Telangiectasia >4 cm^2: PBT 38.5% vs. photon 4%, p=0.0013
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	No randomization or allocation concealment Probably no blinding No matched design or risk adjustment

Kahn J 2011	
Methods	
• **Design**	Retrospective study
• **Source of funding and competing interest**	Brian D. Silber funds, Massachusetts General Hospital (to J.L.) and National Institutes of Health/ National Cancer Institute awards R01CA108633 (to A.C.); RC2CA148190 (to A.C.); and the Brain Tumor Funders Collaborative Group (to A.C.) Conflict of interest stated as none
• **Setting**	General hospital, USA
• **Sample size**	N=32
• **Duration and follow-up**	Inclusion: 1991 – 2005 Median follow-up: 24 mo
• **Statistical analysis**	Actuarial overall survival and time to progression with the Kaplan–Meier method; Cox proportional hazards model
Patient characteristics	
• **Eligibility criteria**	Patients with primary intramedullary spinal cord gliomas treated by photon intensity-modulated radiotherapy or conformal proton radiotherapy
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Tumour types: ependymomas (N=14), astrocytomas (N=17), oligodendroglioma (N=1) WHO 2007 classification: low-grade tumour (N=26), high-grade tumour (N=4), unspecified (N=2) Age in years: median=34, range: 2-84 Gender: 50% male Caucasian: 90.6% Adjuvant chemotherapy: n=10 Dose in Gy: 50-55 (N=26); 45-50 (N=6)
Interventions	
• **Intervention group**	Conformal proton radiotherapy (N=10: 6 with LGG)
• **Control group**	Photon intensity-modulated radiotherapy (N=22: 20 with LGG)
Results	
• **Overall survival (or mortality)**	Overall 5-year survival: 65% (95%CI 42%-82%) Multivariate analysis: protons vs. photon beam therapy: HR=40, p = 0.02
• **Recurrence-free survival**	Tumour recurrence or progression: 41% of all patients

	Local recurrence: proton 20% vs. photon 23%; not reported separately for LGG Brain metastasis recurrence: proton 10% vs. photon 5%; not reported separately for LGG Time to progression or recurrence in months (all patients): median=16, range: 1-111
• **Progression-free survival**	5-year progression-free survival (all patients): 61% (95%CI 39-77%)
• **Quality of life**	Not reported
• **Tumour or cancer control**	Not reported
• **Complications / side effects**	Fatigue (41%), erythema (16%), nausea and vomiting (28%), skin irritation (25%), back pain (13%), arm pain (13%), leg pain (6%), dysphagia and odynophagia (9%) No comparison made No patients with significant long-term toxicity
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Retrospective design, no randomization or allocation concealment No blinding Probably no concurrency of the treatment groups 5 patients lost-to-follow-up, but unclear in which group(s)

Maemura K 2017	
Methods	
• **Design**	Prospective comparative study
• **Source of funding and competing interest**	Not reported
• **Setting**	University centre, Japan
• **Sample size**	N=25
• **Duration and follow-up**	Inclusion between Jan 2010 and Dec 2015; follow-up not reported
• **Statistical analysis**	Comparability of the photon and proton groups was verified with Student's t tests and chi square statistics Cross-tabulations were analyzed with chi square or Fisher's exact tests, where appropriate Overall survival was estimated from the start of primary chemotherapy using the Kaplan-Meier method, and the time to progression (TTP) at the primary tumor site or distant sites was also estimated

Patient characteristics	
• **Eligibility criteria**	Patients with locally advanced and unresectable pancreatic cancer who received radiotherapy; age older than 20 years, Karnofsky performance score >70, no prior radiotherapy or chemotherapy for another malignancy within the past 5 years; histologically or cytologically confirmed adenocarcinoma determined via endoscopic ultrasound-guided fine needle aspiration, as well as acceptable baseline hematological, hepatic, and renal function
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Mean age: proton 64.5y vs. photon 64.2y Male sex: proton 50% vs. photon 47%
Interventions: all patients received induction chemotherapy (gemcitabine + S-1) and post-radiotherapy chemotherapy (S-1)	
• **Intervention group**	Proton beam radiotherapy: N=10
• **Control group**	Hyperfractionated acceleration radiotherapy with concomitant S-1: N=15
Results	
• **Overall survival (or mortality)**	Median overall survival: proton 22.3 mo vs. photon 23.4 mo 1-year overall survival: 80% vs. 86.7% 2-year overall survival: 45% vs. 33.3% 3-year overall survival: 22.5% vs. 26.6%
• **Recurrence-free survival**	Not reported
• **Progression-free survival**	Median time-to-progression: 15.4 mo for both groups
• **Quality of life**	Not reported
• **Tumour or cancer control**	Partial response or stable disease: proton 80%vs. photon 93% (p>0.05)
• **Complications / side effects**	Toxicity during radiotherapy: - Hematological: proton: 1 grade 2 leukopenia, 1 grade 2 thrombocytopenia; photon: 2 grade 2 leukopenia, 3 grade 3 leukopenia, 3 grade 2 thromobcytopenia, 1 grade 3 thrombocytopenia - Non-hematological: proton: 1 grade 2 ulcer, 1 grade 3 ulcer; photon: 1 grade 2 nausea, 3 grade 2 anorexia
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	No randomization or allocation concealment Probably no blinding No matched design or risk adjustment

Otsuka M 2003	
Methods	
• **Design**	Retrospective comparative study
• **Source of funding and competing interest**	Not reported
• **Setting**	University centre, Japan
• **Sample size**	N=8
• **Duration and follow-up**	Inclusion between 1983 and 1998; follow-up not reported
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	Patients with recurrent hepatocellular carcinoma, with following criteria: (1) refusal of or no eligibility for rehepatectomy; (2) TAE and PEIT were difficult to perform or resulted in incomplete necrosis; and (3) the target tumour should be confined to single-treatment volume
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Age in years: median=58, range: 49 -65 Gender: 100% male Primary tumor: T1: 2; T2: 3, T3: 3 Initial recurrence: T1: 2; T2: 1; T3: 5 Treatment: transcatheter arterial embolization 7; hepatectomy: 1 No patients had lymph node metastasis or distant metastasis Tumour size in cm: median = 3.15, range 1.2- 4.5 Single tumour: N=4
Interventions	
• **Intervention group**	Protons: N=5 (250 MeV; 68.8–84.5Gy) (multiple tumours were also treated with protons if they were located within two treatment volumes)
• **Control group**	Photon-based radiotherapy: N=3 (6MV; 60 or 70Gy)
Results	
• **Overall survival (or mortality)**	Median time to death: 18 mo Median survival after recurrence (all patients): 39 mo (range 13-102 mo)

• **Recurrence-free survival**	Not reported
• **Progression-free survival**	Not reported
• **Quality of life**	Not reported
• **Tumour or cancer control**	Local control rate (all patients): 78% In 2 patients treated with proton therapy, the tumour reappeared in the radiation field, vs. none in the photon group
• **Complications / side effects**	No bone marrow depression or gastrointestinal complications
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Retrospective design Very small sample size No real statistical comparison provided No matching or multivariate analysis

4.3. Single-arm studies

Bush DA 2011	
Methods	
• **Design**	Single-arm prospective phase 2 study (NCT00614913)
• **Source of funding and competing interest**	Supported by funds from the Ken Venturi Endowment for proton therapy research Conflict of interests not stated
• **Setting**	Single university centre, USA
• **Sample size**	N=76
• **Duration and follow-up**	Apr 1998 - Oct 2006 Follow-up until death
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	Patients with cirrhosis who had radiological features or biopsy-proven hepatocellular carcinoma
• **Exclusion criteria**	Patients without cirrhosis, patients with extrahepatic metastasis, >3 lesions, tense ascites

• **Patient & disease characteristics**	Mean age: 62.7y Mean tumour size: 5.5cm Tumour size > 5 cm: 48% Child-Pugh class C: 24% MELD score >15: 16% Solitary lesion: 86%
Interventions	
• **Intervention group**	Proton beam therapy: 63 Gy delivered over a 3-week period in 15 fractions of 4.2 Gy
• **Control group**	-
Results	
• **Complications / side effects**	Acute toxicity during proton therapy: - Mild fatigue and skin reactions consisting of erythema (grade 1) - 5 patients experienced grade 2 gastrointestinal adverse effects - No treatment interruption or discontinuation No statistically significant change in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, or albumin levels or prothrombin time MELD scores: no significant change after 3 and 6 months
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear from which population the patients were selected (no reporting of ineligible patients)

Bush DA 2014	
Methods	
• **Design**	Single-arm phase 2 trial (NCT00614172)
• **Source of funding and competing interest**	Funding not reported Conflict of interests reported as none
• **Setting**	Single university centre, USA
• **Sample size**	N=100
• **Duration and follow-up**	Start and end dates not reported

	Median follow-up: 60 months
• **Statistical analysis**	-
Patient characteristics	
• **Eligibility criteria**	Patients with invasive nonlobular breast carcinoma with a maximal dimension of 3 cm; treatment with partial mastectomy with negative margins, pathologically negative lymph nodes
• **Exclusion criteria**	Patients with invasive lobular carcinoma; primary tumours >3 cm; presence of extensive ductal carcinoma in situ
• **Patient & disease characteristics**	Mean age: 63y Ductal histology: 90% Mean tumour size: 1.3 cm Stage: T1a 8%, T1b 44%, T1c 34%, T2 14%
Interventions	
• **Intervention group**	Postoperative proton beam radiation therapy to the surgical bed (40 Gy in 10 fractions, once daily over 2 weeks)
• **Control group**	-
Results	
• **Complications / side effects**	Acute toxicity during therapy and 3 months following treatment completion: - Mild to moderate radiation dermatitis (grade 1-2): 62% - No cases of grade 3 or higher acute skin reactions Late reactions: - Grade 1 telangiectasia in 7% - Clinical fat necrosis after 1 year: 1% - No rib fractures, clinical pneumonitis, or cardiac events
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear from which population the patients were selected (no reporting of ineligible patients) Unclear how toxicity was evaluated

Chiba T 2005	
Methods	
• **Design**	Retrospective single-arm study

• **Source of funding and competing interest**	Grant-in-Aid for Cancer Research (15-9) and Second Term Comprehensive 10-Year Strategy for Cancer Control (H-15-006) from the Ministry of Health, Labour, and Welfare of the Japanese Government Conflicts of interest: not reported
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=162
• **Duration and follow-up**	Nov 1985 - Jul 1998 Median follow-up: 31.7 mo
• **Statistical analysis**	Survival rates, Kaplan-Meier method, log-rank test
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma, considered unsuitable for surgery for various reasons Criteria in detail: (a) medically inoperable conditions attributable to coexisting advanced cirrhosis (i.e., indocyanin green R15 > 25%, serum total bilirubin level 34.2-59.9 Amol/L) and other intercurrent diseases; (b) HCC(s) not suitable for surgical resection and considered difficult to control with nonsurgical treatments, such as transcatheter arterial embolization and percutaneous ethanol injection; (c) patient's refusal of surgery Three or fewer tumours in the liver
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age: 62.5y Gender: 76.5% male Liver cirrhosis: 95% Single tumour: 49.4% Tumour size <3cm: 26.6%; >5cm: 17.2% Stages II and IIIB: 60%
Interventions	
• **Intervention group**	Proton beam therapy with or without transarterial embolization and percutaneous ethanol injection (median total dose of proton irradiation: 72 Gy in 16 fractions over 29 days)
• **Control group**	-
Results	
• **Complications / side effects**	No treatment discontinuation because of acute reactions Acute-subacute treatment sequelae: elevation of bilirubin 2.1%, anemia 1.1%, leukocytopenia 0.5%, thrombocytopenia 3.2%, elevation of transaminase level 9.7%

	Late treatment sequelae (N=5), all grade 2 or higher: infection biloma 1.1%, common bile duct stenosis 0.5%, gastrointestinal tract bleeding 1.1%
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear from which population the patients were selected (no reporting of ineligible patients)

Dagan R 2016	
Methods	
• **Design**	Single-arm retrospective study
• **Source of funding and competing interest**	Funding not reported Conflict of interests reported as none
• **Setting**	University centre, USA
• **Sample size**	N=84
• **Duration and follow-up**	Recruitment 2007 - 2013 Median follow-up 2.4 years
• **Statistical analysis**	Kaplan-Meier analysis, proportional hazards regression
Patient characteristics	
• **Eligibility criteria**	Patients with sinonasal cancer, aged >18 years, curative treatment including primary or postoperative proton therapy, minimum potential follow-up of 6 months from radiotherapy completion
• **Exclusion criteria**	Melanoma, sarcoma, and lymphoma, distant metastases, history of head and neck radiotherapy, active secondary malignancy other than squamous or basal cell skin cancers
• **Patient & disease characteristics**	Median age: 59y Gender: 58% male Presentation: 92% primary Primary site: nasal cavity or ethmoid 80%, maxillary 18%, frontal or sphenoid 2% Chemotherapy: 75% Surgical resection: 87% T3 25%, T4 69%
Interventions	

• **Intervention group**	Primary (13%) or adjuvant (87%) proton therapy (median dose 73.8 Gy, with 85% of patients receiving more than 70 Gy)
• **Control group**	-
Results	
• **Complications / side effects**	24% of patients had a significant toxicity (grade 3 to 5): - Unilateral vision loss occurred: 2 patients (grade 3 in 1 and grade 4 in 1) - Bone or soft-tissue necrosis: 7 patients (grade 3 in 5 and grade 4 in 1) - 4 patients with prolonged use of feeding tubes - Grade 2 CNS necrosis requiring steroids: 11% - Additional grade 3 events: infection and CSF leak - Death in 3 patients was attributed at least in part to therapy: 1 patient with brain necrosis, 1 patient with relapsed NHL, 1 patient with dural metastases
• **Secondary tumours**	The single secondary malignancy (grade 4) was an out-of-field unknown primary adenocarcinoma involving the liver less than 5 years after treatment of a squamous cell carcinoma of the maxillary sinus
Limitations and other comments	
• **Limitations**	Unclear if this was the complete cohort of patients treated between 2007 and 2013 Narrative reporting of the adverse events, mixed use of absolute numbers and percentages

Fukuda K 2017	
Methods	
• **Design**	Single-arm study (UMIN Clinical Trials Registry: UMIN000025342)
• **Source of funding and competing interest**	Funded by the Japan Society for the Promotion of Science (Grant/Award Number: '24390286', '24659556' No conflict of interest to declare
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=129
• **Duration and follow-up**	2002 to 2009 Duration of follow-up not reported
• **Statistical analysis**	Kaplan–Meier method; Cox proportional hazards model
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma treated with proton beam therapy

	Age ≥ 20, Eastern Cooperative Oncology Group performance status 0-2, Child–Pugh grade A or B, previously untreated HCC, no massive ascites, non-irradiated normal liver volume ≥ 500 mL
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age 72y Gender: 66.7% male Child–Pugh class: A 78.3%, B 21.7% Solitary tumour: 74.4%
Interventions	
• **Intervention group**	Proton beam therapy (66.0-77.0 GyE in 10-35 fractions)
• **Control group**	-
Results	
• **Complications / side effects**	No adverse events higher than grade 2, except for hematologic abnormalities Hematologic toxicities were difficult to assess the relation to proton beam therapy, because cirrhotic patients usually have pancytopenia due to splenomegaly (20% of the patients had grade 2 (<75000/mm3) and 5.5% grade 3 (<50000/mm3) thrombocytopenia before treatment) No patient required a blood transfusion or treatment interruption Radiation dermatitis was common, but no patient had grade 3 or higher dermatitis
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Probably selection bias because of heterogeneous referral Rather narrative presentation of toxicity results

Fukumitsu N 2009	
Methods	
• **Design**	Single-arm study
• **Source of funding and competing interest**	Supported in part by Grant-in-Aid for Cancer Research (No.15-9) from the Japanese Ministry of Health, Labor and Welfare Conflict of interest stated as none
• **Setting**	Single university centre, Japan (Tsukuba)

• **Sample size**	N=51
• **Duration and follow-up**	Inclusion Sep 2001 - Aug 2004 Follow-up periods ranged from 19 to 60 months
• **Statistical analysis**	Log-rank test; Cox proportional hazards; Wilcoxon signed-rank test
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma (HCC) >2 cm away from the porta hepatis or gastrointestinal tract Detailed eligibility criteria: (1) pathologically proven HCC or a clinical diagnosis of HCC as evidenced by arterial enhancement and venous washout on dynamic computed tomography (CT) and elevated tumour markers (serum alpha-fetoproteins >20 ng/mL or protein induced by vitamin K absence or antagonist II >40 AU/ mL in patients with documented hepatitis B or C viral infection; (2) solitary HCC or multiple tumour foci (totalling fewer than three in number), providing all lesions could be included in a single irradiation field with no other uncontrolled HCC; (3) a maximal tumour diameter of ≤10.0 cm; (4) tumour located ≥2 cm away from the porta hepatis or digestive tract; (5) Child-Pugh class A or B; and (6) European Organization for Research and Treatment of Cancer performance status of 0-2
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Age <70 years: 52.9% Gender: 66.7% male Child Pugh class: A 80.4%, B 19.6% Prior treatment: 64.7% Solitary tumour: 60.8%
Interventions	
• **Intervention group**	Proton beam therapy (66 GyE in 10 fractions)
• **Control group**	-
Results	
• **Complications / side effects**	No treatment-related deaths No patients required treatment for reduced WBC or platelet counts Forty patients did not change Child-Pugh class, 3 patients improved from Child-Pugh class B to A, and 8 patients deteriorated from Child-Pugh class A to B. No patients deteriorated to Child-Pugh class C during the follow-up period Late treatment sequelae included rib fracture in 3 patients 8, 10, and 27 months after treatment, and radiation pneumonitis (Grade 3) at the right lung base in 1 patient 3 months after treatment.
• **Secondary tumours**	Not reported
Limitations and other comments	

• **Limitations**	Unclear from which population the patients were selected (no reporting of ineligible patients)

Kawashima M 2011	
Methods	
• **Design**	Single-arm retrospective study
• **Source of funding and competing interest**	Funding not reported Conflict of interest: stated as none
• **Setting**	Single centre, Japan
• **Sample size**	N=60, consecutive patients
• **Duration and follow-up**	May 1999 - Jul 2007 Median follow-up: 20 months
• **Statistical analysis**	Kaplan-Meier, log-rank test, Cox's proportional hazards model
Patient characteristics	
• **Eligibility criteria**	Patients with HCC and uni- or bidimensional measurable HCC nodules of ≤10 cm in maximum diameter on computed tomography (CT) and/ or magnetic resonance imaging (MRI) without evidence of extrahepatic tumour spread; white blood cell count of ≥2,000/mm^3; haemoglobin level of ≥7.5 g/dl; platelet count of ≥25,000/ mm^3; and adequate hepatic function (total bilirubin, ≤3.0 mg/dl; alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase of <5.0_normal; no ascites) Patients with multicentric HCC nodules were only considered if they fulfilled the following two conditions: (1) multiple nodules could be encompassed within a single clinical target volume; and (2) lesions other than those of the targeted tumour were judged to be controlled with prior surgery and/or local ablation therapy
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age 70y Gender: 70% male Child-Pugh classification: A 78%, B 22% Median tumour size 45 mm Macroscopic vascular invasion: 70% Morphology of primary tumour: single nodular 75%; multinodular, aggregating 15%; diffuse 8%; portal vein tumour thrombosis 2%u Prior treatment: none 40%; surgery 17%; local ablation/TACE 43%

Interventions	
• **Intervention group**	Proton beam therapy: 76 GyE in 20 fractions in 46 patients, 65 GyE in 26 fractions in 11 patients, and 60 GyE in 10 fractions in 3 patients
• **Control group**	-
Results	
• **Complications / side effects**	Treatment prolongation because of fever associated with grade 3 elevation of total bilirubin in one patient 14 patients experienced transient grade 3 leukopenia and/or thrombocytopenia without infection or bleeding that necessitated treatment 8 patients experienced grade 3 elevation of transaminases without clinical manifestation of hepatic insufficiency Proton-induced hepatic insufficiency: 11 patients (all 76 GyE), at 1 to 6 months after completion of proton therapy; 6 died 3 patients experienced a gastrointestinal toxicity grade of ≥2: - One patient developed hemorrhagic duodenitis associated with anemia at 2 months of proton therapy - One patient with grade 3 hemorrhagic ulcer at ascending colon - One patient with grade 2 oesophagitis No other adverse events of ≥3 Grade
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Representative sample (consecutive patients) Retrospective study

Kim TH 2018	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	Supported by National Cancer Center Grant (NCC 1710060 and 1710030) Conflict of interests: stated as none
• **Setting**	Single proton centre, Korea
• **Sample size**	N=71
• **Duration and follow-up**	Inclusion May 2013 - Feb 2015 Median follow-up 31.3 mo

• **Statistical analysis**	Kaplan-Meier method; log-rank test; Cox's proportional hazard model
Patient characteristics	
• **Eligibility criteria**	Patients with inoperable or recurrent hepatocellular carcinoma receiving hypofractionated proton beam therapy; gross tumour ≥2 cm from gastrointestinal structures; liver function of Child-Pugh class A or B
• **Exclusion criteria**	Active tumours outside the target volume; history of previous radiotherapy to the target volume; extrahepatic metastases; uncontrolled ascites
• **Patient & disease characteristics**	Median age 63y Gender: 84.5% male Child-Pugh Classification: A 95.8%, B 4.2% Median tumour size: 1.5 cm Without prior treatment to the PBT site: 15.5%
Interventions	
• **Intervention group**	Hypofractionated proton beam therapy: 66 GyE in 10 fractions
• **Control group**	-
Results	
• **Complications / side effects**	No patient experiencing grade ≥3 toxicity Acute toxicities were transient, easily manageable, and caused no interruption in treatment course Change in Child-Pugh score: 8.5% showed a 1-point decrease; 4.2% showed a 1-point increase 4.2% patients experienced grade 1 elevated ALT without evidence of tumour progression 8.5% patients experienced grade 1 leukopenia and thrombocytopenia No late gastrointestinal toxicities, late hepatic failure induced by radiation-induced liver disease or treatment-related death after 3 months after proton beam therapy
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear from which population the patients were selected (no reporting of ineligible patients)

Komatsu S 2011	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	Supported by grants-in aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (C-21591773, C-20591611 and B-22390234) and by grants for Global Center of Excellence Program for Education and Research on Signal Transduction Medicine in the Coming Generation ‘‘Bringing Up Clinician-Scientists in the Alliance Between Basic and Clinical Medicine’’ Conflict of interest: none
• **Setting**	Single proton centre, Japan
• **Sample size**	N=242 (proton therapy patients)
• **Duration and follow-up**	Inclusion May 2001 - Jan 2009 Median follow-up: 31.0 months
• **Statistical analysis**	Kaplan-Meier method; log-rank test; Cox’s proportional hazard model
Patient characteristics	
• **Eligibility criteria**	Patients with HCC
• **Exclusion criteria**	Patients with HCC meeting the following criteria: 1) uncontrolled ascites and 2) tumours that measured >15 cm in greatest dimension (the upper limit of the irradiation field)
• **Patient & disease characteristics**	(Proton treatment only) Age < 70 years: 48% Gender: male 75% Child-Pugh classification: A 76%, B 23%, C 1% Single tumour: 88% Tumour size: <50mm 71%, >100mm 6% Prior treatment to target tumour: 47%
Interventions	
• **Intervention group**	Proton therapy: 52.8-84.0 GyE in 4-38 fractions
• **Control group**	-
Results	
• **Complications / side effects**	All acute toxicities during treatment were transient Grade 3 and higher late toxicities: 8 patients on proton therapy

	No patient died of treatment-related toxicity 5 patients on proton therapy developed refractory skin ulcers Dermatitis: Grade 2 5%; Grade 3 2%; Grade 4 1% Elevation of transaminase level: Grade 2 2%; Grade 3 1% Upper gastrointestinal ulcer: Grade 2 1%; Grade 3 1% Rib fracture: Grade 2 3%; Grade 3 0% Pneumonitis: Grade 2 2%; Grade 3 0% Subcutaneous panniculitis: Grade 2 2%; Grade 3 0% Biloma: Grade 2 0%; Grade 3 1% Low albuminemia: Grade 2 1%; Grade 3 0% Nausea/anorexia/pain/ascites: Grade 2 2%; Grade 3 0 %
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	For 12 patients, post-treatment findings could not be evaluated (reason unclear) Consecutive patients

Matsuzaki Y 1998	
Methods	
• **Design**	Non-randomized, controlled study
• **Source of funding and competing interest**	Not reported
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=117
• **Duration and follow-up**	Inclusion Mar 1995 - Jan 1988 Follow-up: every 6 months for the first 3 years and thereafter up to 6 years
• **Statistical analysis**	Kaplan-Meier method
Patient characteristics	

• **Eligibility criteria**	Patients with hepatocellular carcinoma with single or multinodular tumours who had refused surgery or had unresectable HCC, including multiple tumours, vessel invasions, complications by advanced cirrhosis or chronic renal failure, and myelodysplastic syndrome. Patients with insufficient accumulation of Lipiodol in their lesions following Lipiodol -targeted chemotherapy
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Child A or chronic hepatitis: N=55; Child B: N=37; Child C: N=25 Mean tumour size: 3.9 cm
Interventions	
• **Intervention group**	Proton beam therapy (N=62): monotherapy group N=35, combined with Lipiodol-targeted chemotherapy N=27
• **Control group**	I-TAI therapy (N=42)
Results (because of wrong comparator treated as single-arm study)	
• **Complications / side effects**	No patients experienced any serious adverse reactions No clinical symptoms, such as general fatigue, appetite loss, or nausea, were seen Fever: mono 0%, combined 0% Abdominal pain: mono 0%, combined 0% Pleural effusion: mono 0%, combined 0% Elevation of transaminase: mono 20%, combined 26% Elevation of bilirubin: mono 9%, combined 15% Anemia: mono 3%, combined 4% Leukocytopenia: mono 29%, combined 52% Thrombocytopenia: mono 26%, combined 37%
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear from which population the patients were selected (no reporting of ineligible patients) Few baseline characteristics
McDonald MW 2016	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	Funded by biostatistics and bioinformatics of Winship Cancer Institute of Emory University and NIH/ NCI under award number P30CA138292

	Conflict of interest reported as none
• **Setting**	Single university centre, USA
• **Sample size**	N=61
• **Duration and follow-up**	Inclusion from 2004 to 2014 Median follow-up 15.2 mo
• **Statistical analysis**	Kaplan-Meier method; log-rank test; Cox's proportional hazard model
Patient characteristics	
• **Eligibility criteria**	Adult patients with recurrent or second primary head and neck cancer
• **Exclusion criteria**	Chordoma, sarcomas, and lymphomas; pediatric patients; patients with benign diseases; and those treated with palliative intent
• **Patient & disease characteristics**	Median age: SCC 62.5y, non-SCC 53y Sex male: SCC 78.1%, non-SCC 41.4% Recurrent disease: SCC 87.5%, non-SCC 93.1% Second primary: SCC 12.5%, non-SCC 6.9%
Interventions	
• **Intervention group**	Curative-intent proton reirradiation; median dose 66 Gy for microscopic residual disease, 70.2 Gy for gross disease
• **Control group**	-
Results	
• **Complications / side effects**	Acute (N=61): Dermatitis: Grade 0: 13; Grade 1: 20; Grade 2: 25; Grade 3: 3; Grade 4: 0; Grade 5: 0 Xerostomia: Grade 0: 58; Grade 1: 1; Grade 2: 1; Grade 3: 0; Grade 4: 0; Grade 5: 0 Dysphagia: Grade 0: 58; Grade 1: 1; Grade 2: 2; Grade 3: 0; Grade 4: 0; Grade 5: 0 Mucositis: Grade 0: 52; Grade 1: 0; Grade 2: 7; Grade 3: 2; Grade 4: 0; Grade 5: 0 Ocular: Grade 0: 57; Grade 1: 3; Grade 2: 1; Grade 3: 0; Grade 4: 0; Grade 5: 0 Soft tissue/bone: Grade 0: 57; Grade 1: 0; Grade 2: 1; Grade 3: 3; Grade 4: 0; Grade 5: 0 Central nervous system: Grade 0: 60; Grade 1: 0; Grade 2: 0; Grade 3: 0; Grade 4: 0; Grade 5: 1 Late (N=53): Brain radiation necrosis: Grade 0: 45; Grade 1: 3; Grade 2: 5; Grade 3: 0; Grade 4: 0; Grade 5: 0 Soft tissue/bone: Grade 0: 37; Grade 1: 3; Grade 2: 3; Grade 3: 8; Grade 4: 1; Grade 5: 1 Xerostomia: Grade 0: 50; Grade 1: 1; Grade 2: 2; Grade 3: 0; Grade 4: 0; Grade 5: 0

	Orbital: Grade 0: 52; Grade 1: 0; Grade 2: 1; Grade 3: 0; Grade 4: 0; Grade 5: 0 Central nervous system: Grade 0: 47; Grade 1: 0; Grade 2: 2; Grade 3: 1; Grade 4: 2; Grade 5: 1
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear from which population the patients were selected (no reporting of ineligible patients)

Mizumoto M 2008	
Methods	
• **Design**	Single-arm phase 2 study
• **Source of funding and competing interest**	Supported in part by Grant-in-Aid for Cancer Research 15-9 from the Ministry of Health, Labor, and Welfare of the Japanese Government Conflict of interest stated as none
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=53
• **Duration and follow-up**	Sept 2001 - Dec 2004 Follow-up duration not reported
• **Statistical analysis**	Kaplan-Meier method; log-rank test; Cox's proportional hazard model
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma located within 2 cm from the main portal vein meeting the following criteria: (1) no tumour outside the target volume; (2) Eastern Cooperative Oncology Group performance status of 2 or less; (3) hepatic function characterized as a Child-Pugh score of 10 or less; (4) no extrahepatic metastasis; (5) white blood cell count of 1000/ml or greater, haemoglobin level of 6.5 g/dl or greater, and platelet count of 25000/ml or greater; (6) no uncontrolled ascites
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age: 69y Gender: 77% male Child-Pugh: A 87%, B 11%, C 2% Tumour size (mm): <30: 24%, 30–49: 34%, 50–99: 34%, ≥100: 8% Single tumour: 42% Previous treatment: 72%

	Clinical Stage: I: 32%; II: 16 30%; III: 38%
Interventions	
• **Intervention group**	Proton beam therapy: 72.6 GyE in 22 fractions
• **Control group**	-
Results	
• **Complications / side effects**	Acute treatment-related toxicity was generally mild: - Skin: Grade 0: 22, Grade 1: 28, Grade 2: 3, Grade 3: 0 - Gastrointestinal: Grade 0: 49, Grade 1: 2, Grade 2: 2, Grade 3: 0 - No other non-haematologic toxicities of Grade 3 or higher - 3 patients had leukocytopenia, with further deterioration by 2 grades during treatment - 12 patients were found to have Grade 3 toxicity level blood cell counts or liver function test results - No interruption in treatment because of acute treatment-related toxicities No patient had late toxicities of Grade 3 or higher Child-Pugh scores increased or decreased by one level in 41 of 45 patients, with two level deteriorations occurring in the remaining 4 patients
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Single-arm study with few limitations

Mizumoto M 2011	
Methods	
• **Design**	Comparative study of three proton treatment protocols
• **Source of funding and competing interest**	Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government Conflict of interest stated as none
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=266
• **Duration and follow-up**	Jan 2001 - Dec 2007

	Follow-up duration not reported
• **Statistical analysis**	Overall & progression free survival; Kaplan-Meier method, Cox proportional hazard model
Patient characteristics	
• **Eligibility criteria**	Patients with treatment of hepatocellular carcinoma and no active tumours outside the target volume; performance status ≤2; Child-Pugh score ≤10; no extrahepatic metastasis; white blood cell count ≥ 1000 /mm3, haemoglobin level ≥ 6.5 g/dl, and platelet count ≥ 25000/mm3; and no uncontrolled ascites
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age: 70y Gender: 72.6% male Multiple tumours: 53% Prior treatment: 63%
Interventions	
• **Intervention group**	Proton beam therapy A: 66 GyE in 10 fractions (N=104)
• **Control group**	Proton beam therapy B: 72.6 GyE in 22 fractions (N=95) Proton beam therapy C: 77 GyE in 35 fractions (N=60) Seven patients with double lesions underwent two different protocols
Results (treated as one cohort)	
• **Complications / side effects**	Acute radiation dermatitis: Grade 0: N=125; Grade 1: N=127; Grade 2: N=12; Grade 3: N=2 Symptomatic late toxicity: 3 had a rib fracture, 3 had dermatitis (2 patients of Grade 1 and 1 patient of Grade 3), and 6 had perforation, bleeding or inflammation of the digestive tract (3 of Grade 2, 3 of Grade 3)
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear recruitment scheme Unclear how toxicity was assessed Overlap with Mizumoto 2012

Mizumoto M 2012	
Methods	
• **Design**	Retrospective single-arm study

• **Source of funding and competing interest**	Supported in part by a Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government Conflict of interests stated as none
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=259
• **Duration and follow-up**	Jan 2001 - Dec 2007 Duration follow-up unclear
• **Statistical analysis**	Logistic regression model, receiver operating characteristic
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma; no active tumours outside the target volume; performance status ≤2; Child-Pugh score ≤10; no extrahepatic metastasis; white blood cell count ≥1000/mm^3, haemoglobin level ≥6.5 g/dl, platelet count ≥ 25000/mm^3; no uncontrolled ascites
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age 70y Gender: 72% male Child-Pugh score 5: 39%, 6: 37%, 7: 13%, 8: 7%, 9: 3%, 10: 1% Tumour size (mm) <30: 37%, 30-49: 36%, 50-99: 24%, ≥100: 3% Solitary tumour: 48% Prior treatment: 63%
Interventions	
• **Intervention group**	Proton beam therapy A: 66 GyE in 10 fractions (N=104) Proton beam therapy B: 72.6 GyE in 22 fractions (N=95) Proton beam therapy C: 77 GyE in 35 fractions (N=60)
• **Control group**	-
Results	
• **Complications / side effects**	On the final day of treatment, the Child-Pugh score increased by 0, 1, and 2 in 96, 44, and 1 of the 241 patients included in the analysis At 6 months (150 patients), increases in the Child-Pugh score of 0, 1, and ≥ 2 occurred in 120, 17, and 13 patients, respectively At 12 months (91 patients), increases of 0, 1 and ≥ 2 occurred in 66, 15, and 10 patients, respectively At 24 months (49 patients) increases of 0, 1, and ≥ 2 occurred in, 34, 4, and 11 patients, respectively

	Among the patients with an increase in Child-Pugh score ≥ 2, 2 of 13, 5 of 10, and 9 of 11 died of liver failure without tumour progression at 6, 12, and 24 months, respectively
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear recruitment scheme Unclear how toxicity was assessed Overlap with Mizumoto 2011

Nakayama H 2009	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	Funding not reported No conflicts of interest
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=318
• **Duration and follow-up**	Nov 2001 - Dec 2007 Median observation period 19.3 months
• **Statistical analysis**	Kaplan-Meier method; log-rank test; Cox's proportional hazard model
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma fulfilling the following criteria: 1) pathologically proven hepatocellular carcinoma or a clinical diagnosis of hepatocellular carcinoma based on arterial enhancement and venous washout on dynamic computed tomography (CT) scan as well as elevated tumour markers (serum a-fetoprotein >20 ng/mL or protein induced by vitamin K absence or antagonist II >40 AU/mL) in patients with documented hepatitis B or C viral infection; 2) solitary hepatocellular carcinoma or multiple tumour foci totalling <3 in number or any number of lesions provided all could be covered in the same irradiation field; 3) European Organization for Research and Treatment of Cancer performance status of 0 to 2; and 4) hepatocellular carcinoma not suitable for surgery or considered difficult to control with nonsurgical treatments, such as TACE and ablation therapies, or patient's refusal of surgery and/or other nonsurgical treatments
• **Exclusion criteria**	1) uncontrolled ascites; 2) extensive hepatocellular carcinoma in close proximity to the gastrointestinal tract
• **Patient & disease characteristics**	Mean age: 69y Gender: 72.3% male

	Child-Pugh: A: 73.6%; B: 24.2%; C: 2.2% Initial treatment for HCC: Proton 43.4%; PEI or RFA 45.3%; TACE or TAE 11.3%
Interventions	
• **Intervention group**	Proton beam therapy: 77.0 GyE in 35 fractions (N=66), 72.6 GyE in 22 fractions (N=85), 66.0 GyE in 10 fractions (N=104), 55.0 GyE in 10 fractions (N=7), other variable individualized schemes (N=18), unclear for remaining 38 patients
• **Control group**	-
Results	
• **Complications / side effects**	Treatment-related toxicity was minimal: - Skin: Grade 2: 28; Grade 3: 4 - Musculoskeletal: Grade 2: 3 - Gastrointestinal: Grade 2: 3; Grade 3: 1 - Haematologic grade 3 or higher: 6 No treatment-related death No treatment discontinuation because of liver toxicity
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Probably overlap with Mizumoto 2011 & 2012 Retrospective design

Oshiro Y 2017	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	Supported in part by a Grant-in-Aid for Scientific Research (B) (15H04901) Conflict of interest stated as none
• **Setting**	Single university centre, Japan (Tsukuba)
• **Sample size**	N=83
• **Duration and follow-up**	2002 - 2010 Median follow-up 45.0 months
• **Statistical analysis**	Kaplan-Meier method, log-rank test

Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma who received multiple courses of definitive proton beam therapy
• **Exclusion criteria**	Patients who received proton beam therapy for multiple tumours at one time
• **Patient & disease characteristics**	Median age: 69y Gender: 79.5% male Previous treatment before PBT: yes/no: 53/30 Child-Pugh before first PBT: A 73; B 10 Median tumour size before first PBT
Interventions	
• **Intervention group**	Repeated proton beam therapy with expiratory gating; dose fractionation of first treatment: 60 GyE in 10 fractions (N=42); 72.6 GyE in 22 fractions (N=34); 74 GyE in 37 fractions (N=13); other (N=3)
• **Control group**	-
Results	
• **Complications / side effects**	No ≥ grade 3 acute toxicity 1 patient had intestinal bleeding and underwent hemicolectomy 8 months after the first treatment Eight patients (9.6%) died of hepatic failure, but there was no radiation-induced liver dysfunction, clinical syndrome of anicteric hepatomegaly, ascites, or elevated liver enzymes between 2 weeks and 4 months after radiotherapy. Four of the 8 deaths occurred more than 1 year after the last treatment, and proton treatment was not the direct cause of liver failure
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Few details on actual inclusion criteria

Phan J 2016	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	Funding not reported Conflict of interest stated as none
• **Setting**	Single university centre, USA

• **Sample size**	N=60
• **Duration and follow-up**	Apr 2011 - Jun 2015 Median follow-up: 13.6 months
• **Statistical analysis**	Chi-square and Student t tests; Kaplan-Meier methods; log-rank tests; Cox proportional hazards regression
Patient characteristics	
• **Eligibility criteria**	Patients with biopsy-confirmed diagnoses of head and neck cancer at initial treatment and at recurrence; 18 years or older
• **Exclusion criteria**	Patients treated with palliative intent (<45 Gy), with distant metastases discovered during the workup, or without documented prior course of head and neck irradiation
• **Patient & disease characteristics**	Median age: SCC 66y, non-SCC 60.5y Gender: SCC 83% male, non-SCC 50% male Recurrence: SSC 93%, non-SSC 90%; second primary: SSC 8%, non-SSC 10%
Interventions	
• **Intervention group**	Proton beam re-irradiation (passive scatter proton therapy 25%; intensity modulated proton therapy 75%)
• **Control group**	-
Results	
• **Complications / side effects**	Acute grade 3 toxicity: 30%; 1 treatment discontinuation because of comorbidities; 1 acute grade 5 event Late grade 3 toxicity: 20%; no patient experienced late grade 4 toxicity, but 2 patients had potentially treatment-related grade 5 toxicity Acute toxicity: Mucositis: grade 1/2 5%; grade 3+ 10% Odynophagia: grade 1/2 5%; grade 3+ 10% Dysphagia: grade 1/2 5%; grade 3+ 5% Xerostomia: grade 1/2 3%; grade 3+ 3% Pain: grade 1/2 3%; grade 3+ 8% Dermatitis: grade 1/2 10%; grade 3+ 13% Weight loss: grade 3+ 3% Feeding tube: grade 3+ 10% Late toxicity: Mucositis: 0%

	Odynophagia: 0% Dysphagia: grade 1/2 2%; grade 3+ 2% Xerostomia: grade 1/2 0%; grade 3+ 2% Pain: 0% Dermatitis: 0% Weight loss: 0% Feeding tube: grade 3+ 10% Ototoxicity: grade 1/2 3% Osteoradionecrosis: grade 1/2 2%; grade 3+ 0% Neurotoxicity: grade 1/2 2%; grade 3+ 3% Tracheostomy: grade 1/2 0%; grade 3+ 3%
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Retrospective design

Romesser PB 2016	
Methods	
• **Design**	Single-arm retrospective study; prospective database (NCT01255748)
• **Source of funding and competing interest**	No funding Conflict of interests: not stated
• **Setting**	Multicentre study, USA
• **Sample size**	N=92
• **Duration and follow-up**	Feb 2011 - Sep 2014 Median follow-up 10.4 mo
• **Statistical analysis**	Kaplan-Meier method
Patient characteristics	
• **Eligibility criteria**	Patients with locally recurrent head and neck cancer with a history of at least one prior course of definitive intent external beam radiotherapy
• **Exclusion criteria**	-

• **Patient & disease characteristics**	Median age 63y Gender: 70.7% male New primary: 13% SSC (squamous cell carcinoma) histology: 56.5%
Interventions	
• **Intervention group**	Proton beam re-irradiation
• **Control group**	-
Results	
• **Complications / side effects**	Acute toxicity: Dysphagia: grade 0 37.9%, grade 1 28.8%, grade 2 24.2%, grade 3 9.1% Mucositis: grade 0 40.7%, grade 1 31.9%, grade 2 17.6%, grade 3 9.9% Nausea: grade 0 69.2%, grade 1 23.1%, grade 2 7.7%, grade 3 0.0% Dysgeusia: grade 0 54.9%, grade 1 25.3%, grade 2 19.8%, grade 3 0.0% Esophagitis: grade 0 62.1%, grade 1 18.2%, grade 2 10.6%, grade 3 9.1% Dermatitis: grade 0 11.0%, grade 1 41.8%, grade 2 44.0%, grade 3 3.3% Late toxicity: N=69 patients Skin: grade 0 63.8%, grade 1 23.2%, grade 2 4.3%, grade 3 1.4%, grade 4 7.2%, grade 5 0.0% Induration/fibrosis: grade 0 67.2%; grade 1 32.8%; grade 2 0.0%; grade 3 0.0%; grade 4 0.0%; grade 5 0.0% Xerostomia: grade 0 58.0%; grade 1 37.7%; grade 2 4.3%; grade 3 0.0%; grade 4 0.0%; grade 5 0.0% Trismus: grade 0 69.2%; grade 1 24.6%; grade 2 6.2%; grade 3 0.0%; grade 4 0.0%; grade 5 0.0% Dysphagia: grade 0 73.2%; grade 1 17.9%; grade 2 1.8%; grade 3 7.1%; grade 4 0.0%; grade 5 0.0% Bleeding: grade 0 97.1%, grade 1 0.0%, grade 2 0.0%, grade 3 0.0%, grade 4 0.0%, grade 5 2.9%
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Retrospective analysis of prospective database

Russo AL 2016	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	Not reported
• **Setting**	Single centre, USA
• **Sample size**	N=54
• **Duration and follow-up**	Oct 1991 - Nov 2008 Median follow-up 82 months
• **Statistical analysis**	Kaplan-Meier, Cox proportional hazards
Patient characteristics	
• **Eligibility criteria**	Patients with newly diagnosed squamous cell carcinoma of the nasal cavity and paranasal sinus, for whom protons could potentially result in improved dosimetric and clinical outcomes when compared with photon therapy; stage III or IV
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age 56y Gender: 50% male Tumour stage: III: 13%, IVA: 24%, IVB: 63%
Interventions	
• **Intervention group**	Proton beam therapy: total median dose 72.8 GyE
• **Control group**	-
Results	
• **Complications / side effects**	Grade 3 toxicity: N=9 Grade 4 toxicity: N=6 No grade 5 toxicity Ocular and visual adverse events: N=14 patients with 1 or more grade 2 late adverse events (5 nasolacrimal stenosis, 2 ectropion, 2 conjunctivitis, 2 blepharitis, 1 dry eye, 1 cataract, 2 keratitis, 2 retinopathy) Wound and soft tissue toxicity:

	- 6 patients experienced grade 3 and 4 sinonasal cutaneous fistulas - 2 patients experienced facial cellulitis (1 grade 2, 1 grade 3) - 1 patient experienced grade 3 trismus requiring a feeding tube Other toxicities: - 7 patients experienced grade 2 nasal stenosis - 8 patients experienced grade 2 neurologic toxicities - 10 patients experienced grade 2 and 2 grade 3 auditory toxicities - 5 patients had bone toxicities, including three grade 2 and one grade 3 - 3 patients experienced grade 2 endocrine toxicities - 1 patient experienced chronic sinusitis
• **Secondary tumours**	1 patient experienced spindle cell sarcomatoid carcinoma in the maxillary sinus 9 years after the completion of radiation
Limitations and other comments	
• **Limitations**	Unclear recruitment scheme

Takatori K 2014	
Methods	
• **Design**	Prospective single-arm study
• **Source of funding and competing interest**	Funding not reported No conflicts of interest
• **Setting**	Single proton centre, Japan
• **Sample size**	N=91
• **Duration and follow-up**	Jan 2010 – Jan 2012
• **Statistical analysis**	Student's t test, X^2 and Fisher's exact test; binary logistic regression
Patient characteristics	
• **Eligibility criteria**	Patients with either locally unresectable or clinically inoperable pancreatic cancer Patients with metastatic disease were included if their distant disease was low-volume and prognosis was favourable with control of the primary tumour Patients with resectable pancreatic tumours were included if they had several reasons for a diagnosis of clinically inoperable, such as high age, severe comorbidities, and patient will

• **Exclusion criteria**	-
• **Patient & disease characteristics**	Mean age: 64.4y Gender: 55% male 38 patients had histologically proven adenocarcinoma of the pancreas, the remainder had a diagnosis of pancreatic cancer based on clinical imaging findings 51 patients had received prior chemotherapy such as gemcitabine or TS-1O (tegafur/gimestat/potassium oxonate) 54 patients were positive for anti-helicobacter pylori (HP) or immunoglobulin-G (IgG) antibodies 31 patients were taking non- steroidal anti-inflammatory drugs (NSAIDs)
Interventions	
• **Intervention group**	Proton beam radiotherapy: 67.5 GyE in 25 fractions
• **Control group**	-
Results	
• **Complications / side effects**	Acute gastrointestinal complications: - Radiation-induced ulcers: 49.4% - No mucosal lesion with spontaneous or active bleeding - No cases of gastrointestinal perforation Late gastrointestinal complications: - Bleeding gastric ulcers: 1 grade 4, 1 grade 5 - 1 grade 5 duodenal perforation
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Few limitations, except from single-arm design

Terashima K 2012	
Methods	
• **Design**	Single-arm phase 1/2 study (UMIN000002173)
• **Source of funding and competing interest**	Sponsors not explicited Conflicts of interest stated as none

• **Setting**	Single proton centre, Japan
• **Sample size**	N=50
• **Duration and follow-up**	Feb 2009 - Aug 2010 Median follow-up: 12.5 months
• **Statistical analysis**	Kaplan-Meier method, unpaired Student's t-test
Patient characteristics	
• **Eligibility criteria**	Patients with locally advanced pancreatic cancer, borderline resectable cancer and unresectable cancer without distant metastases; cytologically or histologically confirmed to be adenocarcinoma; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
• **Exclusion criteria**	Patients with a history of abdominal radiotherapy or previous treatment of pancreatic tumour
• **Patient & disease characteristics**	Characteristics stated by intervention protocol: P1 (N=5), P2 (N=5), P3 (N=40) Median age: 57y, 56y, 64y Gender: male 60%, 40%, 45%
Interventions	
• **Intervention group**	Gemcitabine-concurrent proton radiotherapy: 50 GyE in 25 fractions (P1: N=5); 70.2 GyE in 26 fractions (P2: N=5); 67.5 GyE in 25 fractions (P3: N=40); gemcitabine: 800 mg/m2/week for 3 weeks
• **Control group**	-
Results	
• **Complications / side effects**	P1: - 1 grade 3 leukopenia - 1 grade 3 neutropenia - 1 grade 3 anorexia - 1 grade 3 epigastralgia - 1 grade 3 fatigue - No grade 4 toxicity P2: - 3 grade 3 leukopenia - 2 grade 3 neutropenia - 1 grade 3 anemia - 1 grade 3 thrombocytopenia - 1 grade 3 anorexia

	- 1 late grade 3 gastric ulcer: treatment interruption P3: - 5 patients (13%) could not receive the third gemcitabine administration because of acute hematologic and gastrointestinal toxicities - Leukopenia: acute: 15 grade 3, 1 grade 4 - Neutropenia: acute: 9 grade 3, 2 grade 4 - Thrombocytopenia: acute: 2 grade 3 - Nausea: acute: 2 grade 3 - Vomiting: acute: 1 grade 3 - Anorexia: acute: 3 grade 3; late: 1 grade 3 - Epigastralgia: acute: 2 grade 3 - Gastric ulcer: late: 3 grade 3, 1 grade 5 - Weight loss: acute: 3 grade 3 - Fatigue: acute: 1 grade 3; late: 1 grade 3
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Unclear recruitment scheme

Verma V 2017	
Methods	
• **Design**	Retrospective single-arm study
• **Source of funding and competing interest**	No funding Two authors have minority ownership interest in the Chicago Proton Center through a joint venture with Northwestern Medicine; all other authors have no conflicts of interest
• **Setting**	Single proton centre, USA
• **Sample size**	N=91
• **Duration and follow-up**	2011 - 2016 Median follow-up: 15.5 months
• **Statistical analysis**	Not reported
Patient characteristics	

• **Eligibility criteria**	Patients with locally-advanced breast cancer, receiving primary adjuvant proton beam therapy to either the intact breast or chest wall plus the comprehensive regional lymphatics including axillary levels I-III, SCV, and IMNs
• **Exclusion criteria**	Patients with re-irradiation, aggressive palliation in an inoperable patient, partial breast irradiation, isolated axillary recurrences, or treatment to sites of distant metastatic disease; patients who electively stopped treatment
• **Patient & disease characteristics**	Median age: 54y Gender: 2% male Tumour stage: T1: 21%; T2: 38%; T3: 29%; T4: 12% Nodal stage: N0: 0%; N1: 54%; N2: 16%; N3: 19%; NX: 1%
Interventions	
• **Intervention group**	Adjuvant proton beam therapy targeting the intact breast/chest wall and comprehensive regional nodes including the axilla, supraclavicular fossa, and internal mammary lymph nodes; median dose: 50.4 GyE
• **Control group**	-
Results	
• **Complications / side effects**	Dermatitis: Grade 1: 23%; Grade 2: 72%; Grade 3: 5% Esophagitis: Grade 1: 31%; Grade 2: 33%; Grade 3: 0% Fatigue: Grade 1: 46%; Grade 2: 15%; Grade 3: 0% Breast/chest wall pain: Grade 1: 50%; Grade 2: 29%; Grade 3: 1% Two patients discontinued treatment
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Retrospective design

Yu JI 2018	
Methods	
• **Design**	Prospective single-arm study
• **Source of funding and competing interest**	Supported by a Samsung Medical Center grant (No. GF01130081), a Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. NRF-2015R1D1A1A01060945), and a grant from the Marin Biotechnology Program (No. 20150220) funded by the Ministry of Oceans and Fisheries, Korea Conflict of interest reported as none

• **Setting**	Single university centre, Korea
• **Sample size**	N=101
• **Duration and follow-up**	Jan 2016 - Feb 2017 Median follow-up 4.9 months
• **Statistical analysis**	Not reported
Patient characteristics	
• **Eligibility criteria**	Patients with hepatocellular carcinoma who were not indicated for standard curative local modalities
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age: 63y Gender: 86.1% male Child-Pugh class: A5 72.3%; A6 16.8 %; B7 5.0%; B8 3.0%; B9 2.0%; C10 1.0% No tumour multiplicity: 73.3%
Interventions	
• **Intervention group**	Proton beam therapy (treated with an equivalent dose of 62–92 GyE)
• **Control group**	-
Results	
• **Complications / side effects**	Worsening of Child-Pugh score by 2 was developed in three patients (3.0%) at one month and an additional one patient (1.0%) at three months after treatment completion Acute toxicity after 3-month follow-up: Anemia: Grade 1: 56.4%; Grade 2: 3.0 %; Grade 3: 2.0% Leukopenia: Grade 1: 24.8%; Grade 2: 19.8%; Grade 3: 3.0% Thrombocytopenia: Grade 1: 47.5%; Grade 2: 24.8 %; Grade 3: 9.9 % AST: Grade 1: 39.6%; Grade 2: 2.0 %; Grade 3: 1.0% ALT: Grade 1: 24.8%; Grade 2: 4.0%; Grade 3:1.0 % ALP: Grade 1: 34.7%; Grade 2: 2.0 % Hypoalbuminemia: Grade 1: 15.8%; Grade 2: 8.9 % Hyperbilirubinemia: Grade 1: 10.9%; Grade 2: 11.9 %; Grade 3: 4.0%; Grade 4: 1.0%

	During the follow-up period after completion of proton therapy, two cases (2.0%) of newly developed gastroduodenal ulcers were detected. In three other cases, gastroduodenal changes including erosion and/or inflammation were found within the irradiation field
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Single-arm study with few limitations

Zenda S 2015	
Methods	
• **Design**	Retrospective single-arm analysis
• **Source of funding and competing interest**	Funding not reported Conflict of interest stated as none
• **Setting**	Single centre, Japan
• **Sample size**	N=90
• **Duration and follow-up**	Jan 1999 - Dec 2008 Median follow-up 57.5 months
• **Statistical analysis**	Kaplan-Meier product-limits method, log-rank tests
Patient characteristics	
• **Eligibility criteria**	Patients with malignancies of the nasal cavity, paranasal sinuses, or involving the skull base
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Median age: 57y Gender: 57.7% male Primary site: maxillary sinus 12; ethmoid sinus 8; sphenoid sinus 5; nasal cavity 62; other site 3 Tumour type: squamous cell carcinoma 22; adenoid cystic carcinoma 15; olfactory neuroblastoma 27; melanoma 14; others 12 TNM stage: T1 4; T2 16; T3 9; T4 54;Tx 7; N0 88; N1 3; N2 0
Interventions	

• **Intervention group**	Proton beam therapy: most common regimen was 65 GyE in 26 fractions; for 14 mucosal melanoma patients a 60 GyE in 15 fractions regimen was used
• **Control group**	-
Results	
• **Complications / side effects**	Median time to onset of grade 2 or greater late toxicity, except cataract, was 39.2 months Hearing loss: Grade 1 1; Grade 2 1; Grade 3 3; Grade 4 0 Nerve disorder: Grade 1 0; Grade 2 1; Grade 3 1; Grade 4 0 Encephalomyelitis infection: Grade 1 0; Grade 2 0; Grade 3 0; Grade 4 2 Cataract: Grade 1 1; Grade 2 1; Grade 3 5; Grade 4 0 Optic nerve disorder: Grade 1 0; Grade 2 4; Grade 3 1; Grade 4 4 Brain necrosis: Grade 1 5; Grade 2 1; Grade 3 1; Grade 4 0 Soft tissue necrosis: Grade 1 0; Grade 2 0; Grade 3 1; Grade 4 0 Bone necrosis: Grade 1 0; Grade 2 4; Grade 3 2; Grade 4 0
• **Secondary tumours**	Not reported
Limitations and other comments	
• **Limitations**	Retrospective design

5. GRADE TABLES

5.1. Low-grade glioma

Quality assessment		Limitations *					N patients		Effect		Quality
N studies	Design	1	2	3	4	5	Proton	Photon	Relative (95%CI)	Absolute	
5-year overall survival											
1	Observational study	Serious[1]	No	Serious[2]	Serious[3]	No	10	22	HR = 40 p = 0.02	-	VERY LOW
Local recurrence											
1	Observational study	Serious[1]	No	Serious[2]	Very serious[4]	No	10	22	RR = 0.88 (0.20, 3.79)	-	VERY LOW
Brain metastasis recurrence											
1	Observational study	Serious[1]	No	Serious[2]	Very serious[4]	No	10	22	RR = 2.20 (0.15, 31.74)	-	VERY LOW
Radiation necrosis											
1	Observational study	Serious[5]	No	No	Very serious[4]	No	37	123	RR = 1.66 (0.67, 4.12)	-	VERY LOW
Pseudoprogression											
1	Observational study	Serious[6]	No	No	Very serious[4]	No	34	65	RR = 1.06 (0.39, 2.92)	-	VERY LOW

** 1: Risk of bias; 2: Inconsistency; 3: Indirectness; 4: Imprecision; 5: Other considerations*

[1] No blinding, no concurrency of treatment groups; [2] Some children included, not all patients had low-grade glioma; [3] Low sample size; [4] Optimal information size criterion is not met, and fails to exclude important benefit and harm; [5] No blinding; [6] No blinding of patients, no concurrency of treatment groups.

5.2. Breast cancer

Quality assessment				Limitations *			N patients		Effect		Quality
N studies	Design	1	2	3	4	5	Proton	Photon	Relative (95%CI)	Absolute	
7-year local failure rate											
1	Observational study	Serious[1]	No	No	Very serious[2]	No	19	79	RR = 2.77 (0.50, 15.44)	-	VERY LOW
Overall cosmesis rated as good or excellent by physicians, at 60 months											
1	Observational study	Serious[1]	No	No	Serious[3]	No	16	59	RR = 0.63 (0.40, 0.97)	-	VERY LOW
Overall cosmesis rated as good or excellent by patients, at 60 months											
1	Observational study	Serious[1]	No	No	Serious[4]	No	16	60	RR = 0.94 (0.77, 1.14)	-	VERY LOW
Skin colour changes, at 60 months											
1	Observational study	Serious[1]	No	No	No	No	16	59	RR = 25.81 (3.42, 194.81)	-	VERY LOW
Patchy atrophy in the irradiation portal, at 60 months											
1	Observational study	Serious[1]	No	No	No	No	16	59	RR = 9.83 (2.94, 32.86)	-	VERY LOW
Skin colour changes, at 84 months											
1	Observational study	Serious[1]	No	No	Very serious[5]	No	13	50	p = 0.02	-	VERY LOW
Telangiectasia >4 cm^2, at 84 months											
1	Observational study	Serious[1]	No	No	No	No	13	50	RR = 9.62 (2.10, 44.05)	-	VERY LOW
Rib fracture, at 60 months											
1	Observational study	Serious[1]	No	No	Very serious[6]	No	16	60	RR = 1.25 (0.14, 11.22)	-	VERY LOW

Fat necrosis, at 60 months											
1	Observational study	Serious[1]	No	No	Very serious[6]	No	16	60	RR = 0.75 (0.18, 3.09)	-	VERY LOW

[*] *1: Risk of bias; 2: Inconsistency; 3: Indirectness; 4: Imprecision; 5: Other considerations*

[1] Blinding not reported, no matched design or risk adjustment; [2] 95%CI includes important benefit and harm; [3] Optimal information size criterion is met, but fails to exclude important benefit; [4] Optimal information size criterion is not met, but excludes important benefit and harm; [5] Only p-value provided; [6] Optimal information size criterion is not met, and fails to exclude important benefit and harm

5.3. Pancreatic cancer

Quality assessment				Limitations [*]			N patients		Effect		Quality
N studies	**Design**	**1**	**2**	**3**	**4**	**5**	**Proton**	**Photon**	**Relative (95%CI)**	**Absolute**	
Median overall survival											
1	Observational study	Serious[1]	No	No	Serious[2]	No	10	15	-	22.3 vs. 23.4 months	VERY LOW
Local progression											
1	Observational study	Serious[1]	No	No	Very serious[3]	No	10	15	RR = 0.67 (0.28, 1.58)	-	VERY LOW
Disease control rates											
1	Observational study	Serious[1]	No	No	Very serious[4]	No	10	15	RR = 0.86 (0.61, 1.20)	-	VERY LOW
Acute grade 3 leukopenia											
1	Observational study	Serious[1]	No	No	Very serious[3]	No	10	15	RR = 0.21 (0.01, 3.64)	-	VERY LOW
Acute grade 3 thrombocytopenia											
1	Observational study	Serious[1]	No	No	Very serious[3]	No	10	15	RR = 0.48 (0.02, 10.84)	-	VERY LOW
Acute grade 3 ulcer											

1	Observational study	Serious[1]	No	No	Very serious[3]	No	10	15	RR = 4.36 (0.20, 97.56)	-	VERY LOW

[*] *1: Risk of bias; 2: Inconsistency; 3: Indirectness; 4: Imprecision; 5: Other considerations*

[1] Blinding not reported, no matched design or risk adjustment; [2] No p-value or 95%CI reported; [3] Optimal information size criterion is not met, and fails to exclude important benefit and harm; [4] Optimal information size criterion is not met, and fails to exclude important harm.

5.4. Hepatocellular cancer

Quality assessment				Limitations [*]			N patients		Effect		Quality
N studies	**Design**	**1**	**2**	**3**	**4**	**5**	**Proton**	**Photon**	**Relative (95%CI)**	**Absolute**	
Local recurrence rate											
1	Observational study	Serious[1]	No	No	Very serious[2]	No	5	3	RR = 3.33 (0.21, 52.68)	-	VERY LOW

[*] *1: Risk of bias; 2: Inconsistency; 3: Indirectness; 4: Imprecision; 5: Other considerations*

[1] Blinding not reported, no matched design or risk adjustment; [2] Optimal information size criterion is not met, and fails to exclude important benefit and harm.

6. FOREST PLOTS

Figure 2 – Forest plot: low-grade glioma, local recurrence

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kahn 2011	1	10	1	22	100.0%	2.20 [0.15, 31.74]
Total (95% CI)		**10**		**22**	**100.0%**	**2.20 [0.15, 31.74]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

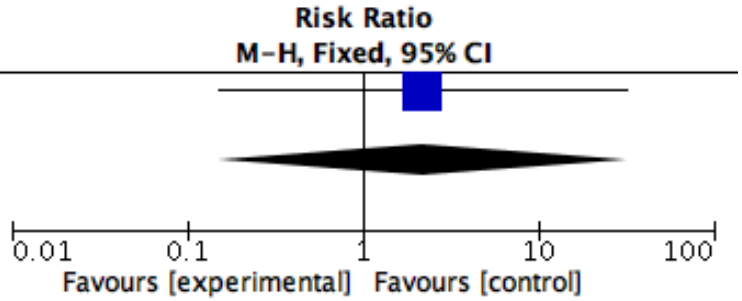

Figure 3 – Forest plot: low-grade glioma, brain metastasis recurrence

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kahn 2011	2	10	5	22	100.0%	0.88 [0.20, 3.79]
Total (95% CI)		**10**		**22**	**100.0%**	**0.88 [0.20, 3.79]**
Total events	2		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

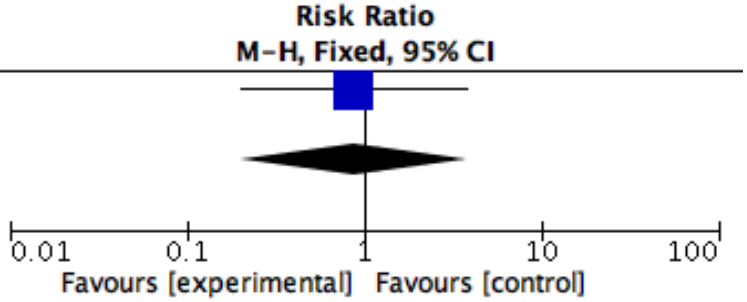

Figure 4 – Forest plot: low-grade glioma, radiation necrosis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Acharya 2018	6	37	12	123	100.0%	1.66 [0.67, 4.12]
Total (95% CI)		**37**		**123**	**100.0%**	**1.66 [0.67, 4.12]**
Total events	6		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)

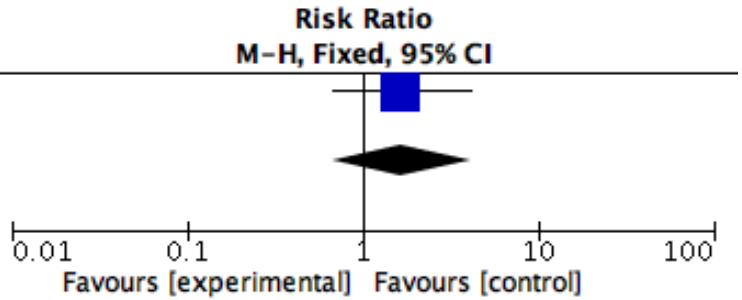

Figure 5 – Forest plot: low-grade glioma, pseudoprogression

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bronk 2018	5	34	9	65	100.0%	1.06 [0.39, 2.92]
Total (95% CI)		**34**		**65**	**100.0%**	**1.06 [0.39, 2.92]**
Total events	5		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)

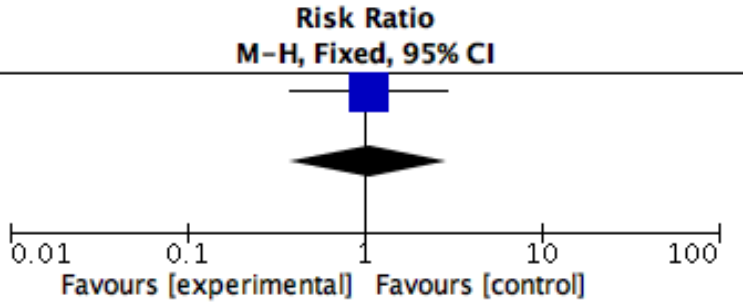

Figure 6 – Forest plot: breast cancer, 7-year local failure

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	2	19	3	79	100.0%	2.77 [0.50, 15.44]
Total (95% CI)		**19**		**79**	**100.0%**	**2.77 [0.50, 15.44]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.24)

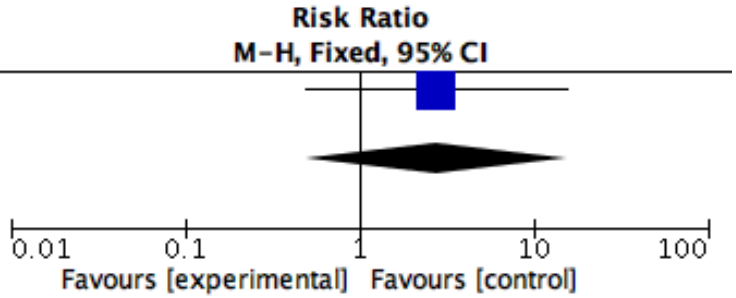

Figure 7 – Forest plot: breast cancer, overall cosmesis rated as good or excellent by physicians, at 60 months

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	9	16	53	59	100.0%	0.63 [0.40, 0.97]
Total (95% CI)		**16**		**59**	**100.0%**	**0.63 [0.40, 0.97]**
Total events	9		53			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.08 (P = 0.04)

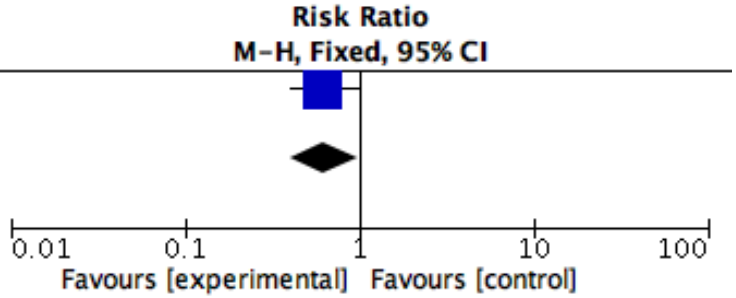

Figure 8 – Forest plot: breast cancer, overall cosmesis rated as good or excellent by patients, at 60 months

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	14	16	56	60	100.0%	0.94 [0.77, 1.14]
Total (95% CI)		**16**		**60**	**100.0%**	**0.94 [0.77, 1.14]**
Total events	14		56			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

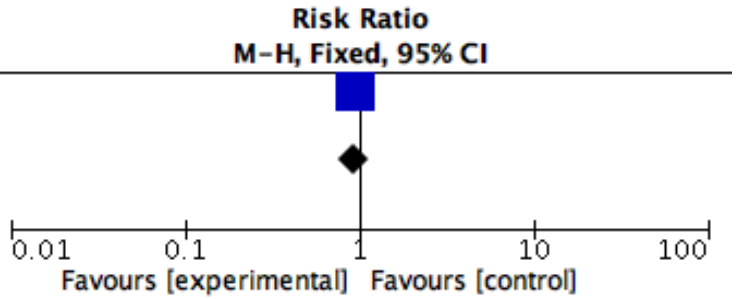

Figure 9 – Forest plot: breast cancer, skin colour change, at 60 months

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	7	16	1	59	100.0%	25.81 [3.42, 194.81]
Total (95% CI)		**16**		**59**	**100.0%**	**25.81 [3.42, 194.81]**
Total events	7		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.15 (P = 0.002)

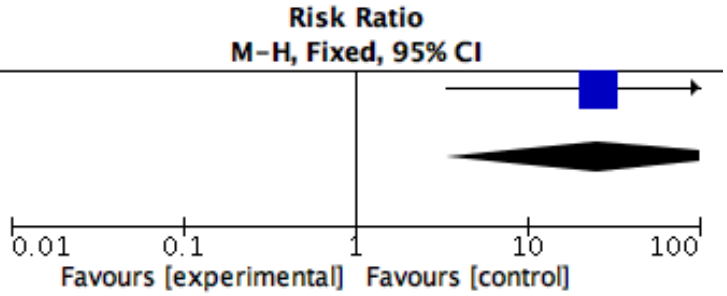

Figure 10 – Forest plot: breast cancer, patchy atrophy in the irradiation portal, at 60 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	8	16	3	59	100.0%	9.83 [2.94, 32.86]
Total (95% CI)		**16**		**59**	**100.0%**	**9.83 [2.94, 32.86]**
Total events	8		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.71 (P = 0.0002)

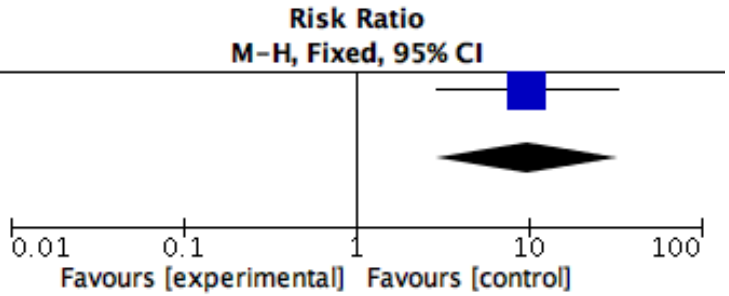

Figure 11 – Forest plot: breast cancer, telangiectasia >4 cm^2, at 84 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	5	13	2	50	100.0%	9.62 [2.10, 44.05]
Total (95% CI)		**13**		**50**	**100.0%**	**9.62 [2.10, 44.05]**
Total events	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.91 (P = 0.004)

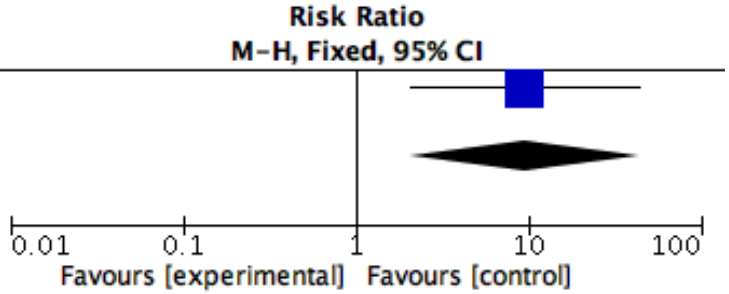

Figure 12 – Forest plot: breast cancer, rib fracture, at 60 months

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	1	16	3	60	100.0%	1.25 [0.14, 11.22]
Total (95% CI)		**16**		**60**	**100.0%**	**1.25 [0.14, 11.22]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)

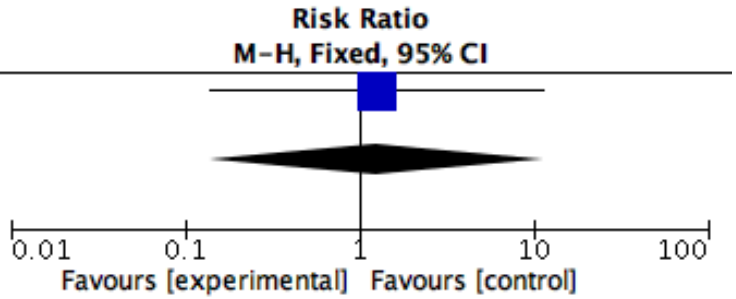

Figure 13 – Forest plot: breast cancer, fat necrosis, at 60 months

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galland-Girodet 2014	2	16	10	60	100.0%	0.75 [0.18, 3.09]
Total (95% CI)		**16**		**60**	**100.0%**	**0.75 [0.18, 3.09]**
Total events	2		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)

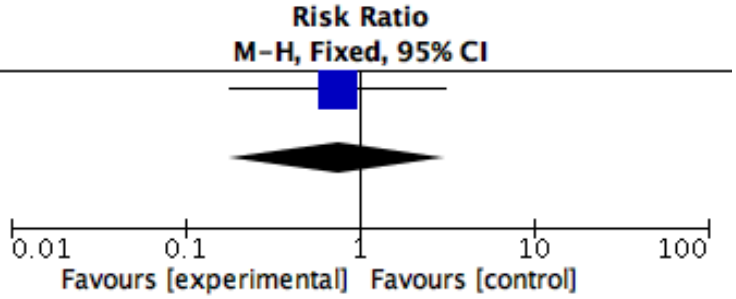

Figure 14 – Forest plot: pancreatic cancer, local progression

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maemura 2017	4	10	9	15	100.0%	0.67 [0.28, 1.58]
Total (95% CI)		**10**		**15**	**100.0%**	**0.67 [0.28, 1.58]**
Total events	4		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)

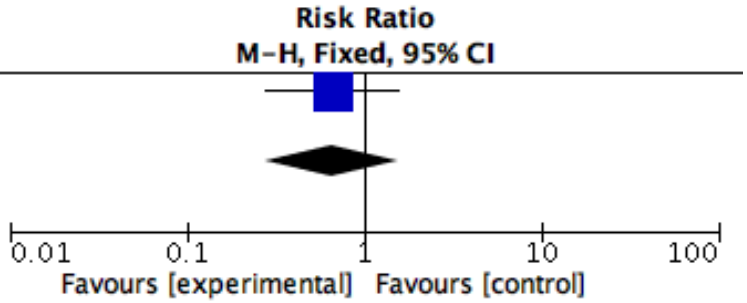

Figure 15 – Forest plot: pancreatic cancer, disease control rates

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maemura 2017	8	10	14	15	100.0%	0.86 [0.61, 1.20]
Total (95% CI)		**10**		**15**	**100.0%**	**0.86 [0.61, 1.20]**
Total events	8		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

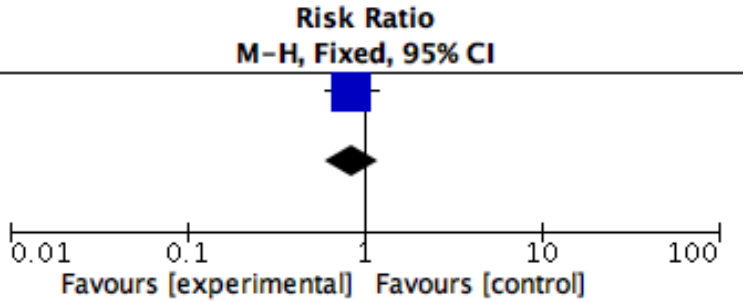

Figure 16 – Forest plot: pancreatic cancer, acute grade 3 leukopenia

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maemura 2017	0	10	3	15	100.0%	0.21 [0.01, 3.64]
Total (95% CI)		**10**		**15**	**100.0%**	**0.21 [0.01, 3.64]**
Total events	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)

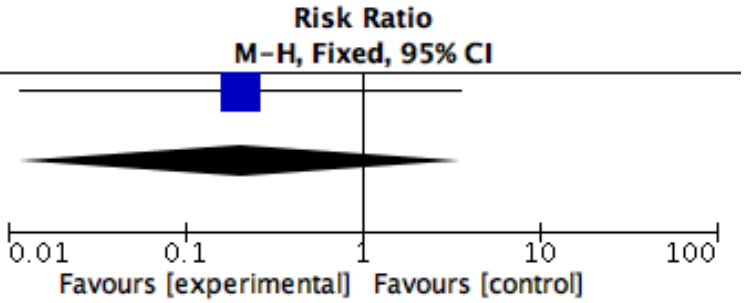

Figure 17 – Forest plot: pancreatic cancer, acute grade 3 thrombocytopenia

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maemura 2017	0	10	1	15	100.0%	0.48 [0.02, 10.84]
Total (95% CI)		**10**		**15**	**100.0%**	**0.48 [0.02, 10.84]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

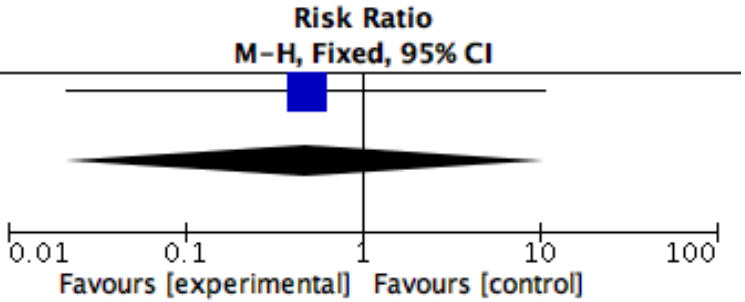

Figure 18 – Forest plot: pancreatic cancer, acute grade 3 ulcer

Study or Subgroup	Proton Events	Proton Total	Photon Events	Photon Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Maemura 2017	1	10	0	15	100.0%	4.36 [0.20, 97.56]
Total (95% CI)		**10**		**15**	**100.0%**	**4.36 [0.20, 97.56]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)

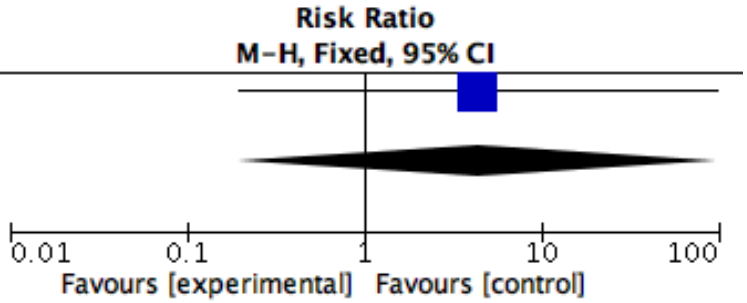

Figure 19 – Forest plot: hepatocellular cancer, local recurrence

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Otsuka 2003	2	5	0	3	100.0%	3.33 [0.21, 52.68]
Total (95% CI)		**5**		**3**	**100.0%**	**3.33 [0.21, 52.68]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)